World Journal of Gastrointestinal Surgery

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DOI: 10.4240/wjgs.v8.i8.574

World J Gastrointest Surg 2016 August 27; 8(8): 574-577
ISSN 1948-9366 (online)

Can the prognosis of colorectal cancer be improved by surgery?

Yasumasa Takii, Satoshi Maruyama, Hitoshi Nogami

Yasumasa Takii, Satoshi Maruyama, Hitoshi Nogami, Niigata Cancer Center Hospital, Niigata 951-8566, Japan

Author contributions: All authors equally contributed to this paper with conception and design of the study, literature review and analysis, drafting and critical revision and editing, and final approval of the final version.

Supported by National Cancer Research and Development Fund, No. 26-A-4.

Conflict-of-interest statement: No potential conflicts of interest.

Manuscript source: Invited manuscript

Correspondence to: Yasumasa Takii, MD, Chief of Gastroenterological Surgery, Niigata Cancer Center Hospital, 15-3 Kawagishi-cho 2-chome, Chuo-ku, Niigata 951-8566, Japan. takii@niigata-cc.jp
Telephone: +81-25-2665111
Fax: +81-25-2333849

Received: March 27, 2016
Peer-review started: March 29, 2016
First decision: May 17, 2016
Revised: June 1, 2016
Accepted: June 27, 2016
Article in press: June 29, 2016
Published online: August 27, 2016

Abstract

Surgical resection is the only curative treatment modality for colorectal cancer limited locally. Evidence for the kind of resection procedure that is effective for improving prognosis is insufficient. Prognosis improvement is expected with the no-touch isolation technique (NTIT), making it the most important resection procedure. We are conducting a multicenter randomized controlled trial (RCT) to confirm the efficacy of NTIT in patients with colorectal cancer. The present review serves as a preface to our trial, as it focuses on basic and clinical studies that support the efficacy of NTIT. The detection ratios of circulating tumor cells (CTCs) of peripheral blood indicate the progress and prognosis of colorectal cancer. In a rabbit liver tumor model, metastases increased after surgical manipulation. Also, CTCs increased during the radical excision of colorectal cancer. However, NTIT decreased the detection of CTCs of intraoperative portal vein blood in patients with colorectal cancer. Although these aforementioned results support the use of NTIT, a previous controlled prospective trial was not able to confirm the clinical benefit of NTIT, as it had an insufficient sample size and many patients were lost to follow-up. Therefore, we initiated a large-scale high-quality RCT to confirm the efficacy of NTIT for colorectal cancer.

Key words: Colorectal cancer; General surgery; No-touch isolation technique; Circulating tumor cells; Randomized controlled trial

Core tip: Currently, we are conducting a multicenter randomized controlled trial to confirm the efficacy of the no-touch isolation technique (NTIT) in patients with colorectal cancer. A previous controlled prospective trial was not able to confirm the clinical benefit of NTIT, as it had an insufficient sample size and many patients were lost to follow-up. However, basic and clinical studies have supported the use of NTIT for treating colorectal cancer. The present review serves as a preface to our

trial, as it provides background information on whether the prognosis of colorectal cancer is improved by surgery.

Takii Y, Maruyama S, Nogami H. Can the prognosis of colorectal cancer be improved by surgery? *World J Gastrointest Surg* 2016; 8(8): 574-577 Available from: URL: http://www.wjgnet.com/1948-9366/full/v8/i8/574.htm DOI: http://dx.doi.org/10.4240/wjgs.v8.i8.574

INTRODUCTION

Surgical resection is the only curative treatment for colorectal cancer limited locally. The purpose of surgical resection of primary colon cancer is complete removal of the tumor, major vascular pedicles, and lymphatic system of the affected colonic segment[1]. Total mesorectal excision[2-5] and complete mesocolic excision (CME)[6] for colon and rectal cancers, respectively, reduce tumor recurrence after curative resection. Furthermore, Japanese D3 dissection is similar to CME[7]. However, evidence for the kind of resection procedure that is effective for improving prognosis is insufficient. The no-touch isolation technique (NTIT) is the most important resection procedure, because prognosis improvement is expected. NTIT was first proposed in the 1950s[8]. In this technique, central vascular ligation is the first priority, and it is followed by mobilization of the tumor-bearing segment of the colon. This technique aims to reduce cancer cells flowing from the primary tumor site into the liver and other organs by ligating the blood vessels first. A retrospective study showed improvement in prognosis with this technique[9], but a randomized controlled trial (RCT) failed to prove its efficacy with statistical significance[10]. Therefore, NTIT is not regarded as a standard technique in current guidelines[1]. Currently, we are conducting a multicenter RCT to confirm the efficacy of NTIT in patients with colorectal cancer undergoing open surgery[11]. In this trial, the conventional technique gives first priority to mobilization of the tumor-bearing segment of the colon, which is followed by central vascular ligation and ligation of other vasculature. Conversely, NTIT gives first priority to central vascular ligation, which is followed by mobilization of the tumor-bearing segment of the colon. This trial is designed to confirm the superiority of NTIT over the conventional technique in terms of disease-free survival. We hypothesize that the 3-year disease-free survival of the NTIT arm will be greater than that of the conventional technique arm (75%) by 6%. According to the method of Schoenfeld and Richter, the sample size will be 840 patients (420 patients per arm) with a one-sided alpha level of 5% and power of 80%, and 259 events are expected to occur within 3 years of accrual and 3 years of follow-up. Considering that some patients will be lost to follow-up, the total target sample size is set at 850 patients. We secured statistically sufficient cases in this RCT, and we described the quality control of the follow-up and the surgery in the protocol. The present review serves as a preface to our trial, as it focuses on basic and clinical studies that support the benefit of NTIT for colorectal cancer.

DISCUSSION

Does the detection ratio of circulating tumor cells of peripheral blood indicate the progress and prognosis of cancer?

Numerous articles have been published about the relationship between cancer-bearing patients and circulating tumor cells (CTCs), but two meta-analyses have generalized this point well.

In the first meta-analysis[12], five studies reported on the incidence of CTCs in lymph node involvement positive and negative groups, and three of those studies showed a statistically significant increase in the lymph node involvement positive groups compared with that in the lymph node involvement negative groups. A meta-analysis of all the studies showed a significantly higher incidence of CTCs in the lymph node involvement positive groups (50%) than in the lymph node involvement negative groups (21%). Five studies reported the rate of hepatic metastases at maximal follow-up in patients who were CTC positive and negative, and two of those studies demonstrated a statistically significant hepatic metastases rate in patients who were CTC positive compared with that in those who were CTC negative. A meta-analysis of all the studies indicated a significantly increased hepatic metastases rate of 21% in patients who were CTC positive compared with 8% in those who were CTC negative. Three studies reported the incidence of CTCs in different stages, and no study showed a significant difference between CTC positive and negative groups. A meta-analysis of all the studies showed a significantly lower incidence of CTCs in stage Ⅰ and Ⅱ groups (17%) than in stage Ⅲ groups (32%). When stage Ⅰ and stage Ⅱ tumors were compared, the incidence of CTCs was higher in stage Ⅱ (19%) than in stage Ⅰ (12%), but this was not statistically significant. Three studies reported disease-free survival with data extracted at 1-3 years. Disease-free survival was significantly higher in the CTC negative groups than in the CTC positive groups at 1 year, 2 years, and 3 years after resection.

In the second meta-analysis[13], 36 studies (3094 patients) were eligible for the final analyses. Pooled analyses showed that the detection of CTCs in the peripheral blood compartment was a statistically significant prognostic factor of recurrence-free survival [HR = 3.06 (95%CI: 1.74-5.38) and overall survival (OS) = 2.70 (1.74-5.38)].

Do metastases increase after surgical manipulation of the tumor?

Nishizaki *et al*[14] perform and experiment on liver tumors in a rabbit model and reported the results. In

this experiment, they inoculated carcinoma in a rabbit liver, and they separated the rabbits into two groups according to the presence or absence of manipulation before hepatectomy. Then they compared the number of tumors in the hepatic vein, number of metastases in the lung, and prognosis between the two groups. The incidence of vascular permeation of liver tumor cells into the hepatic vein was significantly higher in the manipulation group than in the non-manipulation group ($P < 0.01$). On the fourteenth day after tumor resection, the number of metastatic nodules in the lung was significantly increased in the manipulation group compared to that in the non-manipulation group ($P < 0.01$). The survival of rabbits after tumor resection was significantly shorter in the manipulation group than in the non-manipulation group ($P < 0.01$).

Do CTCs increase during the radical excision of colorectal cancer?

Weitz *et al*[15] used cytokeratin 20 reverse transcription polymerase chain reaction (RT-PCR) to detect CTCs in the peripheral vein preoperatively, intraoperatively, and postoperatively. Blood samples were taken from 65 patients who were undergoing resection of primary colorectal cancer. As the depth of tumor invasion deepened, the rate of detection of CTCs increased. Also, as the lymph node metastatic degree advanced, the rate of detection of CTCs increased. In addition, regarding the timing of the measurement, the rate of detection of CTCs was the highest intraoperatively. These data indicate that surgery enhances the release of CTCs into circulation.

Do CTCs increase during the resection of colorectal cancer liver metastasis?

Koch *et al*[16] also used cytokeratin 20 RT-PCR to detect CTC in the central vein preoperatively, intraoperatively, and postoperatively. Blood samples were taken from 37 patients who were undergoing resection of liver metastases. Concerning the timing of the measurement, the rate of detection of CTCs was highest intraoperatively. This was similar to the finding of colorectal cancer primary tumor surgery. When CTCs were detected during the resection of liver metastasis, the prognosis was poor.

Does NTIT decrease the detection of CTCs in intraoperative portal vein blood?

Hayashi *et al*[17] measured CTCs of portal vein blood using the mutant-allele-specific amplification method. They examined a ratio of CTCs of intraoperative portal vein blood by comparing the conventional technique and NTIT. For the conventional technique, CTCs were confirmed in 73% of cases, but for NTIT, CTCs were only confirmed in 14% of cases. As the use of NTIT reduces CTCs during surgical manipulation, they concluded that this technique may be effective for preventing metastases in those with colorectal cancer.

Was the clinical use of NTIT proven in the controlled prospective trial that compared NTIT and the conventional technique?

Wiggers *et al*[10] conducted a controlled prospective trial to assess the effect of NTIT on the treatment of colon cancers. This trial is the only RCT that has been published on this topic. Two hundred and thirty-six patients were prospectively and randomly assigned to undergo NTIT or the conventional technique. OS did not differ significantly between the two groups. This RCT failed to prove the efficacy of NTIT with statistical significance. After the results of this trial were published, NTIT was not regarded as a standard technique in current guidelines. However, there was a trend of good survival and disease-free survival in the NTIT group in the RCT. After a detailed review of the RCT, we concluded that the RCT could not show the superiority of NTIT because it had an insufficient sample size and many patients were lost to follow-up. Therefore, we initiated a large-scale RCT to confirm the efficacy of NTIT in patients with colorectal cancer[11]. Furthermore, we considered a collateral study to obtain basic proof for this clinical trial. We thought that significant data would be needed to confirm the presence or absence of CTCs in the portal vein blood or peripheral blood intraoperatively or postoperatively. However, we were unable to establish this accompaniment study because of cost.

CONCLUSION

Although the results of basic and clinical studies support the benefit of NTIT, a previous controlled prospective trial was not able to confirm the clinical efficacy of NTIT, but it had an insufficient sample size and many patients were lost to follow-up. Therefore, we are currently conducting a large-scale high-quality RCT to confirm the efficacy of NTIT in patients with colorectal cancer.

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P- Reviewer: Mayol J, Stamos MJ **S- Editor**: Qi Y **L- Editor**: A **E- Editor**: Wu HL

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