Primary Tumour Resection Could Improve the Survival of Unresectable Metastatic Colorectal Cancer Patients Receiving Bevacizumab-Containing Chemotherapy

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Key Words
Metastatic colorectal cancer • Primary tumour resection (PTR) • Bevacizumab • Chemotherapy

Abstract
Background: The effect of primary tumour resection (PTR) among metastatic colorectal cancer (mCRC) patients remains controversial. Combination chemotherapy with bevacizumab could improve the clinical outcomes of these patients, which might change the importance of PTR in the multi-disciplinary treatment pattern. Methods: We performed a non-randomized prospective controlled study of mCRC pts whose performance status (PS) scored ≤2 and who received bevacizumab combination chemotherapy (FOLFOX/XELOX/FOLFIRI) as a first-line therapy. These patients were classified into the PTR group and the IPT (intact primary tumour) group according to whether they underwent PTR before receiving the systemic therapy. The progression free survival (PFS) time and overall survival (OS) time, which were recorded from the start of the primary diagnosis until disease progression and death or last follow-up, were analysed. We also compared severe clinical events (such as emergency surgery, radiation therapy, and stent plantation) between the two groups. Results: One hundred and ninety-one mCRC pts (108 male patients and 93 female patients) were entered in this prospective observational study. The median age was 57.5 years old. The clinical characteristics (age, gender, performance status, primary tumour site, RAS status, and the number of metastatic organs) did not significantly differ between the two groups. The median PFS and OS times of the PTR group were superior than those of the IPT group (10.0 vs 7.8 months, p < 0.01 and 22.5 vs 17.8 months, p < 0.01, respectively). The incidences of adverse events associated with systemic therapy were similar between the two groups. Specifically, sixteen patients (21.9%, 16/73) with IPT developed significant primary tumour-related complications, such as bleeding, obstruction or even perforation. Among these patients, five underwent emergency surgery, three patients received a stent, and eight patients underwent radiation therapy. Conclusions: The mCRC patients who received PTR and bevacizumab combination chemotherapy had better clinical outcomes than patients who did not receive PTR. PTR also decreased the incidence of severe clinical events and improved quality of life.

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Introduction

Colorectal cancer is a common type of malignant tumour worldwide. Almost 20 – 25% of patients have stage IV disease at the time of diagnosis. An estimated 75 – 90% of these patients have unresectable metastases [1]. The median survival time of metastatic colorectal adenocarcinoma (mCRC) patients presenting with unresectable distant metastasis is approximately 5 months with best supportive care [2-3]. Since the development of anti-angiogenesis drugs, especially the vascular endothelial growth factor (VEGF) inhibitor bevacizumab and its combination with 5-fluorouracil, irinotecan or oxaliplatin [4], the median survival time of these patients has significantly improved to approximately 24 months [5-9]. Although chemotherapy containing bevacizumab has dramatically advanced the prognosis of these patients, the survival benefits of PTR in CRC patients with synchronous unresectable metastases remains controversial.

Traditionally, among colorectal cancer patients who have unresectable metastatic and an asymptomatic primary tumour, the aim of primary tumour resection (PTR) is to prevent primary tumour-related complications, such as intestinal obstructions, acute significant bleeding, and perforation [10]. However, the efficacy of initial primary tumour resection is uncertain. Recently, results from amount of studies and retrospective analyses have shown that the resection of the primary tumour provides some benefits to patients with unresectable colorectal metastases in terms of both the OS and PFS [11-12]. On the other hand, Poultsides George et al. [13] reported based on a prospective institutional database that most patients with synchronous mCRC who have receive up-front modern combination chemotherapy never require palliative surgery for their intact primary tumour. These data support a strategy consisting of systemic chemotherapy without routine prophylactic resection of primary lesion.

Therefore, we designed this prospective observational study to investigate the ability of PTR to improve the effects of systemic therapy in patients with synchronous unresectable metastases who received a regimen containing bevacizumab.

Materials and Methods

Patients

From October 2011 to November 2013, patients with metastatic colorectal cancer were treated at the Department of Medical Oncology of Zhongshan Hospital Fudan University. Patient survival was followed until March 31, 2015. One hundred and ninety-one patients had expected survive time with good physical status and exhibited fine treatment tolerance during the perioperative period, and 118 of these patients underwent primary tumour resection (PTR group), whereas 73 of these patients only underwent systemic chemotherapy combined with bevacizumab (IPT group) (Fig. 1, Table 1). All patients met the following criteria: 1) age ≤80 years old, 2) initially diagnosed and histologically confirmed as colorectal adenocarcinoma, 3) asymptomatic primary tumour with distant organ metastases, 4) measurable metastatic sites, 5) performance status scored ≤2, 6) life expectancy of more than 3 months, and 7) provided a signed consent form to receive chemotherapy and permit data collection. Patients were excluded if they had inflammatory bowel disease or a bowel obstruction prior to chemotherapy and were ruled out if their WBC ≤4×10^9/L, Hb ≤100 g/L, PLT ≤80×10^9/L or they had liver and kidney dysfunction. This study protocol was approved by the Institutional Ethics Board of Zhongshan Hospital at Fudan University, and informed consent was obtained from all patients.

Definition of severe clinical events

The following clinical events were defined: “Operation therapy-related complication rate” indicates that resection complications occurred within 30 days of the surgery. “Operation mortality” indicates that death occurred within 30 days of the surgery. The “primary tumour-related complication rate” describes the rates of haemorrhage, perforation, and obstruction caused by the primary lesion. The term “primary tumour-related mortality” indicates that death occurred within 30 days of primary tumour-related complications.
Chemotherapy Regimen

Bevacizumab was infused at a dosage of 5 mg/kg every 2 weeks or 7.5 mg/kg every 3 weeks, and oxaliplatin was infused intravenously at a dose of 85 mg/m². Alternatively, irinotecan was infused intravenously at a dose of 180 mg/m² on day 1, followed by Leucovorin, which was delivered at the dose of 400 mg/m² over 2 hrs. This treatment was then immediately followed by 5-FU at a dose of 2.4 g/m², which was continuously infused for 46 hrs. The regimen was administered every 2 weeks. Otherwise, the XELOX regimen (oxaliplatin 130 mg/m² + capecitabine 1000 mg/m² Bid for 14 days) was administered every 3 weeks. Treatment was stopped at any time in case of documented disease progression, unacceptable toxicity, or the patient’s refusal. The dosage was adjusted if patients developed grade 3/4 adverse effects. The FOLFOX, XELOX, and FOLFIRI regimens were administered to 34, 58, and 26 patients in the PTR group, respectively, and 20, 39, and 14 patients in the IPT group, respectively (Table 2).

Assessment measure

The patients were radiologically examined every six to eight weeks to assess treatment response according to clinical guidelines, such as the NCCN guideline, which recommend abdominopelvic computed tomography (CT) scans, liver magnetic resonance imagines (MRI), and chest X-rays. If chest X-rays indicated metastatic disease in the lungs, chest CT scans were performed to confirm the diagnosis. The assessments were performed immediately if clinical signs indicated disease progression. A complete CBC with differentials and chemistry profiles was performed prior to each cycle. Objective tumour responses were measured according to the RECIST 1.1 criterion [14], including complete response (CR), partial response...
(PR), stable disease (SD) and progressive disease (PD). During treatment, haematological toxicities and non-haematological toxicities were assessed according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) scale version 3.0 [14]. Progression free survival (PFS) time was calculated from the start of chemotherapy plus bevacizumab until disease progression and overall survival (OS) time was recorded at the start of treatment which was either chemotherapy or PTR, until the time of death or last follow-up.

Statistical methods

Descriptive statistics were computed using the SPSS11.5 software. Clinical characteristics were examined using the Chi squared test or Fisher’s exact probability test. Time-related parameters were evaluated using the Kaplan-Meier method and were compared by Log-rank test.

Results

One hundred and ninety-one mCRC patients (108 male and 93 female patients) were entered in this prospective observational study. The median age was 57.5 years old, and the clinical characteristics, such as age, gender, PS score, the primary tumour site, RAS gene status, and distant organ metastases, did not significantly differ between the two groups (Table 1). The median follow-up period was 20.0 months. Five patients were lost to follow-up because of a change in their telephone number or address. Forty-seven and seventy patients died of cancer in each group.

A Kaplan-Meier analysis of survival indicated that the median PFS times were 10 months and 7.8 months (p< 0.01) and that the OS times were 22.5 and 17.8 months (p< 0.01) (Fig. 2 and Fig. 3). Clinical outcomes, including therapeutic effects (Table 2), adverse events and complications, were analysed and compared between the two groups (Table 3). Six patients experienced operation-related complications including four cases of infection and two cases of leakage. The surgery-related complication rate was 5.1% (6/118). Sixteen patients in the non-resection group presented primary tumour-related complications, including six cases...
of haemorrhage, two cases of perforation and eight cases of incomplete obstruction. Five patients required emergency surgery, eight patients received pelvic radiotherapy, and three patients received a stent implant (Fig 1). The primary tumour complication rate was 21.9%.

**Discussion**

In general, the main objective of non-radical resection of the primary lesion for patients with unresectable metastatic colorectal cancer is to urgently treat or purposively prevent tumour-related complications, such as bleeding, obstruction and perforation. However, it remains uncertain that surgical resection of the primary tumour could improve quality of life and survival outcomes of asymptomatic mCRC patients.

Some retrospective studies [15-17] have suggested that PTR may also provide a survival benefit. Kim et al. [18] reported that mCRC patients who underwent PTR followed by chemotherapy had significantly longer survival times than patients who received chemotherapy as the first line of treatment, but only 13.9% and 17.5% mCRC patients received bevacizumab in the two cohorts in their study. Ghiringhelli et al. [19] concluded that the addition of bevacizumab to chemotherapy improved outcomes only in patients who had undergone primary tumour resection. However, other studies examining the benefit of PTR obtained conflicting results. A recent systematic review concluded that the resection of the primary tumour did not reduce complications and did not improve OS [20]. A prospective, multicentre phase II NSABP C-10 trial showed that combining mFOLFOX6 with bevacizumab did not result in unacceptable rates of obstruction, perforation, bleeding, or death related to IPT, and survival was not compromised [21].

In this prospective observational cohort study, we found that systemic therapy provided a survival benefit among these asymptomatic mCRC patients only after the local treatment of the primary tumour. That is to say, the anti-angiogenesis targeted drug (bevacizumab) combined with traditional cytotoxic chemotherapy drugs (fluorouracil, oxaliplatin and irinotecan) brought a higher response to metastases at distant organs (liver and lung) than the primary tumour lesion.

In terms of toxicity and perioperative morbidity and mortality, Ahmed et al. [22] reported that the surgical complication and mortality rates were 25.9% and 4.9%, respectively, among
stage IV colorectal cancer patients. The primary tumour-related complication rate was 29.7%, and the emergency colostomy rate was 27.6%. Similarly, Nitzkorski et al. [23] reported that the complication rate related to the primary lesion in 225 stage IV CRC patients receiving chemotherapy alone was 9.8%. Neither age, gender, tumour site, metastasis site, primary tumour site, nor chemotherapy regimen was a risk factor for complication. Seo et al. [24] suggested that the surgical excision of the primary tumour did not increase the rate of local complications in a population of asymptomatic mCRC patients with PS scores < 2. Tebbutt et al. [25] attributed intestinal obstructions among stage IV colorectal cancer patients mainly to peritoneal metastases other than the primary lesion and therefore resecting the primary tumour was safe. In our study, six patients experienced haemorrhages, eight patients experienced obstructions and two patients experienced perforations among patients who had received combination chemotherapy with bevacizumab in the intact primary tumour group. The complication rate was 21.9%. The surgery-related complication rate was 5.1%, and the mortality rate was 2.5% in the primary tumour resection group. We confirmed that the risk of morbidity and mortality from surgery was not higher in patients who underwent PTR after receiving systemic chemotherapy combined with bevacizumab. In addition, the adverse events that occurred in the two groups of patients receiving systemic therapy were similar, suggesting that adverse effects related to systemic chemotherapy combined with bevacizumab were acceptable. If bevacizumab was included in the regimen, an interval of at least 6 weeks between the last dose of bevacizumab and surgery was necessary, and another 6-8 weeks postoperative period was required before the re-initiation of bevacizumab. In patients undergoing PTR, issues regarding the timing of bevacizumab therapy, intestinal obstruction and primary tumour bleeding were less of a concern for the treating physicians. Ablation or combination with the resection of liver metastases could also be implemented as long as additional measurable metastatic lesions continued to responded well.

Significant efforts have already been made to identify biomarkers to predict the efficiency of anti-angiogenesis molecular targeted therapy which can be translated from the bench to clinical studies. Recently, some studies have focused on interventions by non-coding micro-RNAs. Zhang et al. [26] reported that Mir-140-5p targeted VEGFA to inhibit the progression of colorectal cancer and could be used as a predictive biomarker of VEGF inhibitor therapy. Unfortunately, none of molecular biomarkers has been explicitly identified or wildly accepted by physician. Consequently, Ghiringhelli et al. [19] assumed that PTR itself, other than a specific biomarker, was an independent predictive factor that influences the treatment response of bevacizumab. In fact, they postulated that patients who accept PTR may benefit from systemic chemotherapy. We hypothesized that given an effective response brought about by the systemic chemotherapy combined with VEGF inhibitor, aggressive local treatment as PTR (ie eliminating responsive cells medically and removing unresponsive tumour mass surgically) may further improve the survival outcomes of patients with unresectable mCRC. However, debates on the efficacy of PTR continue. At present, oncology practice guidelines [27] from the National Comprehensive Cancer Network recommend that patients with unresectable metastases undergo PTR only if the patients have an unequivocal imminent risk of obstruction or acute significant bleeding. Conversely, the results of recent clinical trials, such as FIRE-3 and CAALGB/SWOG 80405 [28, 29], showed that many patients had undergone surgical resection during the treatment period, and most of these patients underwent PTR before systemic chemotherapy. We hold that non-curative surgery can improve survival after systemic chemotherapy, which may be due to the ability of PTR to reduce the tumour burden, reverse the systemic inflammatory response induced by the primary tumour and relieve tumour-related symptoms [30].

At the moment, most clinical guidelines recommend against the resection of the primary tumour for patients with asymptomatic mCRC. In fact, ethically initiating a prospective randomized controlled clinical trial to examine the benefit of PTR for these patients is difficult. In China, colorectal cancer patients diagnosed with unresectable stage IV CRC often request non-radical surgery to remove the primary lesion despite being asymptomatic, which is why we are proposing to launch a prospective observational cohort study.
In the new era of molecular targeted therapy for mCRC, PTR appears to improve the outcomes for selected patients with unresectable mCRC. Thus, the timing for local treatment, such as PTR, urgently needs to be re-evaluated. We believe that continued advances in modern drug therapy and the appropriate utilization of sequential local treatments, including PTR, will further improve patient survival.

Disclosure Statement

The authors have no conflict of interest

Reference


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