

The combination of systemic chemotherapy and local treatment may improve the survival of patients with unresectable metastatic colorectal cancer

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Received January 17, 2017; Accepted March 8, 2017

DOI: 10.3892/mco.2017.1247

Abstract. With the development of systemic chemotherapy, the survival time of patients with advanced colorectal cancer (CRC) has increased. In addition, local treatments, such as microwave ablation and radioactive seed implantation, have been shown to be effective. However, the number of studies reporting on the effect of systemic chemotherapy combined with local treatments is limited. The present study was conducted to determine the effect of local treatment combined with systemic chemotherapy in patients with initial unresectable metastatic CRC (mCRC). Clinicopathological and follow-up data from 273 patients with initial unresectable mCRC between April, 2007 and October, 2013 were retrospectively analyzed. A total of 51 patients received minimally invasive treatments combined with systemic chemotherapy and 39 patients achieved tumor-free survival (TFS). The median TFS time was 9 months (range, 2-45 months); the median overall survival (OS) time was 40 months (range, 12-108 months). In patients who did not achieve TFS, the OS was 37 months. Thus, patients who achieved TFS exhibited a significantly longer OS compared with those who did not achieve TFS ($P=0.049$). The results of the univariate analysis demonstrated that certain characteristics, such as the number of lesions and maximum tumor diameter, were associated with the achievement of TFS. The patients assessed herein achieved TFS in response to local treatments combined with systemic chemotherapy. Furthermore, the achieved TFS provided an OS benefit.

Introduction

Recent improvements in living standards, changes in dietary habits and ingredients and the increase in the aging population have been associated with increases in the incidence and mortality of colorectal cancer (CRC). Indeed, distant metastases

may be detected in a proportion of newly diagnosed patients, and recurrent or distant metastases have been observed despite radical surgery or postoperative adjuvant therapy. The overall survival (OS) of patients with metastatic CRC (mCRC) is improved by resection of the metastases, with 5-year survival rates of up to 50% following surgery (1), whereas the survival rates remain low (<5%) among patients with unresectable mCRC (2). However, the majority of mCRC patients are considered to be unresectable at diagnosis (3). Although previous studies have demonstrated that preoperative chemotherapy, or chemotherapy combined with targeted agents, may convert initially unresectable CRC metastases to resectable (3,4), certain patients remain unresectable due to extensive extrahepatic disease or insufficient remaining liver parenchyma or multi-organ metastases.

For unresectable mCRC patients, a combination of chemotherapy and a molecular-targeted agent, either antiangiogenic (i.e., bevacizumab) or a monoclonal antibody epidermal growth factor receptor inhibitor (e.g., cetuximab and panitumumab), is currently considered to be the standard therapy. The CALGB 80405 trial enrolled >1,100 wild-type KRAS cases who were randomly assigned to group chemotherapy (either FOLFOX or FOLFIRI) plus either cetuximab or bevacizumab. In the all-RAS wild-type population, the median progression-free survival (PFS) was ~11 months in both arms [hazard ratio (HR)=1.1; $P=0.31$], with a median OS of 31-32 months (HR=0.9; $P=0.40$) (5), which represented a significant improvement. However, in China, these targeted drugs are not included in the health insurance directory, and a proportion of the patients harbor mutations in the RAS or BRAF genes, affecting the application and efficacy of these treatments, as the OS was only 16-22 months for either FOLFOX or FOLFIRI without combination with a molecular-targeted agent (6). Consequently, the rational use of limited resources and the appropriate combination of different treatment modalities to reduce treatment cost, improve the quality of life and prolong survival, is a major focus among Chinese oncologists. Recent oncology studies have reported satisfactory results with local therapy, such as microwave ablation, radioactive seed implantation and intensity-modulated conformal radiotherapy. However, only a limited number of studies have addressed the optimal administration of systemic chemotherapy combined with these local treatments.

The aim of the present retrospective study was to investigate the strategy of the combination of systemic chemotherapy

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Key words: unresectable metastatic colorectal cancer, systemic chemotherapy, local treatment, tumor-free survival, overall survival

with local treatments to improve the OS of patients with initial unresectable mCRC without using molecular-targeted agents.

Patients and methods

Patient selection. Between April, 2007 and October, 2013, 273 consecutive patients with biopsy-proven stage IV CRC were treated at the Third Affiliated Hospital of Soochow University (Changzhou, China). Patients who only received systemic chemotherapy or local treatments, or received molecular-targeted agents, were excluded. Patients who exhibited progressive disease (PD) as defined by the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) (7) after two cycles of chemotherapy were also excluded. Finally, 51 patients who received systemic chemotherapy and local treatment were retrospectively analyzed. The patients were aged 35-75 years, had a World Health Organization performance status of ≤ 2 , and were no longer considered candidates for surgery. The characteristics of the patients are summarized in Table I.

This retrospective study was conducted in accordance with the Declaration of Helsinki including all amendments, and was approved by the Independent Research Ethics Committee of the Third Affiliated Hospital of Soochow University. Written informed consent was obtained from all the patients prior to treatment.

Overall treatment principal. Systemic chemotherapy was applied as the initial treatment. For patients with several (>3) or larger (>5 cm) liver metastases, continuous infusion of floxuridine (FUDR) into the hepatic artery was added. Two or three cycles after the initial chemotherapy, the results of the enhanced spiral-computed tomography (CT) were reviewed. If the disease was controlled and the primary tumor was resectable, surgical removal of the primary tumor was recommended. If the metastatic tumors were reduced to a size of <5 cm, microwave or radiofrequency ablation were first considered. If the metastases were not suitable for ablation, radioactive seed implantation was recommended. In general, external radiation therapy was administered for pelvic, bone and brain metastases. Once the patients achieved tumor-free survival (TFS), an additional four or six cycles of the original chemotherapy regimen were administered to solidify the effect. Follow-up, including a CT scan and assessment of tumor marker levels, was performed every 2-3 months up to the time of progression. If the patients did not achieve TFS, systemic chemotherapy was administered.

Systemic chemotherapy. A total of 40 patients received an intravenous infusion of 5-fluorouracil (5-FU) and leucovorin with oxaliplatin (FOLFOX) as first-line treatment, 8 patients received capecitabine with oxaliplatin (XELOX), 2 patients received irinotecan with capecitabine (XELIRI), and 1 patient received an intravenous infusion of 5-FU and leucovorin with irinotecan (FOLFIRI). The FOLFOX regimen included i.v. leucovorin calcium at a dose of 200 mg/m², bolus 5-FU at a dose of 400 mg/m² and continuous i.v. 5-FU at a dose of 600 mg/m² on day 1, followed by 85 mg/m² oxaliplatin on day 2. The cycle was repeated every 2 weeks. XELOX consisted of a 2-h intravenous infusion of oxaliplatin 130 mg/m² on day 1 plus oral administration of capecitabine 1,000 mg/m² twice daily for 14 days and was repeated every 21 days. XELIRI consisted

of a 2-h intravenous infusion of irinotecan 180 mg/m² on day 1 plus oral administration of capecitabine 1,000 mg/m² twice daily for 14 days, and was repeated every 21 days. FOLFIRI included i.v. leucovorin calcium at a dose of 200 mg/m², bolus 5-FU at a dose of 400 mg/m² and continuous i.v. 5-FU at a dose of 600 mg/m² on day 1, followed by 180 mg/m² irinotecan on day 2, and was repeated every 2 weeks. A total of 29 patients received FOLFIRI as a second-line regimen, 3 patients received FOLFOX, 3 patients did not undergo second-line chemotherapy as they succumbed to the disease, and second-line chemotherapy was not administered to 16 patients as they did not exhibit disease progression after first-line chemotherapy and local treatments at the last follow-up visit.

Local treatment. A total of 17 patients with unresectable liver metastases underwent implantation using a hepatic artery kit and received hepatic arterial infusion (HAI) therapy. FUDR was delivered via a 14-day infusion at 0.15 mg/kg/day, and dexamethasone (DXM) was delivered at 1 mg/m²/day using a pump with FUDR heparin and saline. A total of 38 patients received microwave ablation focused on the liver 49 times, the lung 15 times, and the spleen once, if the metastases were sized <5 cm. A total of 29 patients received radioactive ¹²⁵I seed implantation, in which the liver was targeted 14 times, the lung 20 times, the pelvis 9 times, the adrenal glands 4 times, the retroperitoneal lymph nodes once and the abdomen once, when the metastases were not suitable for microwave ablation. A total of 12 patients received external radiation therapy focused on the pelvis 7 times, the bone 4 times, the brain 3 times and the adrenal glands once. The required instruments, materials and the protocols for local treatments were as described in our previous articles (8-11).

Clinical evaluation and follow-up. According to RECIST 1.1, the response to chemotherapy was classified as complete remission (CR), partial remission (PR), progressive disease (PD), or stable disease (SD). Two or three cycles after the initial chemotherapy, enhanced spiral CT results were reviewed, followed by CT review every three cycles. The final follow-up was conducted on April 1, 2016. Dose adjustments were performed in the event of toxicity and assessed according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 3.0 (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae3.pdf). TFS was defined as the time from non-detection of tumors on CT after the treatments, until the first discovery of local tumor recurrence or distant metastasis, or until the date of the last follow-up. Overall survival (OS) was defined as the time from the diagnosis of unresectable mCRC to the date of death due to any cause or the date of the last follow-up.

Statistical analysis. The survival rates were estimated using the life table method. The survival analysis was performed by applying the log-rank test. The associations of different potential predictive factors with TFS were assessed using the Fisher's exact test for categorical variables or the Wilcoxon rank-sum test for continuous variables. The statistical analysis was performed using SPSS software, version 18.0 (SPSS, Inc., Chicago, IL, USA).

Table I. Patient characteristics (n=51).

Characteristics	n	(%)
Gender		
Male	40	(78.4)
Female	11	(21.6)
Median age, years (range)	62 (35-75)	
Location of primary cancer		
Rectum	21	(41.2)
Colon	30	(59.8)
Resection of primary cancer		
Yes	42	(82.4)
No	9	(17.6)
Location of metastasis		
Liver ^a	14	(27.5)
Lungs	7	(13.7)
>3 locations	30	(58.8)
Line of chemotherapy		
First-line	48	(94.1)
Second- and further line	3	(5.9)

^aThe liver or lung metastases were not resectable.

Results

Remission rates and survival time. According to RECIST 1.1, among the 51 patients who were evaluated, after two or three cycles of initial chemotherapy, 0 patients achieved CR, 36 achieved PR (70.6%) and 15 achieved SD (29.4%), with an objective response rate of 100%. Of the 9 patients with newly diagnosed and unresectable primary tumors, 8 underwent primary tumor resection after treatment, and the resection rate was 88.9%. At the last follow-up, 34 of the 51 patients had succumbed to the disease and 17 remained alive. The median OS was 40 months (range, 12-108 months). With the combination of minimally invasive treatments with systemic chemotherapy, 39 patients obtained TFS. Among those 39 patients, the TFS was 2-45 months, and the median TFS was 9 months. The median OS of patients who achieved and those who did not achieve TFS was 40 and 37 months, respectively. The patients who obtained TFS had a significantly better OS compared with those who did not ($P=0.049$, Fig. 1). The results of the univariate analysis demonstrated that certain characteristics, such as the number of lesions and maximum tumor diameter, were associated with the achievement of TFS (Table II).

Chemotherapy-related toxicity. Grade 3-4 myelosuppression occurred in 32 patients (63.2%), mainly manifesting as neutropenia. Grade 1-2 liver toxicity developed in 37 patients (72.4%), grade 1-2 neurotoxicity occurred in 10 patients (19.7%), whereas no allergic reactions were observed as a consequence of oxaliplatin. Grade 1-2 nausea or vomiting was documented in 27 patients (53.9%). Of the 17 patients who underwent a procedure with a hepatic artery kit with continuous FUDR perfusion, 7 (41.2%) experienced grade 3-4 diarrhea, 15 (88.2%)

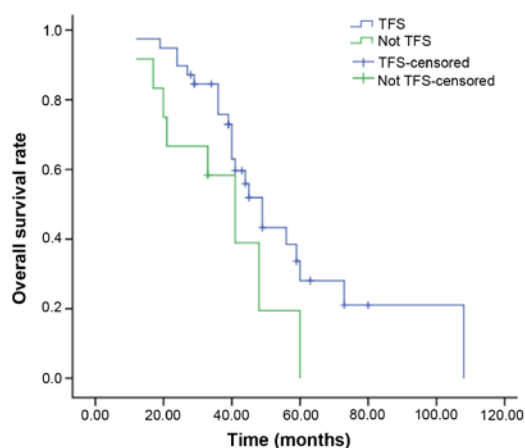


Figure 1. Overall survival of the patients who achieved and those who did not achieve TFS after systemic chemotherapy and local treatments. TFS, tumor-free survival.

had grade 1-2 abdominal pain and 2 (11.8%) experienced a local infection and required debridement. All the side effects were restored following drug withdrawal and symptomatic treatment, and no deaths were reported (Table III).

Severe local treatment-related complications were not observed in any of the patients. Common complications included puncture pain, vomiting, fever, bone marrow suppression, transient liver damage and pneumothorax, all of which responded to symptomatic treatment.

Improvement of clinical symptoms. Among the 15 patients experiencing pain, 11 achieved symptom relief; the remission rate was 73.3%. Chest tightness and shortness of breath were improved in 3 patients with lung metastases; the remission rate was 100%. Of the 51 patients, 18 (35.3%) experienced weight gain.

Discussion

CRC is the third most common malignant tumor worldwide and has the second highest mortality among malignant tumors (12). Metastasis occurs in ~30% patients after the initial diagnosis. Systemic chemotherapy is the principal therapeutic modality in patients with unresectable mCRC. In recent years, palliative chemotherapy for unresectable mCRC has progressed considerably, particularly with the application of irinotecan and oxaliplatin, resulting in an increase in the median survival time from 16 to 22 months (6). In addition, the application of targeted drugs has further improved patient survival (13). However, targeted drugs are still not widely used in China, and RAS or BRAF mutations in patients limit the application and efficacy of molecular-targeted treatments. Thus, there is a need for better understanding the variety of available treatment modalities in order to improve survival and quality of life without significantly increasing the total treatment cost. However, strategies to achieve such goals remain underinvestigated.

Local treatments, such as microwave ablation and radioactive seed implantation, have been shown to be effective (14,15).

In the present study, for patients with several (>3) or larger (>5 cm) liver metastases, continuous infusion of FUDR into the

Table II. Univariate analysis of the predictors of TFS.

Characteristics	TFS (n=39)	No TFS (n=12)	P-value
Gender			0.262
Male	32	8	
Female	7	4	
Site of primary cancer			0.739
Colon	22	8	
Rectum	17	4	
Location of metastasis			0.134
Liver	13	1	
Lungs	6	1	
>3 locations	20	10	
Number of lesions			0.002
≤5	28	2	
>5	11	10	
Maximum diameter of the tumor, cm			0.001
≤5	33	5	
>5	6	7	
Age, years			0.820
Median	63	60	
Range	42-75	35-78	

TFS, tumor-free survival.

Table III. Frequency of chemotherapy-related toxicities.

Toxicities	n	(%)
Myelosuppression	32	(63.2)
Liver damage	37	(72.4)
Neuropathy	10	(19.7)
Diarrhea	7	(41.2)
Allergy	0	(0.0)
Anorexia/nausea	27	(53.9)
Fatigue	6	(11.8)
Hand-foot syndrome	2	(3.9)
Other	2	(3.9)
Any grade ≥3	9	(17.6)

hepatic artery was added. When doxifluridine was infused into the hepatic artery, the drug uptake rate by the liver was 95%, and the drug concentration in the tumors was 16 times higher compared with that assessed using conventional intravenous chemotherapy (16). Continuous infusion using a hepatic arterial kit may be effective in maintaining drug concentrations and extending the delivery time, thereby increasing the drug sensitivity. Shi *et al* (11) reported that CRC patients with liver metastasis who were treated with HAI FUDR and systemic XELOX experienced a high resection rate for asymptomatic

CRC with unresectable liver metastases, as well as a low rate of complications associated with unresectable primary cancer.

Metastasis resection may significantly improve the prognosis of patients with mCRC; however, certain challenges remain for patients with unresectable metastasis but no symptoms from the primary lesions. Controversial retrospective studies have been conducted to determine whether it is appropriate to resect the primary tumor in patients with mCRC (17). In the present study, if the disease was controlled and the primary tumor was considered to be resectable, it was recommended that patients undergo resection of the primary tumor. Systemic chemotherapy combined with resection of the primary tumor provided a proportion of the patients in this group with TFS and improved their quality of life. Thus, it is crucial for clinicians to identify the appropriate opportunities for this treatment.

Following systemic chemotherapy, the metastatic tumors regressed in a proportion of the patients. A number of clinical studies (18,19) support the use of capecitabine as maintenance therapy, as it has been shown to prolong PFS, but provides no OS benefit. It is recommended that such patients receive a local, minimally invasive treatment to achieve TFS. Some residual cancer cells may persist after complete radiographic remission. After a few cycles of chemotherapy, these remaining tumor cells may become resistant to chemotherapeutic drugs; they may not only become resistant to the same type of drug, but may also develop cross-resistance to other, previously unused drugs. Thus, the effect may not be optimal, even in the presence of other chemotherapeutic drugs. In addition, several cycles of chemotherapy may impair the immune system of the patient and result in unendurable toxic adverse effects. These phenomena all promote tumor progression and, in such cases, chemotherapy was terminated and other methods were used to achieve TFS, such as microwave or radiofrequency ablation, radioactive seed implantation, or intensity-modulated conformal radiotherapy, depending on the locations of the metastases in each patient. Petre *et al* (20) used radiofrequency ablation to treat 45 patients with 69 lung metastases resulting from CRC. The 3-year local control rate was 89%, and the 1-, 2- and 3-year OS rates were 95, 72 and 50%, respectively. Zhou *et al* (21) reported that microwave treatment may also enhance local and systemic immune function. Wang *et al* (22) reported a local control rate of 87% using CT-guided ¹²⁵I seed implantation to treat recurrent colorectal cancer, with 1- and 2-year survival rates of 93 and 50%, respectively. In the present study, 29 patients underwent radioactive ¹²⁵I seed implantation, including 14 times in the liver, 20 times in the lung, 9 times in the pelvis, 4 times in the adrenal glands, once in the retroperitoneal lymph nodes and once in the abdominal wall. Compared with other treatment methods, radioactive ¹²⁵I seed implantation was simple, had a reduced impact on the surrounding normal tissue, was reliable and resulted in fewer complications, particularly in patients with local recurrence or metastases in the adrenal glands, retroperitoneal lymph nodes and abdominal wall. Furthermore, this approach effectively controlled local recurrence and tumor growth and improved patient survival. Of note, the successful implementation of this technique depends on the experience of the surgeon. Our sample included a 75-year-old male patient with lung metastasis after ascending colon resection. The lung metastasis was isolated, but due to the poor cardiopulmonary function of the patient, surgical

resection was not possible. The patient received initial systemic chemotherapy and radioactive ¹²⁵I seed implantation, and there were no new metastases after >3 years of follow-up. The patient experienced a significant improvement in his quality of life and prolonged survival. In the present study, certain characteristics, such as the number of lesions and the maximum diameter of the tumor, were associated with patients who achieved TFS. However, if local treatment was successfully performed, its effects were also associated with those characteristics.

The OPTIMOXI study (23) demonstrated that six cycles of oxaliplatin using a simplified LV5-FU solution to maintain the chemotherapeutic effect exerted the same effect on the response rate, PFS and OS, compared with continuous use of oxaliplatin until the patients could no longer tolerate the side effects or experienced disease progression; furthermore, with this treatment, patients were able to avoid grade 3-4 toxicities after six cycles. In centers in which >50% of the patients received a second treatment with the FOLFOX7 program, the OS was >25 months. These results indicate that intense chemotherapy after maintenance therapy may prolong the survival of patients. We also observed that oxaliplatin was effective after a period of inactivity. In the present study, the majority of the patients tolerated FOLFOX or XELOX and FOLFIRI as first-line and second-line chemotherapy, respectively. When the patients achieved TFS, the chemotherapeutic regimen was suspended until the tumors relapsed. Thus, the majority of the patients tolerated the applied treatments, including oxaliplatin as third-line therapy, which was effective in some patients and may prolong OS.

In summary, the results of the present study indicate that, in patients with unresectable mCRC who are not suitable to receive molecular-targeted agents, particularly patients with <5 metastatic lesions or a maximum tumor diameter of <5 cm, systemic chemotherapy may be administered combined with local treatment to achieve TFS, and the TFS benefits are subsequently converted to a prolongation of OS. To the best of our knowledge, this strategy has not been previously reported. However, this was a retrospective study, and the analyzed cohort was small. Additionally, there were some indications for minimally invasive treatments, resulting in a selection bias. Thus, future prospective randomized studies are required to confirm our results. The use of drugs such as capecitabine as maintenance therapy or combined with molecular-targeted agents to prolong TFS and OS should also be assessed in future investigations.

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