Original Article
Initial hepatic artery infusion and systemic chemotherapy for asymptomatic colorectal cancer with un-resectable liver metastasis

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Abstract: Purpose: Hepatic arterial infusion (HAI) has been proved to be an effective strategy to increase the chances of resection for colorectal cancer patients with liver metastasis (CRCLM). Herein, we aimed to evaluate the benefits and risks of initial treatment with HAI floxuridine (FUDR) and systemic XELOX in un-resectable synchronous CRCLM. Materials and methods: HAI catheter systems were implanted radiologically in 54 patients with un-resectable synchronous CRCLM. Upfront HAI FUDR and systemic XELOX were delivered without primary cancer resection. Patients underwent deferred surgery when the metastatic diseases were converted to resectability, or any serious colorectal cancer-related complications occurred. Results: Thirty-eight patients (70.4%) were converted to resectability and underwent staged or synchronous resection of the primary tumor and metastatic disease, with an estimated 3-year survival rate of 76% compared with 15% in un-resected patients. Uni-variate analysis showed that hepatic involvement, number of lesion, and the location of primary cancer did not affect resectability rate. Only 3 patients (5.6%) required palliative surgery to treat complications related to primary cancer. Conclusions: Initial HAI FUDR and systemic XELOX are effective to help patients with CRCLM to obtain a high resection rate for asymptomatic colorectal cancer and un-resectable liver metastases, and associated with a low rate of complications related to the intact primary cancer.

Keywords: Colorectal cancer, synchronous liver metastases, hepatic artery infusion, surgery, chemotherapy

Introduction

About 85% of colorectal cancer patients at stage IV with liver metastases were considered as un-resectable [1, 2]. In the absence of symptoms, the resection of primary tumor in these patients is of uncertain benefit [3]. Recent therapeutic advances recommend initiation of systemic chemotherapy (SCT) as standard of care for these patients without overt obstruction or hemorrhage [3]. In addition to systemic effects on the metastases, the treatment may also inhibit further growth of the primary tumor. Above 90% of patients never require surgery to palliate primary tumor-related complications after initiation of SCT [3, 4]. Furthermore, 13% to 42.9% of patients were converted from un-resectable to a resectable state [4-6]. Although survival time following chemotherapy and sur-

gery in patients with un-resectable disease are lower than those in initially resectable patients, complete resection of the metastases and primary cancer is still the only hope for cure [5]. Therefore, the treatment strategy for patients with un-resectable colorectal cancer liver metastases (CRCLM) should be directed toward resection [2].

Studies have shown that hepatic arterial infusion (HAI) therapy is effective in improving resection rate in patients with un-resectable CRCLM [7-11]. Even patients with extensive hepatic involvement, whether previously treated or untreated with chemotherapy, may become resectable after the combination of HAI and SCT. However, few studies evaluated HAI strategy exclusively in patients with synchronous liver metastases. For those patients, a

decision has to be made on whether the primary tumor has to be resected initially, or chemotherapy can be started with the primary tumor *in situ*. In most previous studies, all patients underwent preemptive resection of primary tumor and were implanted with the HAI catheter system concurrently in case of synchronous CRCLM. In the past, this approach had a strong rationale: (i) initial resection of primary tumor is necessary to prevent the need of urgent procedure because of primary tumor-related complications; (ii) traditional implantation of HAI catheter systems requires laparotomy and extensive dissection to expose gastro-duodenal artery. However, this is a complex surgical procedure associated with potential morbidity, and it can delay or precludes the planned chemotherapy. Currently, due to advances in modern chemotherapy, the initial resection of primary tumor is no longer mandatory in the absence of symptoms. Meanwhile, important progresses have been accomplished on interventional radiology, which permits the safe percutaneous placement of an indwelling catheter in the hepatic artery with a subcutaneously implanted port [12]. Patency rates are on par with surgically implanted systems [13, 14]. Therefore, using innovative catheter placement techniques, upfront HAI therapy combined with modern SCT may be feasible in synchronous CRCLM with primary tumor *in situ*. In the present study, we aimed to evaluate the benefits and risks of initial treatment with HAI FUDR and systemic XELOX in this setting.

Patients and methods

Patient selection

Between June 2007 and December 2012, we treated 223 consecutive patients with biopsy-proven stage IV colorectal cancer in the Third Affiliated Hospital of Soochow University. Fifty-four patients with extensive liver metastases received upfront HAI FUDR and systemic XELOX concurrently without resection of the primary cancer. All of these patients had no or minimal symptoms due to colorectal cancer. Patients who had detectable extra hepatic disease, or underwent initial resection of primary cancer were excluded from the study. The clinical data including gender, age, location of primary tumor, number of metastatic sites, volume of liver disease, baseline level of relevant laboratory values, adverse events related to treatment, timing of primary tumor and/or liver resection, and survival in months from time of

catheter implantation, were collected from a prospective database. The treatment protocol was determined by the multi-disciplinary treatment (MDT) team at the hospital, which was composed of a medical oncologist, radiologist, surgeon, and intervention specialist. All the patients provided informed consent, which was approved by the Ethics Committee of the Third Affiliated Hospital of Soochow University.

Liver metastases were considered technically un-resectable if disease involved all hepatic segments, all three main hepatic veins or both inflow pedicles, or if resection would leave behind an inadequate liver remnant. Bilobar disease or number of metastases did not exclude a patient from consideration for resection, if sufficient liver remained to allow normal hepatic function. All cases were reviewed for resectability at a multi-disciplinary conference.

Implantation of HAI catheter system

All patients underwent computed tomography angiography to examine the hepatic artery anatomy for indications of HAI therapy. The operation of pump implant was performed at a standard digital subtraction angiography (DSA) operation room. After local injection of anesthetic, the Seldinger technique was used to gain access to the right femoral artery. Arteriography of the celiac trunk and superior mesenteric artery was performed respectively to reveal the hepatic arterial anatomy. In patients with multiple hepatic arteries, all the hepatic arteries except the largest one were embolized to redistribute the hepatic arterial flow to enable the use of a single indwelling catheter to infuse chemotherapeutic agents to the entire liver [15]. The gastro-duodenal artery, right gastric artery, and, if necessary, left gastric artery or dorsal pancreatic artery were embolized using metallic coils (Tornade, Cook, Bloomington, IL, USA) in order to prevent extra hepatic drug distribution and gastro-duodenal injury caused by the chemotherapeutic agents. To avoid dislodgment of the catheter tip and hepatic arterial occlusion, the infusion catheter (Celsite, B. Braun, Chasseneuil, France) with side-hole was fixed into the gastro-duodenal artery with metallic coils (n=45) or inserted into the peripheral branch of the hepatic artery (n=9), as described in previous report by Tanaka *et al.* [13]. The position of the side hole was sited at the common hepatic artery to ensure that the chemotherapeutic agents infuse the entire liver from the side-hole. The proximal end

Table 1. Baseline of characteristics (n=54)

Characteristics	n (%)
Age (years)	
Median	62
Range	32-78
Gender	
Male	29 (54.8)
Female	25 (45.2)
ECOG score	
0	21 (38.9)
1	24 (44.4)
2	9 (16.7)
Site of primary cancer	
Right colon	13 (24.1)
Left/sigmoid colon	19 (35.2)
Rectum	22 (40.7)
Hepatic involvement	
<25%	10 (18.5)
25%-50%	17 (31.5)
>50%	27 (50.0)
Lobulor involvement	
Bilobar	38 (70.4)
Unilobar	16 (29.6)
Number of lesion	
≤5	8 (14.8)
6-10	18 (33.3)
≥11	28 (51.9)
Baseline of CEA	
≤200 ng/ml	29 (53.7)
>200 ng/ml	25 (46.3)
Baseline of LDH	
Normal	16 (29.6)
Abnormal	38 (70.4)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; CEA, carcinoembryonic antigen; LDH, lactate dehydrogenase.

of the catheter was connected to the injection port and the device was implanted in a subcutaneous pocket in the right inner thigh. After the administration of chemotherapeutic agents, the implanted port and indwelling catheter system were flushed and filled with 2 mL of heparin solution (1000 IU/mL).

HAI therapy, systemic chemotherapy and surgery

All patients received a 3-week cycle of SCT (XELOX) and HAI FUDR the next day after catheter implantation. The HAI therapy was initiated on day 1 and 21: FUDR was delivered in a 14-day infusion at 0.15 mg/kg/day, and dexamethasone (DXM) was delivered at 1 mg/m^2/day in the pump with floxuridine heparin and saline. XELOX consisted of a 2-hour intravenous infusion of oxaliplatin 130 mg/m^2 on day 1 plus oral administration of capecitabine 1000 mg/m^2 twice daily for 14 days. Dose adjustment was made in the event of toxicity, assessed according to National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0. The HAI therapy was stopped if serious technical catheter-related problems, hepatic progression of disease or excessive toxicity occurred. Response to chemotherapy was assessed by spiral-CT scan according to the RECIST criteria [16]. Epigastric pain prompted workup with an upper gastrointestinal endoscopy. If an ulcer or gastro-duodenitis was documented, HAI therapy was held for 1 month to allow healing and the dosage of FUDR and DXM was reduced by 50% in subsequent therapies.

Resection of the primary colorectal cancer was indicated if obstruction or significant bleeding occurred. Synchronous or staged resection of colorectal and metastatic cancer was carried out when metastases were converted to resectable disease, evaluated by the MDT team. Radiofrequency ablation (RFA) might be recommended if the size of metastatic node was less than 2 cm in diameter. Chemotherapy was stopped at least 3 weeks prior to the elective surgery.

Statistical analyses

The main endpoint of the study was resection rate. Overall survival (OS) was defined as the time from the date of catheter implantation to the date of death or the date of the last follow-up. The 3-year survival rates were estimated by using the Life Table method. The survival analysis was performed by using the log-rank test. Associations of the different potential predictive factors with resectability were assessed by using the Fisher's exact test for categorical variables, or by using the exact Wilcoxon rank sum test for continuous variables.

Results

Fifty-four patients (29 males and 25 females) with asymptomatic colorectal cancer and unresectable synchronous liver-only metastases
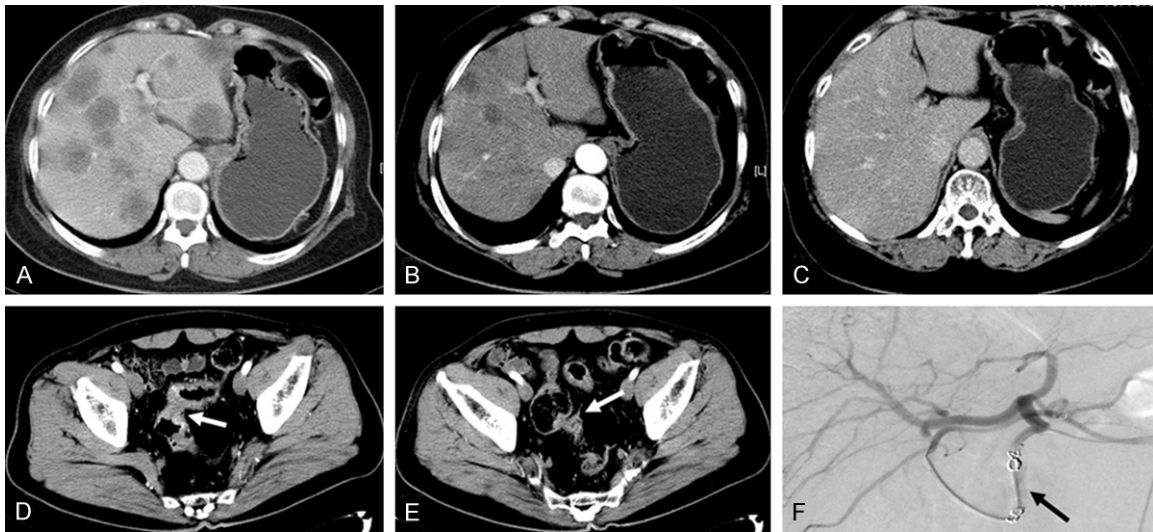
Figure 1. A typical patient's CT imaging and angiography through infusion catheter. A. CT image shows extensive liver metastases at baseline; B. Liver metastases are shrinking after 2 cycles of treatment; C. Liver metastases are complete response after 4 cycles of treatment; D. Sigmoid cancer (white arrow) at baseline; E. Sigmoid cancer is partial response after 4 cycles of treatment; F. Angiography shows the infusion catheter with side-hole is fixed into the gastroduodenal artery with metallic coils (black arrow). This patients had no tumor found in liver during the surgery and received enterectomy alone. No recurrence occurs by the end of follow-up (3 years after surgery).

Table 2. Univariate analysis of predictors for resectability

Characteristics	Resected (n=38)	Unresected (n=16)	P
Gender			0.770
Male	19	10	
Female	18	7	
Site of primary cancer			0.145
Colon	20	12	
Rectum	18	4	
Hepatic involvement			0.372
≤50%	21	6	
>50%	17	10	
Number of lesion			0.379
≤10	20	6	
>11	18	10	
Lobulor involvement			0.338
Bilobar	25	13	
Unilobar	13	3	
Baseline of CEA			0.384
≤200 ng/ml	22	7	
>200 ng/ml	16	9	
Age (year)			0.820
Median	63	60	
Range	42-78	32-78	
Baseline of LDH (U/L)			0.095
Median	272	316	
Range	104-1077	164-2047	

Abbreviations: CEA, carcinoembryonic antigen; LDH, lactate dehydrogenase.

were included in the study. All the patients had high-risk liver metastases and were not selected for upfront resection. Patient characteristics are summarized in **Table 1**. Thirty patients (55.6%) had an elevated ALT baseline level, 46 had 6 or more lesions in liver, 38 (70.4%) had bilobar disease, and 27 (50.0%) had hepatic involvement more than 50%. Hepatic response rate was 100%, including complete response (CR) in 10 patients (18.5%) and partial response (PR) in 44 (81.5%). The local control rate at primary site was 94.4%, including CR in 2 patients (3.7%), PR in 35 (64.8%) and stable disease (SD) in 14 (25.9%) (A typical patient's CT imaging and angiography are shown in **Figure 1**). Three patients (5.6%) had progressive disease at the primary site, and 4 (7.4%) developed extra hepatic metastases. Thirty-eight patients were evaluated as resectable after a median of 4 cycles (range, 2 to 7) of trial treatment, with the resectability rate at 70.4%. Subgroup analysis according the extension of hepatic disease showed the resectability rate
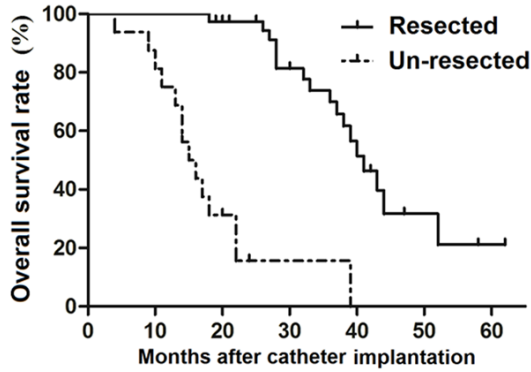
Figure 2. Kaplan-Meier estimates of OS for resected (n=38) and unresected (n=16) patients, respectively, calculated from the date of catheter implantation (*P*<0.0001, log-rank test).

was 63.0% in patients with hepatic involvement more than 50%. Results of univariate analysis showed neither the characteristics of liver metastases nor the location of primary cancer affected resectability rate. The resectability rate also did not differ according to sex, age, baseline CEA and baseline LDH (**Table 2**).

Thirty-eight patients underwent curative-intent resection (the location of primary tumor was the right colon in 10 patients, the left or sigmoid colon in 13 patients, and the rectum in 15 patients). The median interval from diagnosis to resection was 5.5 months (range, 3 to 9 months), and the median interval from the stop of chemotherapy to resection was 26 days (range, 22 to 33 days). Of these patients, 14 underwent simultaneous colon and liver resection, 9 underwent initial colon cancer resection followed by liver resection/ablation, 11 underwent initial liver resection/ablation followed by rectal cancer resection, and 4 out of 10 patients who achieved CR had no tumor found in liver during the surgery and received primary tumor resection alone. To treat the downstaged liver metastases, exclusive percutaneous RFA were performed in 7 patients for 19 lesions, major hepatectomy in 17, and minor hepatectomy in 10 (combined with RFA in 4 patients for 6 lesions). In patients with two-step procedures, no patient received additional chemotherapy in the interval. Colorectal pathologic samples were available for 38 patients (R0=36, R1=2). Two patient had complete tumor necrosis in the primary site. Hepatic samples were available for 27 patients. Five patients had no disease in liver and 3 had microscopic residual tumor in liver (R0=24, R1=3). No mortality

occurred during the first 3 months after operation. Thirty-four patients received postoperative systemic XELOX and HAI therapy concurrently, 3 patients received XELOX alone, and 1 patient did not receive postoperative chemotherapy. The median number of total HAI therapy was 9 (range 3-18). Six patients underwent adjuvant radiotherapy after rectal resection.

Of the 16 patients who remained un-resectable, 4 had extra hepatic metastases, 12 had 2 or more major vessel involved. Twelve patients received second-line chemotherapy, and 9 received third-line chemotherapy. None of them was converted to resectability after following treatments. Thirteen patients died from progressive systemic disease and 2 were alive without complications related to primary cancer until the end of the follow-up. Three patients (5.6% of entire cohort) required emergency surgery for complications related to the primary cancer (2 for intestinal occlusion and one for hemorrhage. The median time from diagnosis to emergency surgery was 11 months (range, 3 to 17 months), and the median survival after surgery was 4 months (range, 1.5 to 7 months). In addition, 4 rectal cancer patients underwent palliative radiotherapy for pain and modest bleeding.

The median follow-up period was 40 months (range, 18 to 62 months) in resected patients and 18 months (range, 4 to 37 months) in un-resected patients. On May 31, 2014, 23 patients were alive, including 21 resected patients and 2 un-resected patients. The estimated 3-year survival rate was 76% (95% CI 68%-84%) in resected patients, and 15% (95% CI 5%-25%) in un-resected patients. The resected patients had significantly better OS than the un-resected patients (P<0.0001, log-rank test, **Figure 2**).

Among the 38 resected patients, 22 patients were diagnosed with recurrence. First recurrence site was intra hepatic-only in 7 patients (31.8%), extra hepatic-only in 9 patients (40.9%), and both intra hepatic and extra hepatic in 6 patients (27.2%). The median time to hepatic progression was 24.0 months (95% CI 20.2-27.7), and the median time to over progression was 20.0 months (95% CI 17.1-23.9). Fourteen salvaging resections/ablations for recurrence (8 in liver and 6 in lung) were performed in 10 patients (6 patients were alive without disease by the end of follow-up).

Hepatotoxicity was the most frequent adverse event related to treatments. ALT/AST elevation occurred in 36 patients (66.7%) including grade 1 or 2 in 25 (46.3%) and grade 3 in 11 (20.4%). No patient developed bilirubin concentration >3 mg/l. No patients discontinued FUDR therapy permanently due to hepatotoxicity. The other frequent grade 3 or 4 events related to chemotherapy included: epigastric pain in 8 patients (14.8 %), neutropenia occurred in 7 (13.0%), vomiting in 6 (11.1 %), hand-foot syndrome in 4 (7.4%) and neurotoxicity in 3 (5.6%). Gastrointestinal ulcerations confirmed by gastrointestinal endoscopy occurred in 4 patients (7.4%) who underwent median 5 (range 3 to 7) cycles of infusion. HAI therapy could be continued after ulcerations healing and 50% dose-reduction of FUDR and DXM in 3 patients. Another patient stopped HAI therapy permanently after 5 cycles of therapy because the ulceration reoccurred after dose-reduction. Catheter displacement occurred in 2 patients (3.7%) (HAI therapy was continued after the catheters were corrected by radiological method). Four patients had infection at the site of port implantation required debridement. No patient had catheter occlusion during the follow-up period.

Discussion

Combined hepatic artery infusion (HAI) with systemic chemotherapy (SCT) has the theoretic benefit of suppressing systemic diseases and demonstrating higher hepatic response rates. In the present study, we focused this treatment strategy exclusively on un-resectable synchronous liver metastases. All eligible patients were treated initially with HAI FUDR and systemic XELOX, with the primary tumor in situ. The HAI catheter systems were implanted percutaneously by an innovative radiological method. Patients deferred primary cancer resection until the metastatic disease was converted to resectable disease, or any serious tumor-related complications occurred. This approach does not require surgery at diagnosis. It allows the planned HAI and SCT to start immediately and avoids unnecessary primary tumor resection in patients who may never develop symptoms. Our data showed the resection rate at 70.9%, with only 7.4% of patients undergoing palliative surgery.

The initial treatment strategy chosen for colorectal cancer patients with synchronous liver metastases depends on the symptoms related to the primary cancer and resectability status of liver disease. Usually, a doublet chemotherapy combined with an antibody is the preferred first line treatment for the asymptomatic patients with un-resectable CRCLM. The antibody may be chosen according to RAS-status of the patient's tumor. Based on modern SCT, the reported resection rate was range 13% to 42.9% [3, 4]. Recently, HAI chemotherapy is also acceptable as first-line treatment in un-resectable CRCLM [17]. Combined with SCT, HAI therapy is helpful not only in improving the hepatic response rate, but also increasing the magnitude of individual tumor shrinkage in liver, which significantly improved the resection rate in initially un-resectable CRCLM [12, 18]. In this study, 84% had 6 or more lesions in liver and 50% of patients had hepatic involvement more than 50%. We chose HAI and SCT as initial treatment mainly for extensive involvement of liver with metastatic tumor. Our data showed that 100% of patients achieved objective response in liver metastases, including 18.5% CR. About 70% of patients were converted to resectability. Of note, the criteria for resectability may differ among centers. It is complicated to objectively evaluate the conversion power of chemotherapy in metastatic liver disease, by comparing the resection rates among studies performed in different centers. In the present study, we clearly defined the criteria for un-resectability, and all patients were evaluated and treated by the same multidisciplinary team in a single center. Considering the extensive hepatic involvement at baseline and excellent hepatic response together, our data indicate initial HAI and systemic XELOX is a powerful strategy for a high resection rate in extensive synchronous CRCLM.

Resection of both the primary tumor and the liver metastases with an intention of cure was the principal goal of the present study. In order to clear all the malignant lesions and minimize the risks of operation, we used different surgical strategies according to the disease site and the extent of the surgery needed. "Liver-first" approach (resection of the liver metastases first) was the preferred option in rectal cancer. As described before, this approach is considered the best when the primary tumor was asymptomatic or easy to manage [19, 20]. Synchronous resection was mostly indicated in colon cancer patients with limited hepatic involvement that could be completely removed

by minor hepatectomy and/or radiofrequency ablation. In contrast, we chose two-stage resection when major hepatectomy was necessary. HAI therapy has been reportedly associated with a high true CR rate in patients with liver metastases that disappeared on imaging [12, 21]. In the present study, among of 10 patients who achieved radiological CR, 6 patients underwent liver resection, and 5 patients were approved as pathological CR. In summary, all 38 patients who were evaluated as resectable after the trial treatments successfully underwent the pre-planned surgical procedures in our study. The resected patients had a 3-year survival rate of 76% in the present study, which was significantly higher compared to 15% in patients who remained un-resectable.

A series of studies showed that chemotherapy and targeted agents is safe in stage IV patients with their primary tumor in situ [3, 4, 22, 23]. In our study, emergency surgery occurred in only 3 patients (5.6% of entire cohort). These results compare similarly to a previous study by using FOLFOX6 as the first-line treatment [4]. Obviously, the low emergency surgery rate in the present study mainly contributed to local control power of systemic XELOX. In addition, due to the conversion power of the combined treatment, 70% of the eligible patients obtained conversion and underwent selective surgery after treatment. The median interval between diagnosis and surgery was only 5.5 months. The primary tumors were removed before the potential complications occurred. This may be another reason for the low rate of urgent surgery in our study.

In our study, the adverse events possibly related to extra hepatic perfusion of FUDR, such as gastrointestinal ulceration and epigastric pain, cannot be ignored, although the main branch vessels from the arteries associated with the stomach or duodenum were routinely embolized before catheter implantation. In the study, 4 patients had gastrointestinal ulceration including 1 had to stop HAI therapy and 3 required dose reduction. About 15% of patients had grade 3 abdominal pain, which was significantly higher than the rate of 5% reported in NO16966 study evaluating XELOX as first-line treatment for MCRC [24]. Hepatotoxicity is another disadvantage of HAI therapy. About 20% of patients had grade 3 ALT/AST rate in our study. Fortunately, hepatotoxicity was reversible in all

patients and no patients permanently discontinued HAI therapy. Nonetheless, the treatment-related complications were reversible in most patients, and the ability to give the planned treatment was clinically acceptable in our study.

In summary, our data showed that initial HAI and systemic XELOX resulted in a high resection rate from patients with asymptomatic colorectal cancer and un-resectable liver metastases, and associated with a low rate of complications related to the primary cancer. However, this is a retrospective study and has limitations because of its small sample and lack a control group with similarly un-resectable CRCLM, which was initially treated with modern systemic chemotherapy alone. A multi-center randomized study is needed to evaluate whether the favorable resection rate translated into prolonged survival.

Disclosure of conflict of interest

None.

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