Efficacy of Transarterial Chemoembolization on Lesion Reduction in Colorectal Liver Metastases

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Abstract- Following failure of systemic chemotherapy, transarterial chemoembolization (TACE) is an available method to control unresectable liver metastases from colorectal carcinoma (CRC). The aim of present study was to evaluate the efficacy of chemoembolization for inoperable metastatic liver lesions from CRC. Forty-five CRC patients with liver metastases resistant to systemic chemotherapy were enrolled in our study. For each patient, three session of TACE were conducted with 45 days interval. A combination of mitomycin, doxorubicin, and lipiodol were used for TACE. A tri-phasic computed tomography scan and biochemical laboratory tests were performed for all patients at baseline and 30 days after each TACE. Image analysis included measurement of lesion diameters as well as contrast enhancement. Eleven patients deceased before completing three session and the final analyses were performed on the remaining 34 patients. Evaluation of a total 93 lesions in all patients after chemoembolization sessions revealed a 25.88% reduction in anteroposterior (AP) diameter, 33.92% transverse (T) diameter, and 42.22% in product of APxT diameter of lesions (P<0.001 for all instances). CT scan showed a total disappearance of 33% of lesions and evident reduction in contrast enhancement in 16% of them. There were no changes in contrast enhancement in 51% of lesions. Evaluation of single largest lesion in each patient revealed 57.32% reduction in AP diameter, 59.66% in T diameter, and 62.17% in product of APxT diameters (P<0.001 for all diameters). TACE offers a viable option for CRC patients with unresectable liver metastases by significantly reducing lesion size and contrast enhancement.

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Keywords: Colorectal carcinoma; Liver metastases; Transarterial chemoembolization; Chemotherapy

Introduction

Hepatic metastases are the leading cause of death in patients with colorectal carcinoma (CRC). Liver metastases are present in up to 80% of patients with CRC and in 20-25% of them at the time of initial diagnosis (1).

Surgical resection is the only curative treatment in patients with colorectal liver metastases. However, it is amenable in less than 20% of patients with isolated liver metastases (usually up to five, in one lobe of liver) (2,3). The outcome of systemic chemotherapy for patients with unresectable liver lesions have been relatively poor, with a 20% response rate for treatment with 5-flouorouracil

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(5-FU) and 40-57% response rates for the addition of irinotecan or oxaliplatin to 5-FU-based regiments (2,4-6). Alternative therapies include radiofrequency ablation (RFA), laser induced thermotherapy (LITT), cryotherapy, microwave therapy, percutaneous alcohol injection, hepatic arterial infusion (HAI) of chemotherapeutic drugs, and trasnarterial chemoembolization (TACE) (1,7,8).

TACE is defined as an intra-arterial administration of chemotherapeutic drugs usually combined with selective embolizing of the feeding arteries of the liver metastases (1,9). Hepatic tumors receive most of their blood supply from the hepatic artery while the normal parenchyma has predominantly venous supply from the portal vein (10). Embolization of tumor arteries results in increasing vascular permeability and thereby promotes penetration of chemotherapeutic drugs into the tumor. In addition vascular occlusion caused by the embolic agent results in prolongation of exposure of the tumor tissue to chemotherapy (11,12).

The aim of this study was to determine the tumor response rate of patients who undergo TACE using a combination of mitomycin, doxorubicin, and lipiodol for unresectable colorectal hepatic metastases.

Patients and Methods

Patient selection

In the first step of the study, CRC patients with unresectable liver metastasis, who visited Imam Khomeini hospital cancer institute between June 2009 and November 2010, were contacted. Patients with unresectable metastases in whom systemic chemotherapy failed to regress the masses and/or its further induction is accompanied with considerable risks, could benefit TACE. Eligible candidates for TACE were informed and instructed regarding benefits and complications of the procedure, and also other possible treatment options (i.e. palliative care) were discussed. In second step, patients agreed to undergo TACE procedure were evaluated and excluded if meeting any of the following criteria: 1) Age older than 85 years old; 2) history of malignancies other than CRC; 3) Liver metastasis occupying more than 75% of liver mass determined by CT scan; 4) history of inflammatory bowel disease; 5) history of viral hepatitis (B, C); 6) clinically apparent jaundice (Direct bilirubin >5); 7) imaging evidence of complete obstruction of portal vein; (8) Major disorder(s) of the cardiovascular, renal (creatinine >2 mg/dl), pulmonary, or hematologic systems (hemoglobin <8 mg/dl). Moreover during study conduct, patients deceased before completing all three cycles of TACE were also excluded from final analysis.

Data collection

Initial evaluation included a thorough clinical interview, physical examination, imaging studies, and biochemical evaluation. Imaging studies incorporated a hepatic angiography and computed tomography scan. Vascular anatomy of the arterial vessels of the abdomen, and vascularity of the hepatic lesions were assessed via angiography. A tri-phasic computed CT scan was obtained from each patient at baseline and repeated 30 days after every session of TACE; hence, a total of four CT scans were performed. Number and size of each lesion manifest in CT scan was recorded, along with degree of enhancement. In cases where more than 5 lesions existed, the five largest lesions were selected to be representative of liver lesions. For each lesion an anteroposterior diameter (AP), a transverse diameter (T), and a product of former and latter diameters (APxT) were calculated.

Biochemical evaluation included complete blood count, as well as measurement of alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), total and direct bilirubin, prothrombin time (PT), partial thromboplastin time (PTT), and serum creatinine. Biochemical measurements were repeated 30 days after each TACE session.

TACE procedure

TACE procedure was conducted using a combination of mitomycin (10 mg), doxorubicin (50 mg), and lipiodol (10 cc). Chemotherapy agents were administered via selective hepatic artery catheterization. Three sessions of TACE was performed for each patient with 45 days interval. After TACE patients were admitted to the ward for observation overnight and were monitored for possible complications of the procedure as well as adverse reactions to the drugs administered (i.e. pain, fever, nausea, vomiting, and local infection). If necessary, the hospital stay was extended until full recovery. For chemoprophylaxis against infection, ceftriaxone (1 g, IV) was administered before TACE. Patients also received a repeated dose after the procedure. During procedure, an intravenous dose of ranitidine (50 mg), granisetrone hydrochloride (3 mg), and metoclopramide (10 mg) was administered to control the post-embolization syndrome. All methods and procedures incorporated in this study were in accordance with declaration of Helsinki. Patients were provided with written informed consents and study

received ethics approval from ethics committee of Tehran University of Medical Sciences.

Statistical analysis

Statistical analysis was carried out using statistical package for the social sciences (SPSS) version 17.0 for windows (SPSS Inc. Chicago, IL, USA). Continuous variables are expressed as mean ± standard deviation and categorical variables in proportion. Lesion measurements (AP, T, APxT) between baseline and third TACE session were compared with paired t-test. Comparisons were made on both lesion level (all lesions taken together irrespective of patients), and on patient level (single largest lesion in each patient was selected to be representative of patient's liver metastases). A *P*-value less than 0.05 was considered statistically significant.

Results

Eleven of total 45 patients enrolled in this study deceased before the last session of TACE. Baseline characteristics of remaining 34 patients (53% female) are shown in Table 1. All patients received the complete regimen in three sessions and all TACE procedures were technically successful. Mean age of patients was 52.12 ± 14.08 years ranging from 24 to 79 years old. Fifteen patients (44%) received prior systemic chemotherapy and 16 of them had previously been treated with hepatic resection surgery. The number of hepatic lesions was as follows: one lesion in 14 (41%), two lesions in four (12%), three lesions in three (9%), four lesions in three (9%), and five lesions or more in ten (29%) patients. The extent of hepatic involvement in 19 patients (56%) was less than 25%, 11 (32%) had involvement between 25% and 50%, and the remaining four (12%) between 51% and 75%.

The morphologic response of hepatic lesions was verified at tri-phasic CT scan one month after third session of TACE. Evaluation of a total of 93 lesions in all patients after chemoembolization sessions revealed a 25.88% (P<0.001) reduction in AP diameter, 33.92% (P<0.001) in T diameter, and 42.22% (P<0.001) in product of APxT diameter of lesions (Figure 1).

Table 1. Baseline characteristics of study participants.

Age	52.12 ± 14.08
Female; n (%)	18 (53%)
Tumor resection	16 (47%)
Previous chemotherapy	15 (44%)
% liver involvement	
< 25%	19 (56%)
25-50%	11 (32%)
51-75%	4 (12%)
ALT	35.94 ± 20.04
AST	49.97 ± 22.99
Direct Bilirubin	2.44 ± 3.10
Total Bilirubin	11.78 ± 6.67
Prothrombin Time	13.56 ± 1.47
Partial Thromboplastin Time	30.61 ± 5.60
Creatinine	0.93 ± 0.31

Table 2. Main outcomes of TACE for total and single largest lesions.

	Baseline	After TACE	% reduction	*P*-value
Total lesions				
Anteroposterior diameter	35.71 ± 21.93	26.47 ± 17.64	25.88%	<0.001
Transverse diameter	26.47 ± 16.08	17.49 ± 11.28	33.92%	<0.001
APxT	1710.58 ± 1326.90	988.52 ± 657.13	42.22%	<0.001
Metastatic enhancement				
Total disappearance	31 (33%)			
Evident reduction	15 (16%)			
No change	47 (51%)			
Single largest lesion				
AP diameter	53.84 ± 30.13	22.98 ± 31.22	57.32%	<0.001
T diameter	36.81 ± 24.82	14.85 ± 12.79	59.66%	<0.001
APxT	2559.81 ± 1146.95	968.50 ± 677.12	62.17%	<0.001
Metastatic enhancement				
Total disappearance	7 (21%)			
Evident reduction	10 (29%)			
No change	17 (50%)			

Abbreviations: AP, anteroposterior; T, transverse

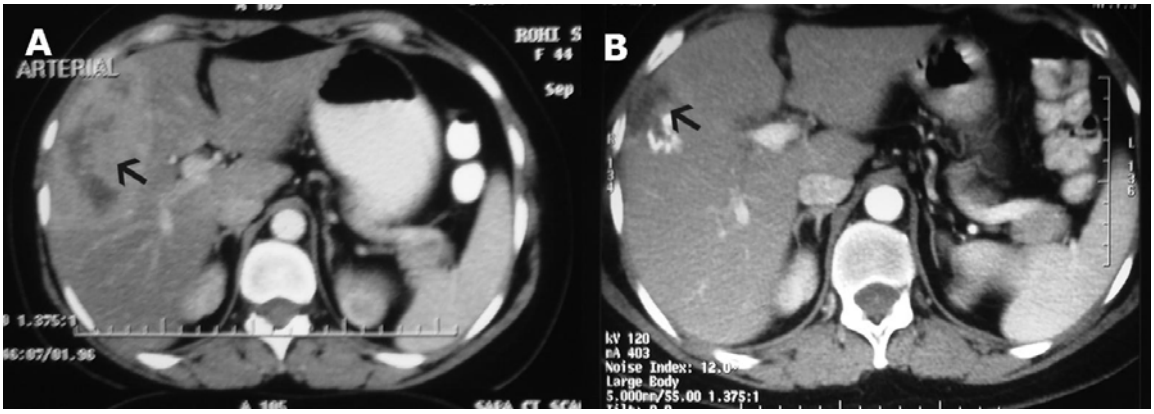

Figure 1. A 44-year-old woman with colorectal hepatic metastasis. A. CT scan with contrast before TACE. A large metastatic lesion in the right lobe of liver. B. CT scan with contrast after third session of TACE. Significant decrease in the size of lesion with small necrotic tissue remaining.

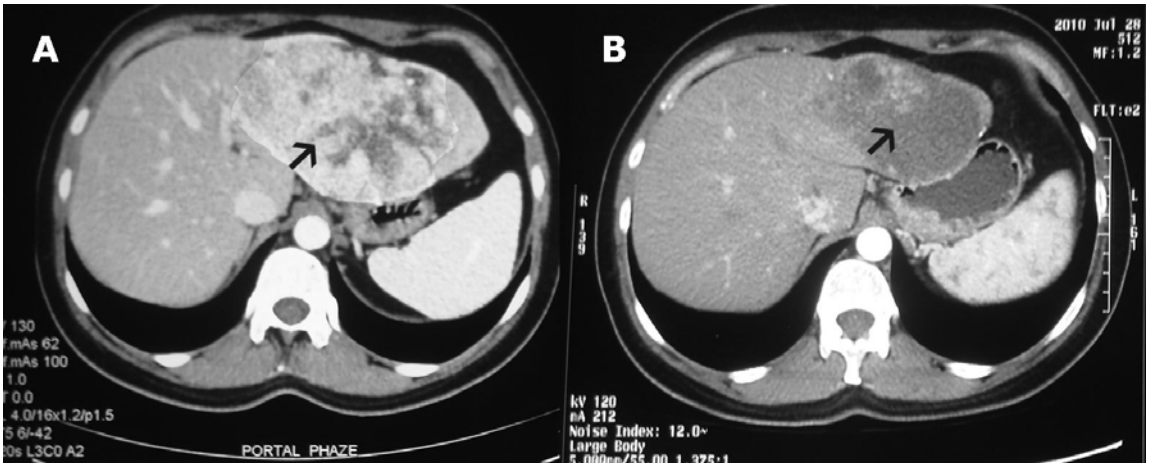

Figure 2. A 58-year-old woman with colorectal hepatic metastasis. A. CT scan with contrast before TACE. The target lesion in the left lobe of liver with intense contrast enhancement. B. CT scan with contrast after third session of TACE. Necrosis of the lesion with disappearance of contrast enhancement.

CT scan showed total disappearance of 33% of lesions and evident reduction in contrast enhancement in 16% of them (Figure 2). There were no changes in contrast enhancement before and after three sessions of TACE in 51% of lesions.

Within one month after last session of TACE, evaluation of single largest lesion in each patient revealed 57.32% reduction in AP diameter (P<0.001), 59.66% in T diameter (P<0.001), and 62.17% in product of APxT diameters (P<0.001). Single largest lesion of seven (21%) patients totally disappeared after third session of TACE, and 10 (29%) of them showed evident reduction in contrast enhancement, while 17 (50%) remained unchanged (Table 2).

Discussion

Metastases are the most malignant lesions of liver. Most of liver metastases originate from gastrointestinal tract malignancies followed by breast cancer due to filtering function of liver in portal blood stream (13). Liver metastases have an elemental role in determining CRC patients' prognosis. Between 15 and 35% of CRC patients, have liver metastasis at the time of first evaluation, whereas two third will have detectable metastatic lesions at the time of death (14). Resection of liver metastases is feasible only if patient has solitary or unilobar involvement. However, often that is not the case and unresectable metastases challenge physicians and significantly affect survival of patients. For patients

with unresectable lesions, chemoembolization through hepatic artery has shown promising results. The goal of TACE is to deliver large amounts of chemotherapeutic agents to the lesion. With this approach, while the lesion is targeted with significant amounts of toxic agents, the remainder of liver and whole body remains drug free, hence reducing the toxic and adverse reactions to a minimum (15).

Several studies performed to date, have evaluated the effectiveness of TACE in patient with liver metastases from CRC combining different agents with varying protocols (14,16-20). Here, we describe the first study of three repeated TACE sessions conducted in an Iranian sample of CRC patients. In our observation, a total of 34 patients went through all sessions and survived at least 30 days post third session.

The present study indicated that there is an average 42.22% reduction in production of AP and T diameters (APxT) per lesion. For enhancement per lesion, in 33% of lesions a total disappearance was noted while 16% and 51% of lesions showed decreased and no changes in enhancement respectively. Additionally, for single largest lesion of each patient there was 62.17% reduction in APxT diameter. A plausible explanation for discrepancy between per lesion and single largest lesion size reduction is that patients with multiple lesions are expected to have more resistant disease with limited response towards TACE and these patients have a greater weight in sum of lesions compared to subjects with solitary or few lesions. However, design of our study did not provide adequate statistical power to test this hypothesis.

In line with our findings, Vogl *et al.* (21) in one of the largest series reported to date, have reported a 14.7% partial response, 48.2% stable disease and 37.1% progressive disease after repeated TACE sessions with at least four weeks intervals. In our study, however no patient had progressive disease at the end of third TACE. In another study of ten patients (16), significant reductions in metastatic contrast enhancement was noted. That is in concert with our observation that 67% of patients experienced either no change or at best a reduction in lesion contrast enhancement. This difference is perhaps stemming from different methodologies employed for reading and interpreting changes in enhancement. Fiorentini *et al.* (17) have noted a high response rate (80%), with reduction of lesional contrast enhancement in all patient affected by liver metastases from CRC. Conversely, a multi-center study conducted between 2006 and 2008 on 55 patients with unresectable metastases to liver from CRC (19), reported a complete response in 5% of subjects (complete response=3, partial response=16, stable disease=25, progressive disease=2, and death=1) after 6 month follow up. You *et al.* (14), evaluated response of liver metastases from CRC to combining systemic chemotherapy with chemoembolization. In this study, the objective tumor response rate was 47.5% which is in concert with our findings. Martin *et al.* (18) reported response rate of 75% after three month and 66% after six month. In line with studies noted above, Muller *et al.* (22) and Voigt *et al.* (23) showed 76.6% and 50% morphologic response respectively.

In a review of studies done by Vogl *et al.* (1), it was concluded that TACE increases the possibility of surgery, improves its outcome and can be used when surgery is not possible or not successful.

In conclusion it seems that TACE provides a viable option for CRC patients with unresectable liver metastases and can benefit their survival. It should be noted however, a considerable degree of discrepancy exists between findings of several research groups, reflecting differing methods in patient inclusion, chemotherapeutic agents employed, sessions of TACE conducted and use of systemic chemotherapy before TACE. Collectively, as observed in our cohort of patients, a subset of circumspectly selected patients can benefit from the lesion-reducing effects of TACE. While these early results are encouraging, effect of TACE on the long-term survival of CRC patients, as well as its late complications on liver function still need to be elucidated. Future aptly designed prospective studies are needed to address these upcoming questions.

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