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BRIEF ARTICLE

Short-term effectiveness of radiochemoembolization for selected hepatic metastases with a combination protocol

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Abstract

AIM: To introduce the combination method of radiochemoembolization for the treatment of selected hepatic metastases.

METHODS: Twenty patients with biopsy proven hepatic metastases were selected from those who underwent transarterial radiochemoembolization, a novel combination protocol, between January 2009 and July 2010. Patients had different sources of liver metastasis. The treatment included transarterial administration of three chemotherapeutic drugs (mitomycin, doxorubicin and cisplatin), followed by embolization with large (50-150 μm) radioisotope particles of chromic 32P. Multiphasic computer tomography or computer tomography studies, with and without contrast medium injections, were performed for all patients for a short-term period before and after the treatment sessions. The short-term effectiveness of this procedure was evaluated by modified response evaluation criteria in solid tumors (mRECIST), which also takes necrosis into account. The subjective percentage of necrosis was also assessed. The response evaluation methods were based on the changes in size, number, and the enhancement patterns of the lesions between the pre- and post-treatment imaging studies.

RESULTS: Patients had liver metastasis from colorectal carcinomas, breast cancer, lung cancer and carcinoid tumors. The response rate based on the mRECIST criteria was 5% for complete response, 60% for partial response, 10% for stable disease, and 25% for progressive disease. Regarding the subjective necrosis percentage, 5% of patients had complete response, 50% had partial response, 25% had stable disease, and 20% had progressive disease. Based on traditional RECIST criteria, 3 patients (15%) had partial response, 13 patients (65%) had stable disease, and 4 patients (20%) had disease progression. In most patients, colorectal carcinoma was the source of metastasis (13 patients). Based on the mRECIST criteria, 8 out of these 13 patients had partial responses, while one remained stable, and 5 showed progressive disease. We also had 5 cases of breast cancer metastasis which mostly remained stable (4 cases), with only one partial response after the procedure. Six patients had bilobar involvement; three of them received two courses of radiochemoembolization. The follow up imaging study of these patients was performed after the second session. In the studied patients there was no evidence of extrahepatic occurrence, including pulmonary radioactive deposition, which was proven by Bremsstrahlung scintigraphy performed after the treatment sessions. For the short-term follow-ups for the 2 mo after the therapy, no treatment related death was reported. The mostly common side effect was post-embolization

syndrome, presented as vomiting, abdominal pain, and fever. Nineteen (95%) patients experienced this syndrome in different severities. Two patient had ascites (with pleural effusion in one patient) not related to hepatic failure. Moreover, no cases of acute liver failure, hepatic infarction, hepatic abscess, biliary necrosis, tumor rupture, surgical cholecystitis, or non-targeted gut embolization were reported. Systemic toxicities such as alopecia, marrow suppression, renal toxicity, or cardiac failure did not occur in our study group.

CONCLUSION: Radiochemoembolization is safe and effective for selected hepatic metastases in a short-term follow-up. Further studies are required to show the long-term effects and possible complications of this approach.

Key words: Hepatic metastasis; Radiochemoembolization; Phosphorus radioisotopes; Treatment; Outcome

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INTRODUCTION

Although complete surgical resection of the hepatic portion affected by metastasis is usually the best treatment option, most patients with hepatic metastasis are not amenable to resection or have some contraindications to the surgery[1]. As alternatives to standard systemic chemotherapy, some recent palliative therapies have been developed for unresectable hepatic metastases, which include transarterial administration of chemotherapeutic drugs or radiopharmaceuticals, selective tumor vessel embolization and percutaneous tumor ablation with ethanol injection, cryotherapy, radiofrequency, or the use of microwaves[1,2].

Transcatheter arterial chemoembolization (TACE) is a dual minimally invasive therapeutic approach combining transarterial administration of chemotherapeutic drugs and hepatic artery embolization[3]. Although there are many advantages of this combination, it does produce marked tumoral ischemia at the time of drug administration which potentiates the effect of cytotoxic agents and augments tumoral cell apoptosis[4,5].

Radioembolization, on the other hand, is a technique that preferentially targets hepatic lesions by infusing the hepatic arteries that supply the tumor with radioactive microspheres[6]. Traversing the hepatic vascular plexus, these microspheres embed within the tumor arterioles, where they deliver high-energy low-penetrating radiation doses to the tumoral cells, while the normal hepatic tissue is relatively preserved[6,7]. As can be determined from the method's name, radioembolization has also microembolic effects and leads to subsequent vessel occlusion[8].

Regarding the effectiveness of radioembolization and chemoembolization for hepatic malignant neoplasms[2,9], we assumed that the local combination of the two methods (i.e., radiochemoembolization) would be more effective. It has been shown that radioembolization in combination with systemic chemotherapy is an effective first-line therapy for liver metastases[10]. The most commonly used agent for radioembolization of hepatic tumors is Yttrium-90 (^{90}Y) in the form of ^{90}Y microspheres[9], which has a half-life of 64 h[11]. In this study, however, a phosphorus-32 containing particle was adopted as the radiopharmaceutical. In the process of phosphorus-32 (^{32}P) decay, the molecule emits relatively high energy beta particles[12]. Although there are reports of safe clinical ^{32}P application for hepatic tumors[12-16], larger particles were used in the current study to reduce systemic toxicities even more by decreasing hepatic-to-systemic shunt. In addition, the higher half-life of ^{32}P (14.3 d[17]) would provide a longer irradiation time in order to achieve chemo-radiation effects.

The primary purpose of this study is to introduce the radiochemoembolization method for the treatment of hepatic metastases. Short-term effectiveness of this treatment based on imaging criteria was also assessed. As World Health Organization (WHO) criteria and response evaluation criteria in solid tumors (RECIST) guidelines are based solely on the degree of tumor shrinkage for assessing tumor response, we used other criteria like modified RECIST (mRECIST), which includes the degree of necrosis to show the effectiveness of the therapy[18]. Finally, *via* a brief review of the literature concerning ^{32}P application and TACE, possible limitations, concerns, and complications that may be encountered with radiochemoembolization were addressed.

MATERIALS AND METHODS

This was a single institution clinical study approved by the ethics committee of our imaging center. A written consent form was obtained from all patients and they were all informed about the novelty of the method. This paper reports the results of 20 patients who underwent radiochemoembolization between January 2009 and July 2010. The inclusion criteria included: biopsy proven hepatic metastatic lesion/lesions from any source; contraindication to ablative therapies and resection; an eastern cooperative oncology group performance status score of 0 to 2[19]; and the patient needed to be at least 18 years of age. Although more than 20 patients met these criteria and received radiochemoembolization, another inclusion criterion was added to only report the results of patients

who had available contrast-enhanced computer tomography (CT) or magnetic resonance imaging (MRI) 1 to 2 mo previous and after the treatment session. Only 20 patients such patients were qualified. Exclusion criteria were: bleeding diathesis that could not be controlled; significant extra-hepatic involvement, generally more than 50% of the whole tumoral bulk outside the liver; imminent threat to the patient's life caused by the disease; greater than 75% involvement of the hepatic parenchyma; severe hepatic dysfunction; and an active uncontrolled infection.

Patients fasted overnight and received a prophylactic antibiotic (ceftriaxone, 1 g) and antiemetics (granisetron, 3 mg; dexamethasone, 8 mg). During the procedure, fentanyl or pethidine were infused to alleviate the pain caused by embolization. All procedures were performed in the angiography room under aseptic conditions. Intravenous hydration was started 1 h before the procedure.

In this study, ^{32}P-containing particles were used (Nuclear Science and Technology Institute, Iran) with $Cr^{32}PO4$ as the active component. These particles had a grain size of 50-150 μm, significantly larger than previously used colloidal ^{32}P particles also based on $Cr^{32}PO4$[13,14,20]. The physical half-life period of ^{32}P is 14.28 d, with an average penetration distance of 3-4 mm in soft tissues (maximum 8 mm)[13]. Ranging from 0.185 to 0.444 GBq, the dose of injected solution was calculated based on liver volume (not tumor burden) which was estimated with CT or MRI. The prepared ^{32}P solution was dissolved in 1-3 mL of radiographic contrast. The chemotherapeutic mixture consisted of 50 to 100 mg of cisplatin, 50 mg of doxorubicin, and 8-10 mg of mitomycin-C dissolved in 10 mL of radiographic contrast and 10 mL of normal Saline.

Using the Seldinger technique, a catheter was introduced through the femoral artery and selective catheterization of the hepatic artery was performed. A 3-F hydrophilic microcatheter (Cook, United States) used with a 0.014 or 0.021 guide wire was suffice to catheterize the desired artery. This standard catheter allows rapid injection of viscous radiochemoembolic emulsions and is unlikely to clog with particles. A digital subtraction angiography was performed to confirm that there was no hepatic arteriovenous fistula or duodenogastric reflux. For patients who had bilobar involvement, the treatment mixture was infused in both lobes simultaneously or separately in two sessions (3-4 wk apart) depending on the patient's liver function test and number of metastases. Only in one case (case 4) was coil embolization of gastroduodenal artery was performed before radiochemoembolization.

After placing the catheter in a suitable location, the chemotherapeutic mixture was infused and continuously monitored *via* fluoroscopy to avoid reflux into the untargeted arterial bed. Following this step, again under fluoroscopic surveillance, chromic ^{32}P solution was infused for vessel occlusion. If reflux happened, the infusion would be paused until the arterial flow resumed and then restarted at a lower speed.

After the procedure, intravenous hydration, antibiotics, and antiemetic therapies were continued for 24 h and analgesics were supplied for control of pain as needed. All the patients were discharged on the day after the procedure. Oral antibiotics were continued for 5 d, as well as oral antiemetics and analgesics if needed. Twenty-four to 72 h after radiochemoembolization of hepatic tumors, bremsstrahlung scintigraphy was performed in all patients to document ^{32}P particles that accumulated in tumoral locations of the liver, and also to ensure that there were no extrahepatic radioactive deposits.

For evaluating the short-term effectiveness of radiochemoembolization by means of imaging studies, two scans, whether CT or magnetic resonance (MR), were performed 1 to 2 mo before and after the treatment session. CT examinations were performed using a multidetector scanner (Sensation 64, Siemens, Germany), with 5-mm sections (120 kV, 250 mAs). Triphasic liver imaging (including unenhanced, arterial and portal venous phase images) was acquired. Contrast-enhanced scans were performed after approximately 30 s in the arterial phase and after 70 s in the venous phase from the injection of the contrast agent iohexol (Omnipaque 350, Amersham Health; 125 mL at a rate of 3-5 mL/s). MR studies were performed using a 1.5 Tesla machine (Magnetom Symphony, Siemens, Germany). The protocol consisted of axial and coronal thin-section T2-weighted HASTE, axial unenhanced spoiled-T1-weighted gradient echo with fat suppression, and dynamic axial fat-suppressed contrast-enhanced spoiled-T1-weighted gradient-echo sequences for the arterial and venous phases (45, 60 and 90 s) and also the delayed phase (2-5 min) after contrast infusion. The contrast agent was gadopentetate dimeglumine (Magnevist, Berlex Pharmaceuticals, 20 mL), followed by 20 mL of saline flush.

Evaluation of tumor response to therapy was based on mRECIST criteria and subjective percentage of necrosis. Firstly, up to two hepatic target lesions were selected in pre-treatment imaging studies. Said lesions must (1) be capable of being accurately measured in at least one dimension as 1 cm or more; (2) be suitable for repeat measurement; and (3) have intratumoral enhancement after contrast injection. If more than two lesions could met these criteria, the one with larger enhancing portions would be selected. All other hepatic lesions were only recorded and not measured at the baseline; their presence or absence would be noted in the follow-up exams. A viable tumor was defined as a portion of the target lesion which had an uptake of the contrast agent in any phase of the contrast enhanced studies. For the mRECIST criteria, the change in the longest diameter of viable tumors was considered for the evaluation of the response to treatment. On the other hand, necrosis was a portion of the target lesions which remained without contrast enhancement. Based on these necrotic portions, a subjective percentage of necrosis was attributed to each target lesion. Every individual patient had a sum of longest viable tumor diameters and necrosis percentages of target lesions. According to the changes in these amounts, responses were categorized into complete response, partial response, stable disease and progressive disease (Table 1).

Table 1 Assessment of target lesion response

mRECIST		RECIST		Subjective percentage of necrosis	
CR	Disappearance of any intratumoral enhancement in all target lesions	CR	Disappearance of all target lesions	CR	Disappearance of any intratumoral enhancement in all target lesions
PR	At least a 30% decrease in the sum of diameters of viable target lesions	PR	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of the diameters of target lesions	PR	At least a 30% increase in the sum of target lesion necrosis percentages
SD	Any cases that do not qualify for either partial response or progressive disease	SD	Any cases that do not qualify for either partial response or progressive disease	SD	Any cases that do not qualify for either partial response or progressive disease
PD	An increase of at least 20% in the sum of the diameters of viable target lesions or new lesion appearance	PD	An increase of at least 20% in the sum of the diameters of target lesions or new lesion appearance	PD	A decrease of at least 20% in the sum of target lesion necrosis percentages or new lesion appearance

mRECIST: Modified response evaluation criteria in solid tumors; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease.

Table 2 Description of lesions for each patient and local tumor control outcomes with regard to different criteria

No.	Sex	Age (yr)	No. of lesions	Location	Primary source	New lesion	mRECIST	RECIST	Necrosis	Sum of viable diameters (mm)		Sum of necrosis percentages (%)		Sum of diameters (mm)	
										Baseline	Post-procedural	Baseline	Post-procedural	Baseline	Post-procedural
1	F	41	Multi	U	BRE	No	PR	SD	PR	57	18	0	100	57	44
2	F	29	Multi	U	BRE	No	SD	SD	SD	34	34	5	5	34	34
3	F	35	1	U	BRE	No	PR	SD	PR	50	33	30	50	60	45
4	F	39	Multi	B	BRE	No	PR	SD	PR	57	39	20	100	65	54
5	F	38	Multi	B	BRE	Yes	PD	PR	PD	72	-[1]	30	-	72	-
6	F	27	2	U	CAR	No	CR	PR	CR	92	0	0	200	92	42
7	M	81	3	U	CRC	No	PR	SD	PR	73	23	40	95	107	95
8	M	40	1	U	CRC	No	PR	PR	SD	55	33	5	5	55	33
9	F	41	1	U	CRC	No	PR	SD	PR	65	45	40	80	80	68
10	F	47	1	U	CRC	No	PR	SD	PR	144	103	50	80	226	217
11	F	59	1	U	CRC	Yes	PD	PD	PD	70	-	0	-	70	-
12	M	60	Multi	U	CRC	Yes	PD	PD	PD	50	-	0	-	50	-
13	M	57	1	U	CRC	Yes	PD	PD	PD	25	-	70	-	35	-
14	M	55	1	U	CRC	No	PD	PD	SD	56	102	5	5	56	102
15	M	77	Multi	U	CRC	No	SD	SD	SD	107	107	15	15	116	116
16	F	62	Multi	B	CRC	No	PR	SD	SD	40	7	155	195	68	55
17	F	57	Multi	B	CRC	No	PR	SD	PR	50	35	90	180	65	55
18	M	74	Multi	B	CRC	No	PR	SD	PR	213	116	10	130	213	159
19	F	48	Multi	B	CRC	No	PR	SD	PR	245	160	5	120	265	260
20	F	51	Multi	U	LUN	No	PR	SD	PR	142	61	20	175	150	127

[1]For patients with new lesions in the follow-up scan, the measurements were not performed and the patient was marked as progressive disease (PD); CR: Complete response; PR: Partial response; SD: Stable disease; U: Unilobar; B: Bilobar; F: Female; M: Male; BRE: Breast cancer; CRC: Colorectal carcinoma; CAR: Carcinoid tumor; LUN: Lung cancer; mRECIST: Modified response evaluation criteria in solid tumors.

RESULTS

Patients had different sources of liver metastasis, but most were from colorectal cancer. None of our patients had a history of surgery for hepatic metastases. The demographic, clinical, radiological and response data of the studied patients are shown in Table 2.

The mean and median of the baseline total viable diameters (i.e., the sum of the maximum diameters of the viable portions of target lesions in each patient) were 84.85 mm and 61 mm (range: 25-245 mm), respectively. The response rate, based on mRECIST criteria, was 5% for complete response (Figure 1A and B), 60% for partial response (Figure 1C and D), 10% for stable disease, and 25% for progressive disease (Figure 1E and F).

The baseline sum of the estimated percentage of necrosis in target lesions was calculated for each patient, and had a mean and median of 29.5% and 17.5%, respectively (range: 0% to 155%). Regarding the necrosis percentage, 5% of patients had complete response, 50% had partial response, 25% had stable disease and 20% had progression. Based on traditional RECIST criteria 3 patients (15%) had partial response, 13 patients (65%) had stable disease, and 4 patients (20%) had disease progression.

In most patients, colorectal carcinoma was the source of metastasis (13 patients). Based on mRECIST, 8 out of these 13 patients had partial responses while one remained stable and 5 showed progressive disease. We also had 5 cases of metastasis from breast cancer, which mostly remained stable (4 cases) with only case of one partial response after the procedure.

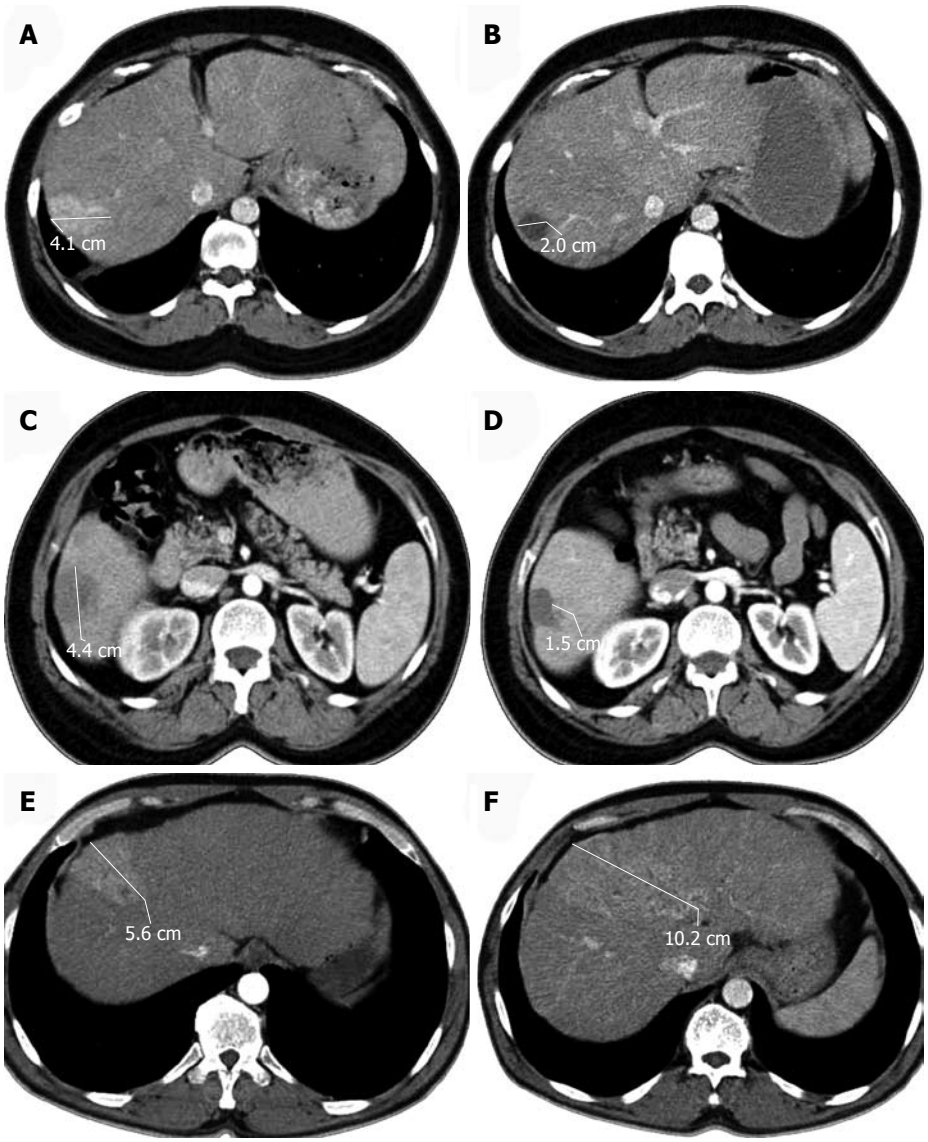

Figure 1 Radiochemoembolization images. A, B: Pre- (A) and post- (B) radiochemoembolization images in a 27 year-old female with a metastatic carcinoid tumor. There is no evidence of enhancing of the viable tumor after treatment. Based on modified response evaluation criteria in solid tumors (mRECIST) criteria, the response is complete, but regarding RECIST criteria we have a partial response; C, D: Pre- (C) and post- (D) radiochemoembolization images in a 41 year-old female with a metastatic carcinoid tumor. Based on modified response evaluation criteria in solid tumors criteria the response is partial; E, F: Pre- (E) and post- (F) radiochemoembolization images in a 55 year-old male with a metastatic colorectal carcinoma. Based on modified response evaluation criteria in solid tumors criteria the response is progressive.

Six patients had bilobar involvement, with three of them receiving two courses of radiochemoembolization. The follow-up imaging study of these patients was performed after the second session. In the studied patients there was no evidence of extrahepatic occurrence (such as pulmonary radioactive deposition), which was proven by Bremsstrahlung scintigraphy performed after the treatment.

For short-term follow-ups for the 2 mo after the therapy, no treatment-related death was reported. The most common side effect was post-embolization syndrome, presented as vomiting, abdominal pain and fever. Nineteen (95%) patients experienced this syndrome in different severities. Two patient had ascites (with pleural effusion for one patient) not related to hepatic failure. Moreover, no cases of acute liver failure, hepatic infarction, hepatic abscess, biliary necrosis, tumor rupture, surgical cholecystitis, or non-targeted gut embolization were reported[2]. Systemic toxicities, such as alopecia, marrow suppression, renal toxicity, or cardiac failure did not occur in our study group.

DISCUSSION

Liver metastases are one of the most difficult therapeutic challenges in oncological management, and are not usually amenable to resection. Many studies have been performed to find more effective palliative options for non-operable metastatic tumors. Although systemic chemotherapy still has a role[10,21], there are attempts at focusing treatment on hepatic tumors[22]. The present study introduced a novel combination of two effective treatment

options, TACE and radioembolization, for metastatic hepatic lesions.

In the current study, large-molecule chromic phosphate containing ^{32}P particles were used. Colloidal ^{32}P, another chromic phosphate-containing agent, has been previously used for radiosynovectomy *via* intrasynovial injection[23], treatment of stage I and II ovarian carcinoma *via* intraperitoneal instillation[24,25], and for regional radiotherapy of some tumors *via* direct intratumoral injection[13,20]. The usual forms of colloidal ^{32}P particles are small, approximately 1 μm[14,26], and might leak into systemic circulation, causing irradiation to undesired parts of body and toxicity. For intrasynovial and intraperitoneal application, as the risk of leakage is low, the colloidal ^{32}P solution is safely used[23]. For direct intratumoral injection on the other hand, the retention of colloidal ^{32}P radioactivity at the site of a solid tumor requires the co-administration of macroaggregated albumin[27]. However, the risk of leakage from the injection site is still present due to intratumoral interstitial pressure[14].

There was only one report of intravascular injection of ^{32}P colloid in our literature review. Kim *et al*[28] administered colloidal ^{32}P *via* the portal vein to prevent growth of occult metastases in the liver. They concluded that the mentioned approach would be expected to prevent liver metastases of completely resected colorectal cancers. Other studies on radioactive phosphorus use phosphorus-32 glass microspheres (^{32}P-GMS) with grain sizes of 46-76 μm to reduce systemic toxicity[13]. Although transarterial administration of this compound has been used safely for hepatic primary or metastatic tumors[13,15,16], the main use for a radioactive pharmaceutical for this purpose is a ^{90}Y microsphere with a particle size of 20-35 μm[9]. There has also been an early report of ^{90}Y systemic leakage[29].

In terms of systemic toxicity, the used compound did not have a higher risk than ^{32}P-GMS or ^{90}Y microspheres. We can, however, raise an advantage for ^{32}P over ^{90}Y regarding our purpose. The half life of this radioactive element (14.28 d) provides a significantly longer period of irradiation than ^{90}Y with its half-life of 64 h[11,13]. Considering the 2 half-lives, there was almost 28 d of radiation for the optimal chemoradiation effect in the presence of chemotherapy drugs.

Another consideration is our chemotherapeutic mixture. Although there is no consensus on the best chemotherapeutic agent for TACE, doxorubicin is the most commonly used drug for the purpose[30]. The most commonly combined drug regimen for TACE, including cisplatin, doxorubicin, and mitomycin C[2,30] was used in this study. In combination with radiotherapy, however, we needed to find some supports and check if there were previous contraindications in the literature. Cisplatin is similar to other platinum-based agents that act as a radiosensitizer[31]. There was one clinical trial combining hepatic radioembolization with ^{90}Y and a systemic chemotherapy regimen containing the platinum-based agent, oxaliplatin[32]. Concerning doxorubicin, which is also a potent radiosensitizer[33], we found no previous usage for hepatic malignancies in combination with radiotherapy, although its co-administration has been used in other body parts[34-36]. Another study on nude mice for medullary thyroid cancer showed the combination of radioimmunotherapy and doxorubicin chemotherapy had synergistic therapeutic efficacy, which may be due to the radiosensitizing effect of doxorubicin[37]. Like doxorubicin, mitomycin C has also had concurrent administration with radiotherapy in several studies[38-40]. Therefore, there is no proven contraindication to applying radiotherapy along with this chemotherapeutic regimen. Moreover, it is expected that in the case of cisplatin and doxorubicin, which are radiosensitizers, the effect of therapy would be more effective than just the addition of TACE and radioembolization effects.

The mRECIST criteria were originally designed for hepatocellular carcinoma (HCC) and are based on the changes in the viable portion of hepatic lesions. Older methods of image-based response evaluation of solid tumors only assess the change in anatomic size of target lesions[18]. Measurements were either by the bilinear product approach (WHO criteria) or by single linear summation (RECIST criteria)[41]. As acknowledged before, relying solely on the changes in tumor size can be misleading[42]. Modified RECIST and a subjective percentage of necrosis criteria take tumor necrosis induced by treatment into account[18].

Studies which used ^{90}Y radioembolization for metastatic hepatic lesions from mixed sources generally relied on WHO and RECIST criteria to assess the treatment response (Table 3). Expanding the response rate to cases with complete or partial response, there were reports of 13% to 42.8% responsiveness with regard to WHO and RECIST criteria. Only Peynircioğlu *et al*[43] reported that all of their patients had at least a partial response in target lesions. Considering necrosis in combination with anatomic size, Miller *et al*[7] showed an increase in response rate from 19% to 50%. The studies on metastatic hepatic lesions using a chemotherapy regimen of doxorubicin, cisplatin, and mitomycin-c for TACE are summarized in Table 4. Only papers which reported an imaging-based response rate were included. WHO and RECIST criteria showed a response rate that differed from 8% to 60% in these studies. A paper by Artinyan *et al*[44] on mixed-source hepatic metastases showed a response rate of 14.8%.

Firusian *et al*[20] reported 5 cases of hepatic metastasis for which direct intratumoral colloidal ^{32}P injection led to three complete and two partial responses. No toxicity was encountered in these 5 patients and there were no alterations in hepatic function. In a study by Gao *et al*[13] on 60 patients with refractory solid tumors, including 25 cases of HCC and 5 cases of hepatic metastatic carcinoma, they administered ^{32}P-GMS *via* the hepatic artery for thirty-two cases. Among all 60 patients, 31 cases achieved complete response (51.7%), 25 cases partial response (41.7%) and 4 cases no effect. Most patients had post-procedural nausea and vomiting. There were also reports of discomfort or pain in the right upper abdominal quad-

Table 3 Studies on Yttrium-90 radioembolization for metastatic hepatic lesions from mixed sources

Study	Procedure	Agent	Absorbed dose or mean activity delivered[1]	Number of patients	Response criteria	Response measured at (months post treatment)	Response rate	Complications
Blanchard *et al*[49], 1989	Radioembolization	^{90}Y plastic microspheres	NA	15	WHO	NA	Partial response in 5 (33.3%), minimal response in 2 (13.3%)	Gastritis or gastric ulceration in 6 (in three this was proven to be due to unintended infusion of microspheres into the gastric circulation)
Andrews *et al*[50], 1994	Radioembolization	^{90}Y glass microspheres	150 Gy	24	WHO	2	Partial response in 5 (20.8%), minimal response in 4 (16.7%), stable disease in 7 (29.2%), progressive disease in 8 (33.3%)	Mild gastrointestinal symptoms in 4 (unrelated to treatment)
Miller *et al*[7], 2007	Radioembolization	^{90}Y glass microspheres	100-120 Gy	42	WHO	2.3[2]	Complete/partial response in 8 (19%), stable disease in 22 (52%), progressive disease in 23	Radiation cholecystitis in 10, liver edema in 18
					RECIST	3.9[2]	Complete/partial response in 10 (24%), stable disease in 21 (50%), progressive disease in 23	
					Necrosis	1[2]	Complete/partial response in 19 (45%)	
					Combined	1.1[2]	Complete/partial response in 21 (50%), stable disease in 11 (26%)	
Sato *et al*[8], 2008	Radioembolization	^{90}Y glass microspheres	112.8 Gy/ 1.83 GBq	137	WHO	1-3	Complete response (2.1%), partial response (40.7%)	Fatigue (56%), vague abdominal pain (26%), nausea (23%)
Lim *et al*[51], 2005	Radioembolization	^{90}Y resin microspheres	NA	46	RECIST	2	Partial response in 12 (27%), stable disease in 12 (27%), progressive disease in 19 (44%)	Between 2 and 8 wk of lethargy, anorexia, nausea and right upper quadrant pain in most patients, severe gastric/duodenal ulceration in 4 (8%), portal hypertension in 1, radiation hepatitis in 1
Yu *et al*[52], 2006	Radioembolization	^{90}Y resin microspheres	42 Gy	49	RECIST	NA	Response rate of 29%	Fatigue in 18 (37%), vague abdominal pain in 10 (20%), nausea/vomiting in 10 (20%), ascites and/or leg edema in 3 (6%)
Szyszko *et al*[53], 2007	Radioembolization	^{90}Y resin microspheres	1.9 GBq	21	RECIST	1-2	Partial response in 2 (13%), stable disease in 9 (60%), progressive disease in 4 (27%)	NA
Stuart *et al*[54], 2008	Radioembolization	^{90}Y resin microspheres	NA	30	RECIST	NA	Partial response or stable disease in 14 (47%)	Gastrointestinal ulceration in 1 (3%)
Kennedy *et al*[55], 2009	Radioembolization	^{90}Y resin microspheres	1.1 ± 0.6 GBq	502[3]	RECIST	3	Complete response in 23 (4.5%), partial response in 48 (9.5%), stable disease in 386 (76.8%), progressive disease in 45 (9%)	Fatigue and upper abdominal pain (29%), gastritis and overt gastric ulceration (2%), severe liver disease (4%)
Peynircioğlu *et al*[43], 2010	Radioembolization	90Y resin microspheres	1.24 GBq	10	RECIST	1-2	All patients had at least partial response of the target lesions	Post-procedural mild to moderate fatigue in all patients for 7 d, with mild to moderate fever and abdominal pain in some patients
Omed *et al*[56], 2010	Radioembolization	^{90}Y resin microspheres	NA	11	RECIST	NA	Partial response (20%), stable disease (50%), progressive disease (30%)	No major complications, 82% of patients experienced side-effects, mainly nausea, vomiting and abdominal pain
Cianni *et al*[57], 2010	Radioembolization	^{90}Y resin microspheres	1.64 Gbq	110	RECIST	2	Complete/partial response in 45, stable disease in 42, progressive disease in 23	Hepatic failure in 1, gastritis in 6, cholecystitis in 2

[1]The absorbed dose in Gy and/or the mean delivered activity in Gbq are provided with respect to their availability; [2]median; [3]the total number of patients in the study was 680, but the response evaluation criteria in solid tumor (RECIST) criteria were only available for 502 patients. ^{92}Y: Yttrium-90; WHO: World Health Organization; NA: Not available.

rant within 1 wk after treatment[13].

There are significant differences between lesion outcomes rated by the mRECIST and RECIST criteria in our series. In agreement with many other reports, in short-term follow-up the degree of necrosis is a major factor for response evaluation and a criteria lacking this factor may

Table 4 Studies on chemoembolization for metastatic hepatic lesions with cisplatin, doxorubicin and mitomycin

Study	Primary diagnosis	Procedure	Chemotherapeutic agents	Embolic material	Number of patients	Response criteria	Response measured at months treatment	Response rate	Complications
Diaco *et al*[58], 1995	Carcinoid tumor	Chemoembolization	Cisplatin, doxorubicin, mitomycin	NA	10	WHO	NA	Partial response (60%), stable disease (30%)	NA
Drougas *et al*[59], 1998	Carcinoid tumor	Chemoembolization	Doxorubicin (60 mg), cisplatin (100 mg), and mitomycin (30 mg)	Polyvinyl alcohol	13[1]	WHO	3	Partial response in 1 (8%), minimal response in 10 (77%), stable disease in 1 (8%), progressive disease in 1 (8%)	Nausea/vomiting in 100%, increased transaminases in 100%, pain in 100%, fever in 29%, myelosuppression in 29%, arterial thrombosis in 8%, dysrhythmia in 8%, mental status changes in 4%
Tellez *et al*[60], 1998	Colorectal carcinoma	Chemoembolization	Cisplatin, doxorubicin, mitomycin	Angiostat (a bovine collagen material)	27	Designed by authors[2]	NA	Radiological response in 17 of 27 patients (63%)	Fever in 83%, RUQ pain in 100%, nausea/vomiting in 83%, gastritis in 17%, lethargy in 60%
Buijs *et al*[45], 2007	Breast cancer	Chemoembolization	Doxorubicin (50 mg), cisplatin (100 mg), and mitomycin (10 mg) in a 1:1 mixture with iodized oil	300- to 500-μm embolic microspheres	14[3]	RECIST	1-2	No complete response, partial response in 7 lesions (26%)[6]	NA
Ruutiainen *et al*[61], 2007	Neuroendocrine tumor	Chemoembolization	Cisplatin, doxorubicin, mitomycin in a mixture with iodized oil	150- to 250-μm granular polyvinyl alcohol particles	44	RECIST	1	88% partial response/stable disease	High incidence of postembolization syndrome, severe pain in 3 sessions, severe nausea in 1 session, severe vomiting in 1 session, severe GGT/ALP elevation in 4 sessions, severe AST elevation in 1 session, severe ALT elevation in 1 session, severe infection in 1 session
Artinyan *et al*[44], 2008	Mixed	Chemoembolization	Doxorubicin (50 mg), mitomycin (10 mg), and cisplatin (150 mg)	Polyvinyl alcohol microspheres (300-700 μm)	61[4]	RECIST	At least 1	Partial response in 9 (14.8%), progressive disease in 3 (4.9%)	Bleeding in 2 patients (2%), renal failure in 6 patients (5%), hepatic failure in 7 patients (6%), infection in 3 patients (3%), mortality in 30 d in 7 patients (6%)
Buijs *et al*[48], 2008	Ocular melanoma	Chemoembolization	Doxorubicin (50 mg), cisplatin (100 mg), and mitomycin (10 mg) in a 1:1 mixture with iodized oil	300- to 500-μm embolic microspheres	6[5]	RECIST	1-2	No complete response, partial response in 8 lesions[6]	NA
Albert *et al*[62], 2011	Colorectal carcinoma	Chemoembolization	Cisplatin, doxorubicin, mitomycin in a mixture with ethiodized oil	Polyvinyl alcohol	95[6]	RECIST	NA	Partial response in 9 (14.8%), stable disease in 49 (80.3%), progressive disease in 3 (4.9%)	NA

[1]There were 15 patients at first, however one died before the follow up imaging and one patient's follow-up was out of state. Three patients only received hepatic artery embolization; [2]at least 75% decrease in the density of lesions consistent with necrosis or 25% decrease in the size of the lesions without the development of concomitant lesions; [3]twenty-seven lesions; [4]the total number of patients was 119, but for 61 patients the response evaluation criteria in solid tumors (RECIST) criteria were available; [5]twenty-one lesions, reporting by patient, all patients were considered non-responders to transcatheter arterial chemoembolization because the total tumor burden did not decrease by 30% in any given patient; [6]ninety-five of 141 treatment cycles were evaluable for response. The response rate is calculated per treatment cycle. NA: Not available; RUQ: Right upper quadrant; WHO: World Health Organization; GGT/ALP: Gamma-glutamyl transpeptidase/alkaline phosphatase; AST/ALT: Aspartate aminotransferase/alanine aminotransferase.

underestimate the effectiveness of the therapy[7,42,45-48]. There were differences in the results of mRECIST and necrosis percentage criteria for 3 patients. In these cases the change was in the anatomical size of lesions without a significant change in necrosis percentage. This finding shows that, in addition to its inherent flaw of being subjective, necrosis percentage cannot always reveal the real response. It seems that criteria that gather both anatomic sizes and the degree of necrosis (e.g., mRECIST) are more accurate. In 2 patients with newly appeared lesions (cases 12 and 13) after the treatment, these new lesions were in the lobe other than the one that underwent radiochemoembolization. These lesions could be new metastatic lesions or previously non-visible metastatic

foci in the non-treated lobe. For that reason, assessing the response by patient and not by lobe might have shown lower response rates in this study.

Our patients, like in most other studies on radioembolization and TACE, generally had constitutional and mild gastrointestinal symptoms after treatment sessions. There was no severe toxicity in the short-term follow-up of our series. Various degrees and severities of complications have been previously encountered after TACE and radioembolization procedures (Tables 3 and 4).

One limitation of the current study is the lack of control groups which only receive either TACE or radioembolization. Therefore, statistical comparison between the methods is impossible. However, many studies in this field perform new treatment strategies without a sample group and compare their result with the literature (Tables 3 and 4). Other weaknesses of this study were the short-term follow-up period and the mixed sources of hepatic metastases. The metastatic foci from different sources may have different responses to the administrated therapy. Longer than 2 mo period imaging results, long-term survival rates, time to progression (i.e., the post procedural elapsed time after which imaging studies show progressive disease), and also response rates in larger series of patients with single source of metastasis remain to be reported on the forthcoming steps after completion of regular long-term imaging evaluations and follow-ups.

In conclusion, this study introduces a new treatment approach for hepatic metastatic lesions on a rational basis. This was a combination of TACE and radioembolization which have been used individually for such lesions. It also shows that in short-term follow-ups this method is safe and effective, with a response rate of 65% with regards to the mRECIST criteria. Further studies are required to show the long-term effects and possible complications of this approach.

COMMENTS

Background

Liver metastases are a therapeutic challenge in oncological management. Surgery is frequently impossible due to disease extent and systemic chemotherapy usually fails. Transcatheter arterial chemoembolization and radioembolization are two separately used locoregional palliative therapies for metastatic hepatic lesions.

Research frontiers

Designing new treatments for patients with multiple or unresectable liver metastases is an interesting field of oncology. Transcatheter arterial administration of therapies is rapidly developing with the aid of diverse chemotherapeutic drugs and radiopharmaceuticals. Application of microsphere and particle technology is an evolving area of interventional oncology.

Innovations and breakthroughs

This study presents a novel image-guided combination of transcatheter arterial chemoembolization and radioembolization for advanced hepatic metastases, referred to as radiochemoembolization, which substantially intensifies local treatment effect. The authors used chromic phosphorus-32 molecules embedded in large particles with greater local effects and less systemic toxicities.

Applications

By showing the short-term effectiveness of the new combination method, the study opens the way for further research studies to assess the effects and complications of radiochemoembolization more thoroughly. After the release of results from the ongoing and upcoming studies by the authors and other scientists, an adjusted form of radiochemoembolization might play an important role in the treatment of hepatic metastases.

Terminology

Radiochemoembolization is a newly designed combination of radioembolization and transcatheter arterial chemoembolization, which are minimally invasive therapeutic approaches for administrating radioactive microspheres and chemotherapeutic drugs transarterially.

Peer review

This paper presents the short-term effectiveness of radiochemoembolization for selected hepatic metastases. This is the first report in which the novel combination of two commonly used effective options of treatment is described.

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