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Drug-eluting microspheres transarterial chemoembolization (DEM TACE) in patients with liver metastases. Pilot study

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Summary

Background: Only 10 to 20% of patients with hepatic metastases qualify for radical resection of their lesions.

The treatment issue among the rest of patients is a small clinical response to overall chemiotherapy and the frequent inability to treat patients with percutaneous thermoablation.

In the latter circumstance, parallel to the radical surgery, the reason is the size of the lesion or lack of access to it.

Material/Methods: 15 patients with hepatic metastases, who had been rejected from consideration of radical resection and thermoablation were subjected to chemoembolization of the proper hepatic artery branches. The procedure was performed using Hepasphere 50–100 μm impregnated with 100 mg of Doxorubicine. The primary tumor sites included: colorectal ca, cholangiocarcinoma, gastrinoma, gallbladder ca, pancreatic ca, GIST, lung ca, kidney ca, breast ca and larynx ca. The evolution of the disease was monitored by MRI scanning, which was performed after a mean time of 7.6 weeks from the chemoembolization.

During the study, we compared patients' quality of life (using Edmonton Evaluating System); length of hospital stay, chemoembolization side effects, and remission or progression of the disease by the RECIST 1.1 scale.

Results: 26.7% of patients had remission of the metastatic disease, 33.4% experienced stable desease and 26,7% suffered lesion progression. Two patients did not report to the MRI examination. Chemoembolzation's side effects were small and the quality of patients' live improved. Effectiveness depended on the overal condition of the patient, and the stage of the primary disease.

Conclusions: Chemoembolization is a minimally invasive, safe and possibly effective palliative procedure in patients with hepatic metastases. Further investigation on a larger group of patients is required and will be continued.

Key words: arterial chemoembolization • liver metastases • drug eluting microspheres • Hepasphere • TACE • liver tumor treatment

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Background

Advanced neoplastic disease with development of liver metastases leads to poor prognosis unless resection of the lesions is possible. Unfortunately, only 10 to 20% of patients with liver metastases are suitable candidates for radical resection and liver metastatic disease is considered as life limiting for the majority of patients. There are

Table 1. Patients enrolled in the study.

Patient number	Age	Primery tumor	Resection	Other metastases	Number of tumor nodules	Size of the largest lesion(mm)	Mean survival (weeks)
1	85	Ca laryngis	Yes	Yes	2	45	–
2	47	Gastrinoma	Yes	No	4	68	60
3	71	Gallbladder ca	Yes	Yes	1	82	10
4	74	Colorectal ca	Yes	Yes	5	34	33
5	62	Colorectal ca	Yes	No	5	30	51(alive)
6	57	Pancreatic ca	No	Yes	3	15	22
7	53	GIST	Partial	Yes	10	36	29
8	66	Lung ca microcellulare	No	No	1	21	37(alive)
9	65	Lung ca macrocellulare	Partial	No	1	25	–
10	84	Kidney ca clarocellulare	Yes	No	1	103	24(alive)
11	47	Cholangio-carcinoma	No	Yes	4	90	8 (alive)
12	60	Breast ca	Yes	Yes	3	100	8 (alive)
13	85	Colorectal ca	Yes	No	2	67	7 (alive)
14	60	Lung ca microcellulare	No	Yes	3	51	6 (alive)
15	57	Cholangio-carcinoma	No	No	5	113	6 (alive)

several different approaches to find the best treatment for these patients. The new treatment options extend patient survival, however remain palliative.

Transarterial chemoembolization (TACE) was introduced several years ago and allowed on direct application of chemotherapeutic drug to tumor vessels leading to periodical high concentration of the cytostatic agent within the lesion, later followed by embolization material [1]. This method brings partial response or stable disease in 61% to 75% of patients with different kinds of liver metastases [2–5]. Three years ago new method of chemoembolization using drug eluting microspheres (DEM TACE) was developed to extend local release of chemotherapeutic agent within the tumor in a sustained and controlled manner.

Hepasphere 50–100 μm (Biosphere Medical) – acrylic copolimer microspheres are able to absorb cytostatic drugs: doxorubicine, irinotecan, epirubicine and oxaliplatin [6–8]. After contact with either ionized environment, like 0.9%NaCl and blood or nonionic contrast media, microspheres expand in diameter to 200–400 μm and slowly release the cytostatic [9]. The advantage of DEM TACE is to maximize the concentration of chemotherapeutic agent within the tumor up to seven days, while it's concentration in systemic circulation is minimal. That reduces systemic effects and toxicity of cytostatic drugs and gives opportunity to patients with developed side reactions from systemic chemotherapy. Additionally, the malignancy arterial supply is restrained like in traditional embolization [6,10].

The purpose of this pilot study was to evaluate safety and efficacy of transcatheter arterial chemoembolization with drug-eluting microspheres

(DEM TACE) in patients with unresectable liver metastases.

Material and Methods

Fifteen patients with hepatic metastases, who had been rejected from radical resection or thermoablation were subjected to transcatheter arterial chemoembolization using drug-eluting microspheres with doxorubicine.

In this group there were 9 men and 6 women. Patients' age ranged from 47 to 85 (mean 64.9).

The primary tumor sites included: colorectal ca (3), cholangiocarcinoma (2), gastrinoma (1), gallbladder ca (1), pancreatic ca (1), GIST (1), lung ca

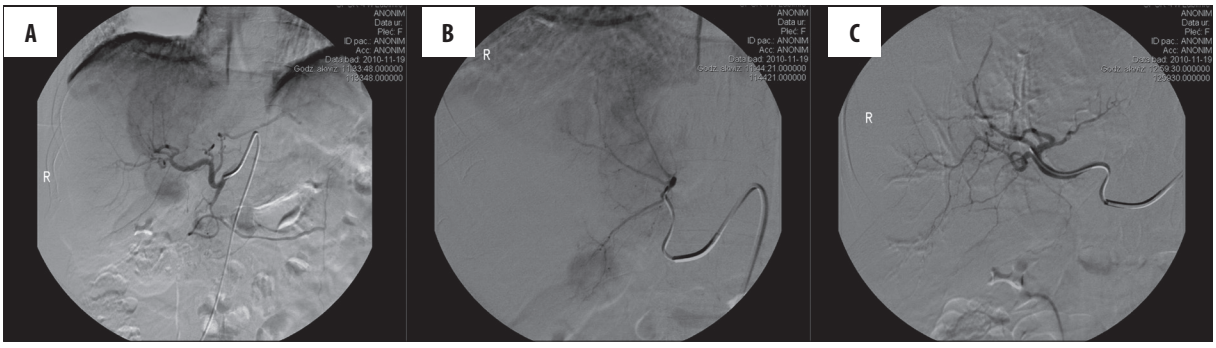

Figure 1. (**A**) Common hepatic artery angiography of the patient with cholangiocarcinoma, (**B**) selective catheterisation of the pathologic branch of right hepatic artery supplying the tumor, (**C**) after chemoembolization angiography without pathological vascularisation of the tumor.

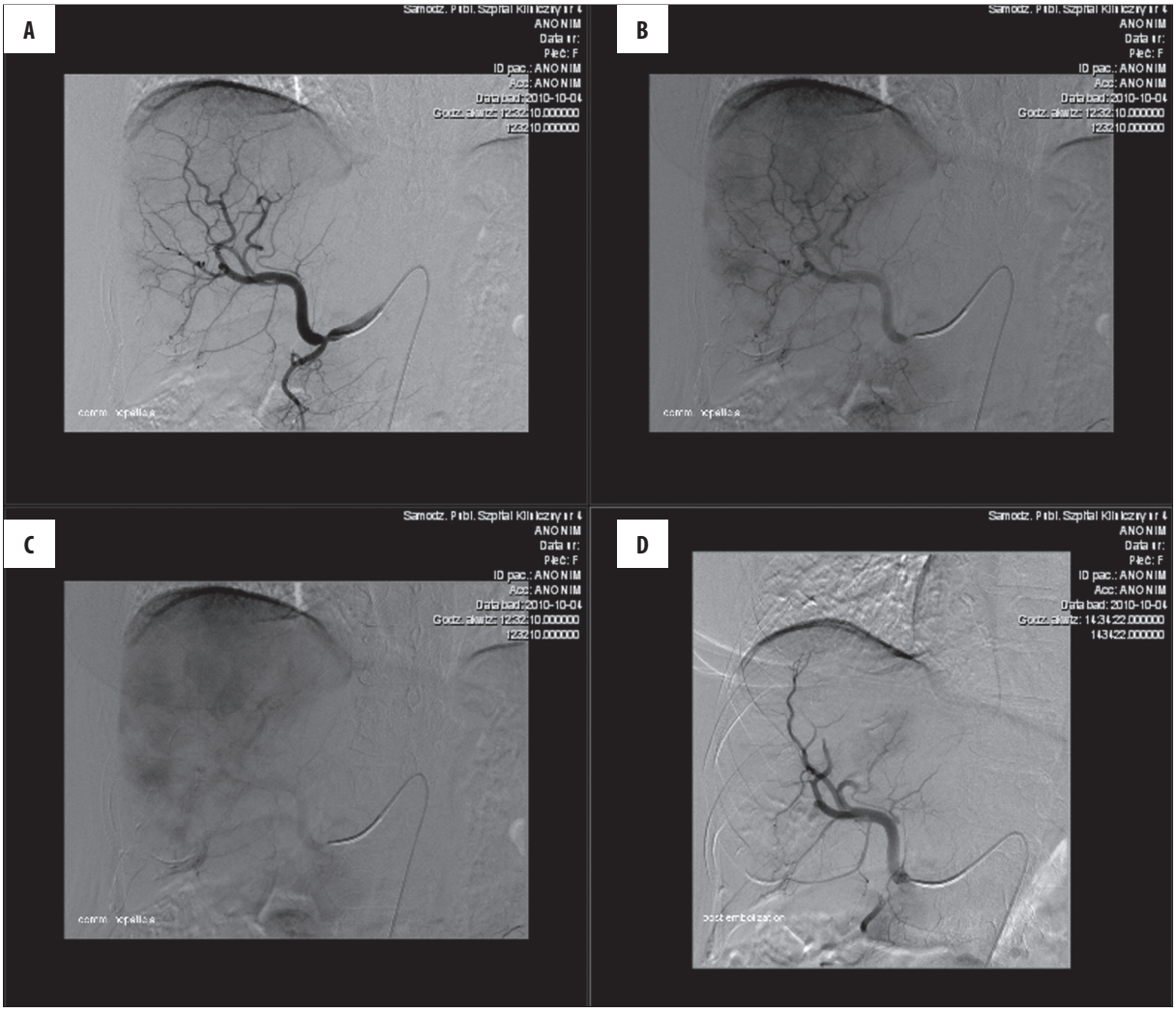

Figure 2. (**A–C**) Common hepatic artery angiography of the patient with breast cancer metastases, (**D**) after chemoembolization angiography with extraction of pathologic vascularization.

(microcellular and macrocellular ca) (3), renal ca (clear cell ca) (1), breast ca (1) and larynx ca (1). Eight out of fifteen patients had radical resection of the primary tumor and eight patients had extrahepatic metastases. All except two patients before or after DEM TACE were subjected to systemic chemotherapy. The mean diameter of the largest metastatic lesion was 57 mm (ranged from 15 to 113 mm) (Table 1).

Before DEM TACE angiography of coeliac trunk and superior mesenteric artery was performed to identify tumor arterial feeders and to check the patency of portal vein. The exclusion criteria were: portal vein thrombosis, liver volume replaced by tumor >70%, blood coagulation disturbances and high kreatinine level. The procedure of DEM TACE was performed using Hepasphere 50–100 μm impregnated with 100 mg of doxorubicine. Two vials of

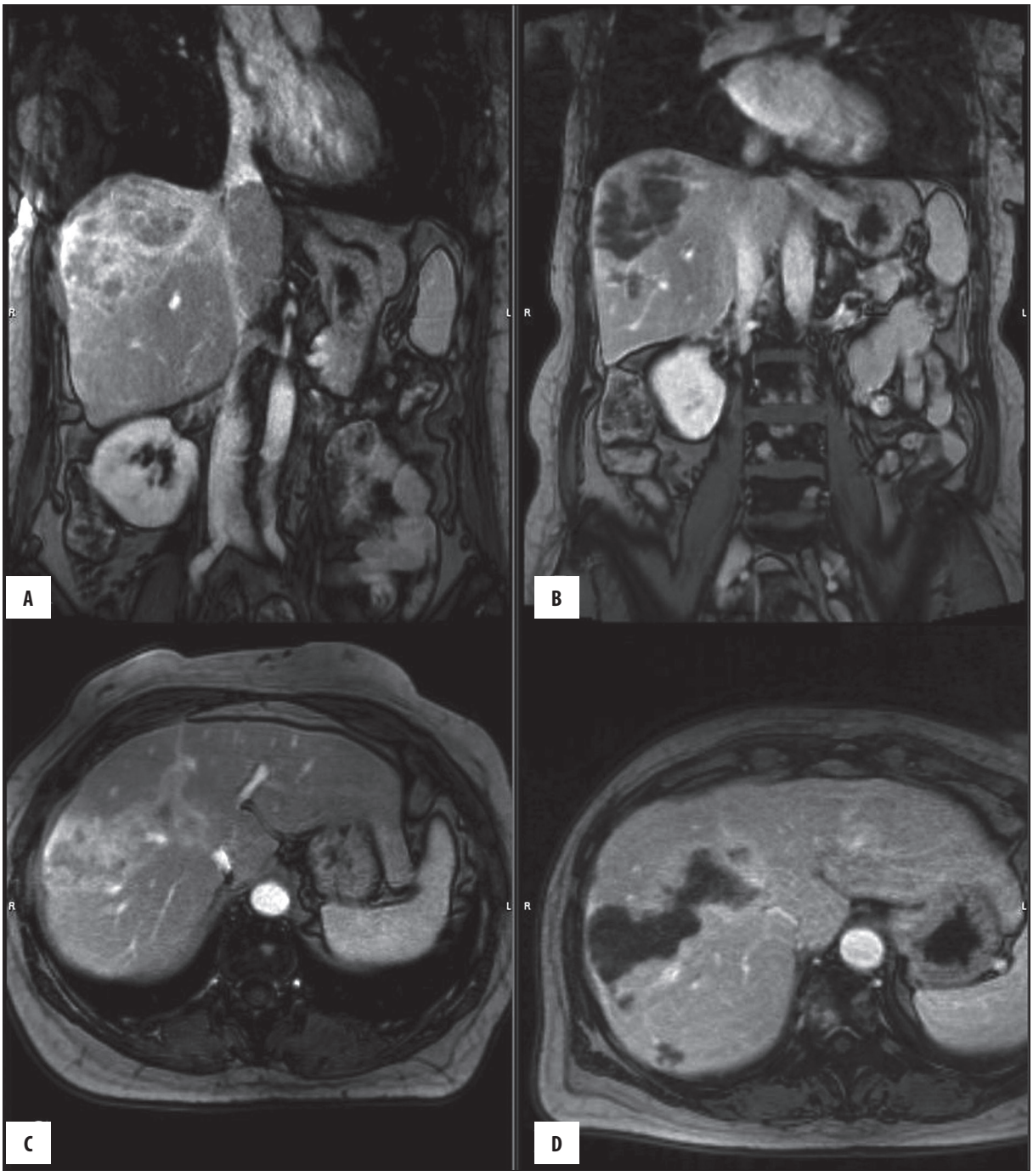

Figure 3. (**A,C**) Gadolinium contrast MRI done before the procedure in the same patient with breast cancer metastases as on Figure 2, (**B,D**) gadolinium contrast MRI control after DEM TACE, extraction of the vascularization of the tumor.

Hepasphere were prepared for each patient. 100 mg of doxorubicine solution was injected into two Hepasphere vials (50 mg/vial) and the whole content was aspirated to 10cc 6 syringes. Afterwards, the syringes were left for at least one hour to absorb the drug. After this time, microspheres were changing the colour to red. Before embolization excesive fluid was removed from syringes and contrast media was added in proportion 1:4. To selectively embolize target arteries and to perform TACE far from gastroduodenal, cystic and right gastric artery microcatheter Progreat (Terumo) was used (Figure 1)

Eleven patients were subjected to 1 chemoembolization, one patient had 2 interventions and three had 3 interventions. Repeated DEM TACE was performed if there was stable meatastatic disease, partial response or new lesions appeared after first approach.

Patients were administered one dose of cephalosporine (2^{nd} or 3^{rd} generation) before the procedure and saline with glucose (i.v. 1000 ml NaCl, 1000 ml 5% glucose) before and after the intervention. After the procedure 8mg of dexamethazone was administered and analgesic and antiemetic

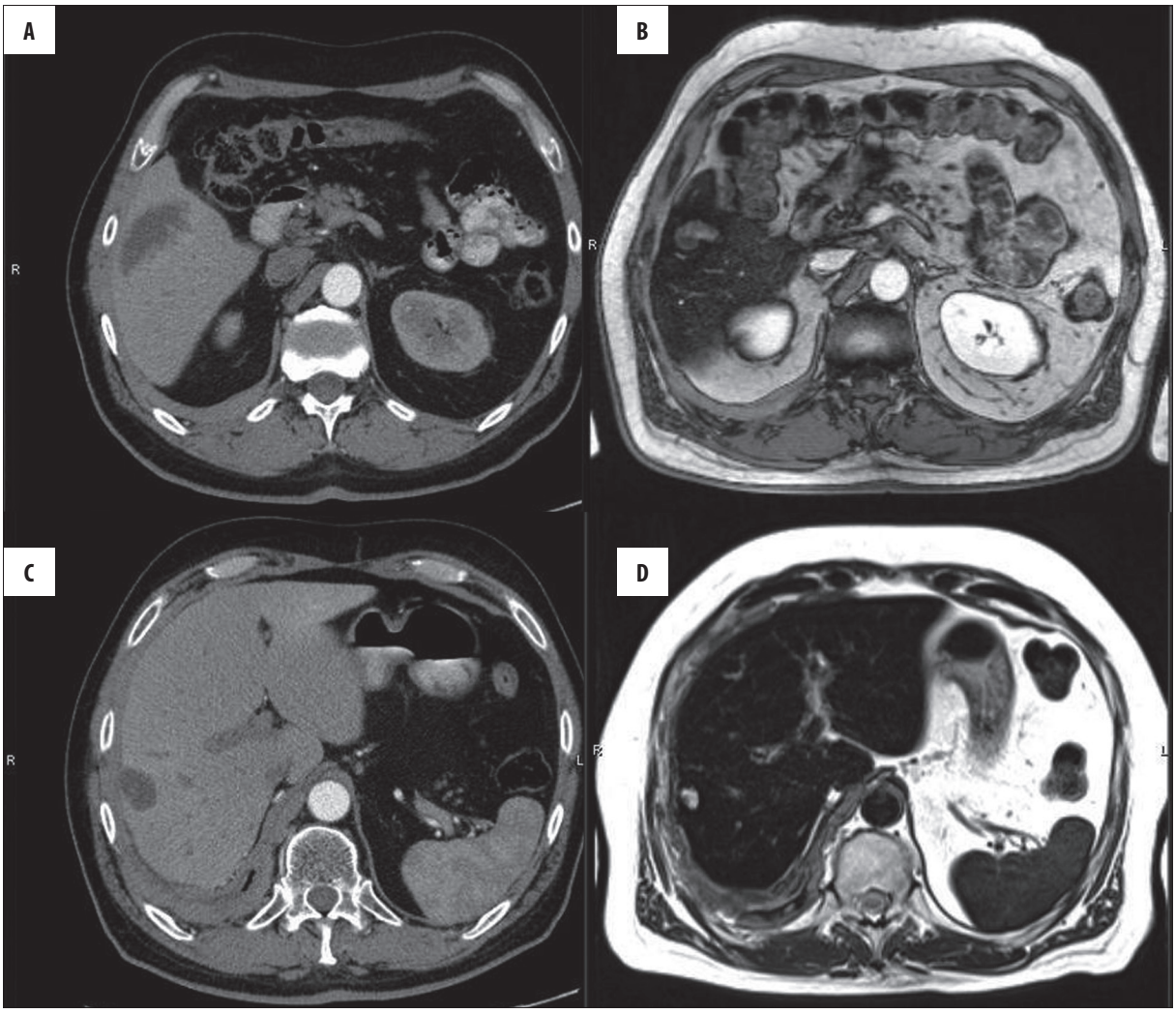

Figure 4. (**A,C**) CT of the patient with microcellular lung cancer metastases done before the procedure, (**B,D**) MRI control after 7 weeks from DEM TACE with regression of the lesions.

drugs if required. The tumor response was monitored by MRI (with paramagnetic contrast agent and DWI), which was performed after a mean time of 7.6 weeks from every DEM TACE (Figures 2, 3) The repeated chemoembolization was performed after the mean intervals of 12.4 weeks.

After treatment, patients' quality of life using Edmonton Symptom Assessment System (ESAS), length of the hospital stay, DEM TACE side effects, and remission or progression of the disease by the RECIST 1.1 scale were evaluated.

Results

Selective catheterization of the target arteries was successful in almost all cases (93.3%). One patient with kidney carcinoma clarocellurare had metastatic lesion supplied from left hepatic artery which was successfully embolized and from very small branches of common hepatic artery which selective catheterization was impossible. The volume of selectively injected Hepaspheres varied from one vial to two vials loaded with, respectively, 50 to 100mg of doxorubicine.

There were no severe complications after the procedure. The main adverse events registered in 80% of patients were: abdominal pain, nausea, vomiting and fever. The mean time of the procedure was 2 hours and the mean time of hospitalisation was 4,7 days.

The average patient's survival from the first DEM TACE was 5,8 months (ranged from 6 to 60 weeks) including patients who are currently alive. Two patients did not report to the MRI control. According to RECIST 1.1 criteria 26.7% of the patients had partial response (≥30% decrease in size of the lesion) and 33.4% had stable disease (≤30% decrease and ≤20% increase in size of the lesion) (Figure 4). 26,7% of patients suffered metastatic progression (≥20% increase in size of the target lesion). Tumors which well responded to the treatment were: gastrinoma, colorectal ca, microcellular lung ca, clear cell renal ca, breast ca and cholangiocarcinoma.

All patients declared better quality of life using ESAS completed during MRI control or before next embolization.

Discussion

Nowadays, there are several different approaches to find the best treatment for patients with unresectable metastatic liver malignancies: systemic chemotherapy, biological therapy, traditional transcatheter chemoembolization TACE and DEM TACE, Yttrium-90 radioembolization, radiofrequency ablationon RFA, microwave ablation and irreversible electroporation IRE. Nevertheless, non of them has been proved to be satisfactory on a large group of patients.

Drug eluting microspheres are widely used for hepatocellular carcinoma therapy and it is well documented that it extends the survival of patients [11–14]. The therapy issue in patients with liver metastatic disease in most cases is poor vascularization of the metastases. Although, it does not mean that they are not vascularized.

There are two kinds of drug-eluting microspheres available:
drug-eluting Beads (DEB), (Biocompatibles) and Hepasphere (Biosphere Medical). The fundamental difference between these two is that Hepasphere are in a dry form and expand their diameter in ionized solution. There are two sizes of Hepasphere 50–100 μm and 150–200 μm in a dry form which expand to, respectively, 200–400 μm and 600–800 μm.

There are few studies presenting the results of DEB TACE in patients with liver metastases from colorectal cancer, cholangiocarcinoma, ocular melanoma and one study concerning treatment using drug-eluting microspheres of metastatic disease from various primary tumors [15–17]. Moreover, traditional TACE was used also in the treatment of metastatic disease from breast cancer and neuroendocrine tumors [3,4].

Bilbao, et.al. conducted a study on kidney animal model comparing four different embolic particles in terms of postembolization patency, deformation, and potential for recanalization. The authors concluded that Hepashere were potent embolization material with distal location compared to others and after four weeks no recanalization was found [10].

Study presented at 12th World Congess on Gastrointestinal Cancer by Martin RC showed the results of combined systemic chemotherapy and hepatic doxorubicine or irinotecan TACE using drug eluting beads in patients with different kinds of liver metastases. Among 56 patients who were subjected to this combined treatment, 38% had colorectal metastatic disease, 14% – metastatic breast ca, 4,4% – cholangiocarcinoma and also: metastatic lung disease, melanoma, sarcoma, pancreatic, bladder, and other malignancies appeared. The response rates were 70% at 6 months and 75% at 12 months; which is higher then in our group of patients. The difference is most probably due to much lower percentage of patients (20%) with colorectal metastatic disease in our study. In Martin's investigation a half of patients suffered extrahepatic tumor disease. 42% experienced adverse effects after treatment and the most common post-embolization symptoms were: nausea, vomiting and pain. This is consistent with our observation. The authors concluded that treatment using doxorubicine or irinotecan drug eluting bead TACE is safe and effective for patients with unresectable hepatic metastatic disease if appropriate technique and treatment are provided.

Stambo GW, Berlet MH, Woeste T, et al. at The International Symposium On Endovascular Therapy (ISET, Hollywood, USA, 18–22 January 2009) presented the results of the investigation on influence and response of doxorubicine and irinotecan eluted beads on HCC and metastases from colorectal cancer. Patients with HCC received doxorubicine treatment, while among 25 patients with colorectal metastases 13 received doxorubicine nad 12 irinotecan drug-eluting beads. 82% of HCC group revealed no further development of the neoplasm, and 91% were still alive at 24 month period of follow up. In the colon ca doxorubicine group 77% responded well to the treatment, but only 8.3% showed good results in irinotecan colon cancer group.

To the contrary, Martin RC, et al. conducted a study of 55 patients with liver colorectal metastases treated with irinotecan drug-eluting beads (DEBIRI) resulted in good tumor response of 66% of patients at 6 months control and 75% at 12 months with overal survival of 19 months among these patients [15].

Aliberti C, et al. presented a study of 11 patients with unresectable intrahepatic cholangiocarcinoma treated with TACE using microspheres loaded with doxorubicine. All patients were alive at the time of the control after 13 months. Only one among 9 patients treated with systemic chemiotherapy was alive at the time of control with a median survival of 7 months [16].

The main limitation of our study is a very heterogenous group of patients, which decreased the power of our observations.

Secondly, there was also a small number of patients. However, we demonstrated that DEM TACE was antitumor effective. Further research is required to study the efficiency of DEM TACE on homogenous, regarding etiology, group of patients with liver metastatic disease.

Conclusions

This pilot study showed that drug eluting microspheres chemoembolization is safe and promising palliative treatment in advanced tumour disease with liver metastatic disease. Further study on bigger group of patients is needed and this investigation will be continued.

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