Intra-arterial chemoembolization with hepasphere 50–100 µm for patients with unresectable hepatocellular carcinoma: Initial experience in Egyptian Liver Hospital

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KEYWORDS
Hepatocellular carcinoma (HCC);
Transarterial chemoembolization (TACE);
Hepasphere 50–100 µm

Abstract  Objective: This study examined the efficacy of transarterial chemoembolization of unresectable hepatocellular carcinoma using hepasphere 50–100 µm.
Methods: A total number of 52 patients with radiologically documented HCC [Child–Pugh score A and B; 32 and 20 respectively] were embolized with hepasphere 50–100 µm. Forty-six patients were HCV positive and 6 patients were HBV positive. Local response of the tumor was evaluated radiologically after 1, 3, 6, 9 months and one year.
Results: TACE with hepasphere 50–100 µm was tolerated by all patients with no major complications. The total number of lesions in 52 patients was 67 lesions. Complete response was seen in 40 patients (76.9%), while residual lesions seen in 12 patients (23.1%). As regards complications, 48 patients (92.3%) developed post-embolization syndrome, 2 patients (3.8%) had isolated partial IVC thrombosis while 2 patients (3.8%) showed combined partial IVC thrombosis and partial thrombosis of posterior branch of right portal vein.
Conclusion: Hepasphere 50–100 µm is efficient for the treatment of hypervascular HCC. Further advances in drug-eluting beads including their size tailored to tumor anatomy may improve the results. Large series of patients, follow up for longer periods and comparison with conventional TACE and TACE with other DEB are needed.

1. Introduction
Primary and secondary hepatic malignancies comprise a significant oncological problem, with tremendous mortality and morbidity. Hepatocellular carcinoma (HCC) is the fifth most
common cancer and the third leading cause of cancer related mortality worldwide (1). Nearly 500,000 cases of HCC representing more than 5% of all cancers are diagnosed every year (2).

Hepatic resection is the initial treatment of choice for localized hepatic malignancies in patients without macrovascular invasion and with well-preserved hepatic function. Unfortunately, only a limited number of patients are candidates for hepatic resection. There are significant recurrence rates of HCC in patients after surgical resection of 50% at 3 years and 70% at 5 years. Although recent advances in surgical techniques and preoperative care have reduced morbidity and mortality related to liver resection, the postoperative complication rate remains as high as 42% in patients with cirrhosis (3).

For the patients with unresectable tumors, chemotherapy would be necessary to treat primary HCC or secondary metastases. Over the years, clinical studies have been carried out to broaden the treatment options. These include systemic chemotherapy, adjuvant therapy, and intra-arterial approaches (4). Palliative therapies via transarterial chemoembolization (TACE) are used for hepatic malignancies not amenable for surgical therapy (5–7).

The simplest form of transarterial chemoembolization (TACE) involves a two-step process, namely (1) intra-arterial administration of chemotherapeutic agents into the tumor-feeding artery via an intraarterially inserted catheter, and (2) selective embolization of the tumor-feeding artery (8,9).

More recently, advances have been made in the materials design, such that the embolic agent itself could be a drug carrier, which appears to be a more convenient and efficient procedure. Specifically these drug loaded carriers are directly injected intra-arterially for the treatment of liver cancer in one operation. Often this kind of drug carrier is referred to the drug-eluting beads (DEB), in the literature typical examples include, hepasphere and irinotecan-eluting beads (9).

Hepasphere (Biosphere Medical Rockland, MA, USA) is biocompatible hydrophilic (absorbent), nonresorbable and expandable microsphere. Hepasphere conformable and swell upon exposure to aqueous solution. It is made of sodium acrylate and vinyl alcohol copolymer. The dry microspheres are supplied in a range of sizes namely 30–60 μm, 50–100 μm, 100–150 μm and 150–200 μm (10).

The aim of this study is to examine the safety and efficacy of transarterial chemoembolization (TACE) of unresectable HCC using hepasphere 50–100 μm drug eluting beads.

2. Materials and methods

This study was a prospective study, started at July 2012 and completed at May 2014. All the patients gave informed consent, and the study was approved by the institutional Ethics Committee. It included 52 patients (44 male and 8 female patients) with radiologically documented HCC according to the American Association for study of liver disease (AASLD). Their ages ranged from 48 to 74 years (mean age was 58.15 years). Patients enrolled were Child–Pugh A in 32 patients (61.5%) and Child–Pugh B in 20 patients (38.5%). All the lesions were not suitable for heat ablation. Inclusion criteria were single lesion >5 cm and located at critical site either adjacent to blood vessel, GIT or subcapsular or multiple lesions which were more than 3 cm each. Liver functions prerequisites for enrollment included serum bilirubin below 2 mg/dl, albumin more than 3 g/dl and prothrombin concentration more than 60%. Exclusion criteria included previous history of hepatic resection for hepatic tumor, patients with previous history of local tumor ablation, either with radiofrequency ablation (RFA) or microwave ablation (MWA), patients with history of treatment with doxorubicin before, patients with arteriovenous shunt by CT scan, extrahepatic disease and patients with portal vein thrombosis.

2.1. Imaging

All images were performed using multidetector CT scan. Baseline triphasic CT scan and another CT scan 4 weeks after the first session of TACE were obtained, then triphasic CT scan 3 months, 6 months, 9 months and one year after the procedure. All the CT examinations were performed using Brilliance-16 scanner (Philips Medical system, Cleveland, USA), at three phases: arterial, portal and delayed venous phases.

2.2. Response assessment

Response assessment was evaluated according to (mRECIST) modified Response Evaluation Criteria In Solid Tumor. If there was still residual enhanced lesion in arterial phase, more than one centimeter in diameter with typical washout in the portal and venous phases, it was considered residual tumor or partial response. Totally hypovascular non-enhanced masses in the arterial phase were considered totally ablated lesions. Response assessment was completed with alpha fetoprotein (AFP) assessment one month after TACE with hepasphere compared to its baseline level, before TACE.

2.3. Technique of TACE

All angiographic techniques and TACE (67 sessions) for 52 patients were performed in well prepared angiographic and interventional room using MD Eleva machine (Philips Medical system, Cleveland, USA). All procedures were performed via the right transfemoral route. After shaving of the groin and sterilizing the skin with antisepsic, local anesthesia using 10 ml of Xylocaine ( Lidocaine hydrochloride 2%) was performed. Then puncture of the right common femoral artery using modified Seldinger technique and catherization of the abdominal aorta over, 0.35 Terumo guide wire, then catheterization of the hepatic artery whether arising from the celiac trunk or superior mesenteric artery using 5 F cobra head catheter were done for vascular mapping. Then catheterization of the tumor feeding artery whether selective or superselective using microcatheter 2.4 Terumo was done. Then after being sure of selective catherization of the tumor feeding artery, pre-embolization angiogram was obtained, followed by slow injection of doxorubicin-hepasphere mixture under fluoroscopy. During injection of the embolic agent multiple angiographic controls were obtained to avoid reflux of the embolic agent to other areas of the liver. If stasis of contrast was seen inside the tumor a waiting time of 3–5 min was done followed by injection of hepasphere in order to be sure from good distribution in the feeding artery as well as tumor bed. Then more
hepaspHERE was injected till back flow occurred and we stop injection. Then the catheter from microspheres was washed by saline followed by slight backward withdrawal of the catheter and post-embolization angiogram.

2.4. Preparation of hepaspHERE

Every vial of hepaspHERE 50–100 μm was loaded with two vials of doxorubicin powder 50 mg, per vial. Every vial of doxorubicin was prepared by the addition of 20 ml of normal saline, then 10 ml of saline-doxorubicin mixture was added to the vial of hepaspHERE and agitated frequently for 10 min (steps suggested by the manufacturer). Then the whole solutions of doxorubicin and hepaspHERE were added together in single 50 ml syringe and agitated periodically for one hour for complete ionic bonding of the doxorubicin. After the loading period all supernatant fluid was extracted and an equal quantity of nonionic contrast medium was added (11).

2.5. Patient medication

Medications just before and during chemoembolization with hepaspHERE included intravenous antibiotics, cefotax (cefotaxime) 750 mg, IV metronidazole/flagylle 500 mg, and IV analgesics as well as continuous dripping of IV fluids.

After the procedure patient was discharged on the same night from the hospital and was advised to take plenty of oral fluids, IV fluids 1000 ml daily for two days, antibiotics as cefotax 500 mg/8 h for 5 days and paracetamol 500 mg oral, only if there is pain or fevers. Patients were advised to visit the hospital at any time if there is swelling or bleeding at the site of puncture or if there is severe abdominal pain.

3. Results

This study included a total number of 52 patients. Their ages ranged from 48 to 74 years (mean age was 58.15 years). Thirty-two patients were Child–Pugh class A (61.5%), and 20 patients were Child–Pugh class B (38.5%). The size of lesions ranged from 2.5 cm, in diameter up to 8.5 cm in diameter with a mean size of 4.95 cm. Forty-six patients (88.5%) had liver cirrhosis due to chronic HCV, while 6 patients were HBV positive (11.5%). Patient demographics, main liver functions, size of the lesions, gender and virology were listed in Table 1.

The total number of lesions in 52 patients was 67 lesions. Forty-one patients (78.8%) had isolated single lesion (41 lesion), 7 patients (13.5%) had two lesions (14 lesions), and 4 patients (7.7%) had 3 lesions (12 lesion). Right lobe lesions were seen in 46 patients (88.5%), left lobe lesions were seen in 2 patients (3.8%) and lesions in both lobes were seen in 4 patients (7.7%). The total number of lesions and frequency of lesions in each lobe were listed in Table 2. Seven patients (13.5%) were previously treated with lipidol-loaded doxorubicin and had significant residual tumor, while 45 patients (86.5%) were treated from the start by hepaspHERE microsphere (Table 3). Total treatment of the lesions with no significant residual tumor was achieved in 40 patients (76.9%), while in 12 patients there was residual tumor that needs a second session (Table 4), so the total number of sessions in 52 patients was 67 sessions. Total response was noted in younger patient (56 ± 5 years) while partial response was patient in older patient (64 ± 8 years) (P value < 0.001) (Table 5). No significant changes were detected as regards serum albumin, serum bilirubin, prothrombin concentration, alphafetoprotein either in complete or partial response after procedure, also the size of lesion did not affect tumor response (P value was insignificant) (Table 5). Good response and adequate tumor treatment were seen in patients with single lesions, younger patients and patients with relatively good liver functions, particularly patients with serum albumin more than 3.2 g/dl. The level of

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Demographics, main liver functions and size of lesions in 52 patients.</th>
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<tbody>
<tr>
<td>Gender</td>
<td>44 Males (84.6%)</td>
</tr>
<tr>
<td></td>
<td>8 Females (15.4%)</td>
</tr>
<tr>
<td>Virology</td>
<td>+ HCV 46 (88.5%)</td>
</tr>
<tr>
<td></td>
<td>+ HBV 6 (11.5%)</td>
</tr>
<tr>
<td>Age</td>
<td>Mean ± SD (Minimum–maximum)</td>
</tr>
<tr>
<td></td>
<td>58.15 ± 7.24 year (48–74)</td>
</tr>
<tr>
<td>Albumin</td>
<td>3.2 ± 0.45 g/dl (2.6–4.2)</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>1.3 ± 0.36 mg/dl (0.9–2.1)</td>
</tr>
<tr>
<td>Prothrombin concentration</td>
<td>70.6 ± 8.7% (60–88)</td>
</tr>
<tr>
<td>Size of lesions</td>
<td>4.6 ± 1.5 cm (2.5–8.5 cm)</td>
</tr>
<tr>
<td>Alphafetoprotein before procedure</td>
<td>1154 ± 1143.3 ng/ dl</td>
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<tr>
<th>Table 2</th>
<th>Number of lesions in each liver lobe and both together in 52 patients.</th>
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<tbody>
<tr>
<td>Site of lesions</td>
<td>Number of lesions</td>
</tr>
<tr>
<td>Single</td>
<td>41 (78.8%)</td>
</tr>
<tr>
<td>Two</td>
<td>7 (13.5%)</td>
</tr>
<tr>
<td>Three</td>
<td>4 (7.7%)</td>
</tr>
<tr>
<td>Left lobe lesions</td>
<td>No</td>
</tr>
<tr>
<td>One</td>
<td>11 (21.2%)</td>
</tr>
<tr>
<td>Both lobes lesions</td>
<td>No</td>
</tr>
<tr>
<td>Yes</td>
<td>4 (7.7%)</td>
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<tr>
<th>Table 3</th>
<th>Number of lesions previously treated and not treated by TACE with lipidol.</th>
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<tbody>
<tr>
<td>Number of patients</td>
<td>(%)</td>
</tr>
<tr>
<td>No previous TACE with lipidol</td>
<td>45</td>
</tr>
<tr>
<td>Previous TACE with lipidol</td>
<td>7</td>
</tr>
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TACE = Transarterial chemoembolization.
serum bilirubin was of paramount. Poor response and high rates of residual tumor were seen in patients with more than one lesion, particularly patients with three lesions, this was listed in Table 6 (see Fig. 1).

3.1. AFP levels and liver enzymes

There was a significant decrease in the level of AFP after embolization in this study. It was elevated in all patients. Mean value of AFP before embolization was (1154 ± 1143 ng/ml) and after embolization mean value reaches about (32 ± 69.75 ng/ml). There was a significant decrease in the level of AFP after embolization denoting good response ($P < 0.001$) Fig. 2 and Tables 1 and 5 (see Figs. 3–7).

3.2. Complications

There were no major complications or procedure related mortality in this series. There was 0% mortality, one month, three months, 6 months and 9 months. Only one mortality was seen after 10 months as she developed liver dysfunction and ascites. The most common complication in this study was postembolization syndrome which was seen in 48 patients (92.3%) and it was treated conservatively. Isolated partial IVC thrombosis was seen in 2 patients (3.8%). Associated partial IVC thrombosis and partial thrombosis of the posterior division of portal vein were seen also in 2 patients (3.8%). It was due to the vicinity of the tumor to the IVC (Table 7). There was a mild insignificant increase in liver enzymes in 50 patients which was asymptomatic, while in two patients there was significant increase in liver enzymes (two and three folds increase respectively), one of them was treated conservatively and improved, while the second developed liver dysfunction, marked ascites, and died after 10 months.

3.3. Statistical analysis

Statistical analysis was carried out via Statistical package for social Science (SPSS) version 17 program on windows XP.

Qualitative data were represented in the form of number and frequency, while quantitative data were represented in the form of mean ± standard deviation (mean ± SD). Kolmogorov–Smirnov test was used to test normality of quantitative data. $\chi^2$, McNemar, Mann–Whitney U and Student’s tests were used to compare variables. Results were considered statistically significant if $p$ value is less than or equal 0.05.
4. Discussion

Conventional transcatheter arterial chemoembolization (TACE) and chemoembolization with drug-eluting beads (DEB-TACE) are increasingly being performed interchangeably in many institutions throughout the world. As both therapies continue to being tested in many phase II and III studies and in combination with other therapies, especially targeted agents, for the treatment of primary and metastatic cancer liver, it is imperative to review their current status and evaluate their impact on patient survival (12).

During the last few years drug-eluting beads have been used in the treatment of unresectable hepatocellular carcinoma. They proved to have good results (13–15,11). They proved to have less toxicity compared with lipidol-based conventional TACE (c-TACE) (16).

A number of studies with drug-eluting embolic materials have concluded that smaller calibers of microspheres are attractive because they achieve more distal embolization (17,18). The new drug-eluting bead hepasphere microsphere is a nontoxic and nonbiodegradable. The particle size is precisely calibrated in the dry state. The dry microspheres absorb fluid and swells within several minutes when exposed to aqueous-based media. The swollen particle is reported to be soft, and easily delivered through the majority of the currently available microcatheters. The dry microspheres are supplied in a range of sizes namely 50–100, 100–150 and 150–200 μm (9).

Hepasphere has been evaluated in an initial clinical study which comprised 50 patients in four centers (19). The microspheres were loaded either with doxorubicin (mean dose

Fig. 2 Box and whisker shows alphafetoprotein pre- and postembolization with significant $P$ value < 0.001.

Fig. 3 Right lobe HCC (segment 7) totally treated with no residual tumor. (A) Triphasic CT scan arterial phase shows a well defined fairly rounded mass with marked heterogenous enhancement. (B, C) Portal and delayed phases respectively show tumor washout. (D) Pre-embolization selective right hepatic angiography shows the vascular tumor with tumor blush. (E) Post-embolization angiography shows complete disappearance of the tumor vascularity with contrast staining of the mass. (F) Follow up noncontrast CT liver after one month shows central hyperdensity mostly intra-tumoral blood. (G–I) Follow up triphasic CT after one month (arterial, portal and delayed phases respectively) shows complete tumor treatment with no residual viable part. (J) Follow up triphasic CT arterial phase after one year shows no residual tumor tissue.
43.7, 18.7 mg) or with epirubicin (mean dose 41.7, 14.6 mg). It has been shown that TACE using hepaspheres is feasible, is well tolerated, has low complication rate and is associated with good tumor response (9).

This study was constructed mainly to study the efficacy and safety of TACE using the new microsphere hepasphere 50–100 μm in patients with unresectable HCC. The results of this study showed that hepasphere 50–100 μm is an effective embolic agent, achieving major tumor necrosis and high rates of response, where total ablation of the tumor with no residual lesions was seen in 40 patients (76.9%) and residual tumors were seen in 12 patients (23.1%). Hepasphere 30–60 μm were used in 45 patients with HCC to study the efficacy and safety of these beads (11). Nearly they have the same results, where they reported high rate of objective response about (68.9%). They concluded that hepasphere microsphere 30–60 μm is an effective and safe. Larger hepasphere achieved lower local response rates with 32% objective response rates for lesions 5 cm (19). Larger hepasphere microsphere achieved a response rate of 43.7% (20). Also it was obvious from this study that, good response and total ablation of the tumor were seen in patients with single lesion (41 patients), younger patients and patients with relatively good liver functions, particularly patients with serum albumin above 3.2 g/dl. In group statistics total ablation was seen in younger patients (46.2 years), while residual tumor was seen in older patients (64.0 years). Also total ablation was seen in patients with relatively higher serum albumin (3.21 g/dl) and residual lesions were seen in patients with relatively low serum albumin (3.15 g/dl). The level of serum bilirubin has no significance in our study as in patients with good response the mean serum bilirubin was 1.285 and in patients with residual tumor the mean serum bilirubin was 1.283. Also in patients with hepatitis B infection, the response was better as compared to the response in patients with chronic HCV infection.

Grosso et al. stated that repeated TACE procedures have been carried out without difficulties for the cases where complete tumor response is not achieved, and they used large hepasphere (19). We have similar results in this study as residual tumor after one session was seen in 12 patients where the procedure of TACE using hepasphere 50–100 μm was repeated safely in the 12 patients. Smaller size of hepasphere as 30–60 μm are new drug embolic agents that achieve homogenous, effective and distal embolization. This is proved by study done in pigs by Dinca et al. (21). The effective factor in good local response of hepasphere 30–60 μm is its higher flexibility in

Fig. 4  Left lobe HCC (segment 2) totally treated. (A) Triphasic CT scan arterial phase shows intensely enhanced left lobe mass. (B, C) Triphasic CT (portal an delayed phases respectively) shows complete washout of the tumor. (D) Super-selective left hepatic angiography (pre-embolization) shows well defined rounded left lobe markedly vascular mass. (E) Post-embolization angiography shows disappearance of the tumor vascularity. (F–H) Follow up triphasic CT scan (arterial, portal and delayed phases respectively) shows complete treatment of the tumor.
in comparison with other drug eluting agents that permit deeper penetration of the smaller vessels inside the tumor bed (22–24). Alpha feto protein level was used as an indicator for tumor response and it was significantly decreased. Its mean value before embolization was 1154 ± 1143 ng/ml, while after embolization, its mean value was significantly lowered reaching about 32 ± 69 ng/ml. According to Wilcoxon signed Ranks test, there was a significant decrease with \( P \) value <0.001. In the study of Malagari et al., the mean values of AFP levels before embolization (baseline) were 745.6 ± 27 ng/ml. Mean values after embolization were 219 ± 37 ng/ml. There was a statistically significant decrease in the levels of AFP after embolization indicating good response of tumor to embolization (\( P < 0.001 \)) (11).

The number and rates of complications in this study were relatively small. There was no procedure related mortality, also no mortality at 1 month, 3, 6 and 9 months. The only mortality in this study was after 10 months, as the patient had chronic HCV and liver cirrhosis on top (Child–Pugh class B), she had right lobe HCC, 5.2 cm, in diameter. After single session of TACE with hepasphere 50–100 \( \mu \)m she developed ascites and liver dysfunction, shortly after the procedure, she was treated conservatively, but after 10 months she developed liver cell failure and died. In the study of Grosso et al., they used hepasphere 50–100 \( \mu \)m, and they had relatively high rates of complications, where they had 3% periprocedural mortality (19). In the series of Malagari et al., they used hepasphere microsphere 30–60 \( \mu \)m, in the treatment of 45 patients with unresectable HCC, there was no procedure related mortality and also there was no 30 day mortality. In this series there was no liver abscess formation, no cholecystitis or hepatic artery damage (11).

Postembolization syndrome was seen in 48 patients (92.4%) and was treated conservatively. Partial thrombosis of the IVC was seen in 4 patients (7.6%), this may be due to close contact of the tumor with the IVC (Table 7). One of these patients experienced severe abdominal pain during the procedure, treated by strong analgesics. Our explanation for this is either due to extension of the tumor to the adjacent IVC or this extension to the IVC was present before the embolization and it passed unnoticed due to relatively poor quality of pre-embolization CT scan, partial IVC thrombosis as a complication of this technique was not reported before in the literature. Also partial thrombosis of the posterior branch portal vein was seen in 2 patients (3.8%) due to the vicinity of tumor to portal vein branch.

The limitations of this study are low number of patients (52) and it does not offer comparison remotely with conventional TACE (C-TACE), receiving doxorubicin loaded lipidol or comparison with TACE using other drug – eluting beads.

In summary, hepasphere 50–100 \( \mu \)m is a highly effective and safe embolic agent for HCC. Tumor necrosis is evident shortly after TACE. However, further beads (DEB), including their size, tailored to tumor anatomy may improve the results, also large series of patients, follow up for longer periods and comparison with C-TACE and TACE with other DEB are needed.
Fig. 6  A case of right lobe multi-focal hepatoma with previous history of TACE with lipidol and still no response. (A) Triphasic CT scan arterial phase shows two right lobe exophytic masses with intense enhancement and hyperdense traces of lipidol. (B, C) Portal and delayed phases show complete washout of both masses. (D) Superselective right hepatic angiogram shows the larger mass with marked vascularity and tumor blush. (E) Post-embolization angiogram shows complete disappearance of tumor vascularity. (F–H) Follow up triphasic study after one month (arterial, portal and delayed phases respectively) shows complete treatment of larger tumor, while the smaller one is still active showing tumor enhancement and washout. (I) Follow up triphasic CT arterial phase after one year shows complete ablation of larger tumor and still active smaller one.

Fig. 7  A case of right lobe HCC with IVC thrombus after TACE with hepsphere. (A) Follow up triphasic CT after one month portal phase shows complete tumor treatment and small partially occluding IVC thrombus. (B) Coronal reformatted image shows the treated tumor and adjacent IVC thrombus.
Table 7 Complications in 52 patients with HCC treated by hepsphere 50–100 µm.

<table>
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<tr>
<th>Number of patients</th>
<th>Percent</th>
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<tr>
<td>Postembolization syndrome</td>
<td>48</td>
</tr>
<tr>
<td>IVC thrombus</td>
<td>2</td>
</tr>
<tr>
<td>PV thrombus + IVC thrombus</td>
<td>2</td>
</tr>
<tr>
<td>Total number of cases</td>
<td>52</td>
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IVC = inferior vena cava. PV = portal vein.

Conflict of interest

None.

References