

Using Epirubicin-loaded DC Beads® for Superselective Embolisation of Liver Tumours – Initial Experiences

a report by

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Hepatocellular carcinoma (HCC) is one of the leading causes of death worldwide, with a peak incidence in Asian countries. Unfortunately, by the time of diagnosis the disease is often so far advanced that the only curative treatment so far – surgery – cannot be performed in the majority of patients. In the past, several treatment strategies were developed to improve the quality and duration of life of patients suffering from HCC. These strategies included radiofrequency (RFA) and ethanol (PAI) ablation,¹ laser interstitial tumour therapy (LIT),² percutaneous alcohol injection (PAI) and transarterial chemoembolisation (TACE).³⁻⁶ In contrast to ablative procedures such as RFA, PAI and LIT, TACE is mainly suitable for the treatment of primary liver tumours such as HCC, which are predominantly supplied by branches of the hepatic arteries. Thus, it is possible to achieve a high concentration of antiproliferative drugs within the tumour in contrast to conventional intravenous (IV) chemotherapy.^{7,8} Due to the dual blood supply of the liver, normal tissue is not altered too much by this therapeutic strategy. Numerous protocols have been published describing the pros and cons of different antiproliferative drugs (including cisplatin, doxorubicin, epirubicin and mitomycin C) either alone or in combination with lipiodol. Furthermore, the use of additional embolic agents such as polyvinyl alcohol (PVA) particles or Gelfoam has been advocated in order to induce local hypoxia.^{9,10} The major disadvantage of conventional TACE is that the intratumoral concentration of the drug vastly decreases by the time it is washed out.

Drug-eluting Beads

Recently, microspheres (DC Beads®, Biocompatibles, UK), a sulfonate modified, PVA-based embolisation agent that can be labelled in the angio

suite on site by the interventional radiologist with antineoplastic drugs such as doxorubicin or irinotecan, came onto the market.^{11,12} Using those particles provides two major advantages over conventional TACE. The drug charged to the particles is released to the surrounding tissue continuously in the first 10–12 days. This results not only in a higher overall intratumoral drug dose, but also in a longer period of drug application so that tumour cells re-entering the cell cycle can be treated over a longer period of time. However, due to the sustained drug release, the plasma levels of the charged drug are supposed to be lower than in conventional TACE, resulting in fewer systemic side effects. Furthermore, as the particles are available in different sizes (100–300µ, 300–500µ, 500–700µ and 700–900µ), effective arterial embolisation that results in local hypoxia can be achieved.

Drug-eluting Beads – Clinical Reports

The first reports describing the effectiveness of doxorubicin-releasing beads in the treatment of HCC have already been published. Varela et al.¹³ observed one- and two-year survival rates of 92 and 89.5%, respectively, in a small group of 27 patients suffering from HCC. In a group of 71 patients, Malagari et al. achieved even better survival rates of around 97% after one year and 91% after two years of follow-up.¹⁴ This is surprising, especially when bearing in mind that 44 patients of Malagari's patient group presented with a Child Pugh score B and 27 presented with a Child Pugh score A. Poon et al. demonstrated the effectiveness of arterial chemoembolisation of HCC using doxorubicin beads according to the modified Response Evaluation Criteria in Solid Tumors (RECIST). Of their patients, 70% experienced a partial or even complete response.¹⁵

Drug-eluting Beads Labelled with Epirubicin Instead of Doxorubicin

In our practice, we used epirubicin in combination with DC Beads instead of doxorubicin, which is technically no problem as both substances can be charged to DC beads. We also used epirubicin for historical reasons. We have been using epirubicin in combination with lipiodol in our standard TACE protocol, thus we decided that it would make sense to have a 'historical' control group when switching to a new therapeutic scheme.

Between July 2005 and December 2007 we treated a total of 66 patients with epirubicin-loaded drug-eluting beads. The majority of patients (83%) suffered from HCC (singular, multifocal or diffuse HCC), and the remaining from metastases (neuroendocrine tumour, cholangiocellular carcinoma, melanoma). Most of the patients received between one and three treatment cycles; however, some patients received more than three cycles. The standard dose given was 50mg epirubicin per 2ml vial of DC Beads. Sometimes, a double-dose strategy with up to 100mg of epirubicin



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French and German Radiological Societies, the European Radiological Society (ERS) and the Radiological Society of North America (RSNA).

was pursued, especially in patients suffering from secondary liver tumours or HCC with large feeding vessels that were easy to catheterise.

In contrast to other groups, who administered up to 150mg of doxorubicin per intervention, we did not charge the maximum dose possible to the beads (i.e. epirubicin 75mg per 2ml vial) because we were afraid of possible toxic local or systemic side effects. Furthermore, as mentioned above, we appreciated a standard-dose (i.e. epirubicin 50mg per embolisation) strategy. This strategy was based on one case we experienced when treating a patient with a large diffuse HCC predominantly affecting the right liver lobe (see 'Illustrated Case Study One'). In this patient, we followed a double-dose strategy and embolised a tumour mass, replacing more than two-thirds of the right liver lobe. The embolisation was successful and the patient was discharged from hospital two days later. However, the patient returned within a fortnight with right upper quadrant pain, fever and elevated liver enzymes. He recovered after 14 days in hospital; however, from then on he was treated with the standard dose of 50mg.

A microcatheter was then used for superselective embolisation in order to treat as much of the tumour as possible while sparing the 'healthy' parts of the liver.

The standard particle sizes we used were 100–300 and 300–500 μ , as we believed that it would be useful to deliver as many of the beads to the tumour tissue as possible. This could have been hampered by using large beads that occluded the tumour vessels at a more proximal level. In all cases, a contrast-enhanced computed tomography (CT) or magnetic resonance (MR) scan was obtained prior to the intervention. In cases where a CT scan was obtained, the pelvic vessels were also examined, thus giving the interventional radiologist an idea as to which material (sheath, etc.) to use. After catheterising the coeliac trunc or the superior mesenteric artery (SMA) (in case of a hepatomesenteric artery) with the help of a guiding catheter, an overview was obtained. A microcatheter was then used for superselective embolisation in order to treat as much of the tumour as possible while sparing the 'healthy' parts of the liver (see 'Illustrated Case Study Two'). One day after intervention, a contrast-enhanced CT was obtained in order to document the areas of the tumour that were embolised properly, as well as documenting possible side effects related to the intervention. Overall, the procedure was tolerated well by most of the patients, even though we gave neither antiemetics nor antibiotics in advance.

The six- and 12-month survival rates achieved for the patients suffering from HCC were 93 and 90%, respectively, which are in line with the results published by Varela et al. but below the survival rates achieved by Malagari et al. One reason for this might be that when we began using DC Beads we exclusively used the 300–500 μ Beads, which probably resulted in lower intratumoral drug doses. Furthermore, we treated nearly every patient, which means that even patients with large tumours replacing more than 50% of the liver were treated, as well as patients with partial portal vein thrombosis, extrahepatic tumour manifestations and

Figure 1a: Contrast-enhanced Computed Tomography Scan in the Arterial Phase Shows Multiple, Poorly Defined Tumour Nodules in the Right Liver Lobe

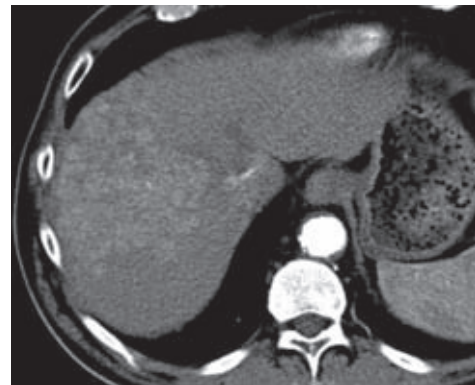


Figure 1b: Lower-level Contrast-enhanced Computed Tomography Scan Presents a Larger Tumour Nodule with Some Necrosis



Figure 1c: An Intra-arterial Angiography Presented Multiple Hypervascular Lesions in the Right Liver Lobe and at Least One Nodule in the Left Liver Lobe

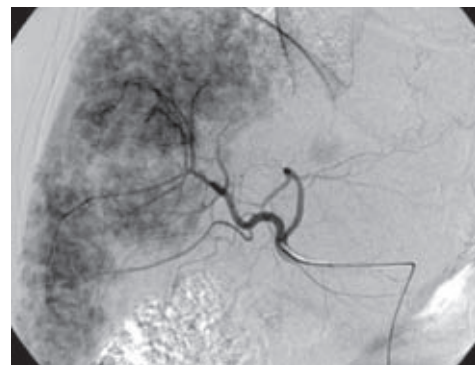


Figure 1d: Using a Microcatheter, Feeding Vessels Were Catheterised as Selectively as Possible



Figure 1e: After Applying 4ml DC Beads Loaded with 100mg of Epirubicin, Most of the Lesions Are Not Visible

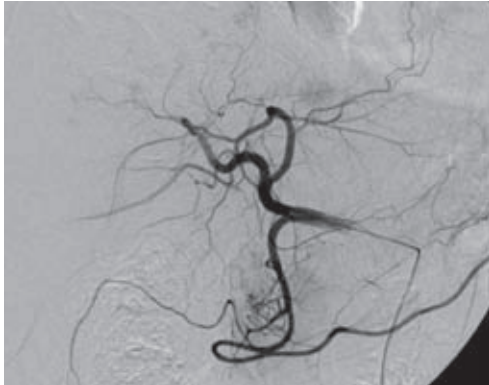
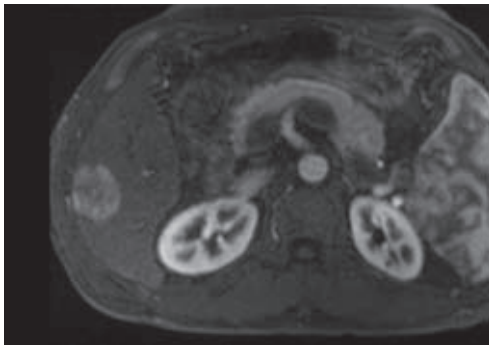


Figure 1f: A Control Computed Tomography Scan 24 Hours After Embolisation Shows the Nearly Complete Embolisation of the Tumour at this Level

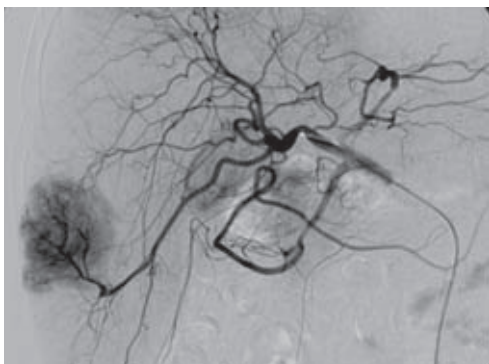


Figure 2a: T1-weighted Dynamic Liver Magnetic Resonance Scan



Scan shows a hypervascular liver lesion in the right lower lobe that was confirmed to be a well circumscribed hepatocellular carcinoma.

Figure 2b: Intra-arterial Angiography Confirmed the Hypervascular Nature of the Liver Lesion and Depicted the Presence of a Main Feeder Vessel



other life-limiting conditions. On the other hand, although the patient population was not well selected, we observed very few complications, and most of these were related to the intervention. We observed two cases of cholecystitis when using the small beads (100–300µ); in one patient a cholecystectomy had to be performed. Additionally, we documented a total of three abscesses (see ‘Illustrated Case Study Three’). In the case of the patient with the large, diffuse growing HCC mentioned above (see ‘Illustrated Case Study One’), we were lucky not to lose the patient after the first ‘double-dose’ intervention, as the laboratory findings temporarily suggested nearby liver failure.

Conclusion

Using epirubicin-loaded particles may be beneficial in the transarterial treatment of primary liver tumours compared with conventional TACE. In our mind, a superselective approach is mandatory in order to minimise the rate of possible complications.

Using epirubicin-loaded particles may be beneficial in the transarterial treatment of primary liver tumours compared with conventional transarterial chemoembolisation.

Illustrated Cases

Case Study One

A 66-year-old male patient suffering from active hepatitis C presented with an ill-defined, multifocal HCC with tumour nodules mainly in the right lobe. CT scans (see *Figures 1a* and *1b*) showed a mainly hypervascular, multinodular HCC with some necrosis (see *Figure 1b*). Intra-arterial angiography performed with a 4F C2 Cobra catheter placed in the main hepatic artery confirmed the diagnosis of a large multinodular lesion (see *Figure 1c*). By using a 2.7F microcatheter (Progreat®, Terumo, Japan) the feeding vessels of the tumour were catheterised (see *Figure 1d*) and the tumour was embolised with a total of 4ml DC Beads enriched with epirubicin 100mg. The control angiography confirmed the vascular denudation of the tumour nodules in the right hepatic lobe (see *Figure 1e*). The nodules in the left lobe were not treated at this session in order to avoid stressing liver function too much in one session. A control CT scan obtained one day after the embolisation confirmed the vascular denudation of the tumour (see *Figure 1f*). Air bubbles within the tumour are a regular finding following DC Bead embolisation; they are not indicative of an abscess.

Case Study Two

A 53-year-old male patient suffering from hepatitis-C-induced liver cirrhosis presented with a well circumscribed, hypervascular HCC nodule in the right liver lobe in liver MR (see *Figure 2a*). Intra-arterial angiography using a 4F C2 Cobra catheter (see *Figure 2b*) confirmed the presence of a hypervascular lesion in the right liver lobe. After applying 2ml DC Beads loaded with epirubicin 50mg to the tumour and the surrounding tissue using a 2.7F microcatheter system (Progreat, Terumo, Japan), the tumour did not opacify any more (see *Figure 2c*). A control CT scan obtained one day after TACE confirmed the embolisation of the tumour. As in Case



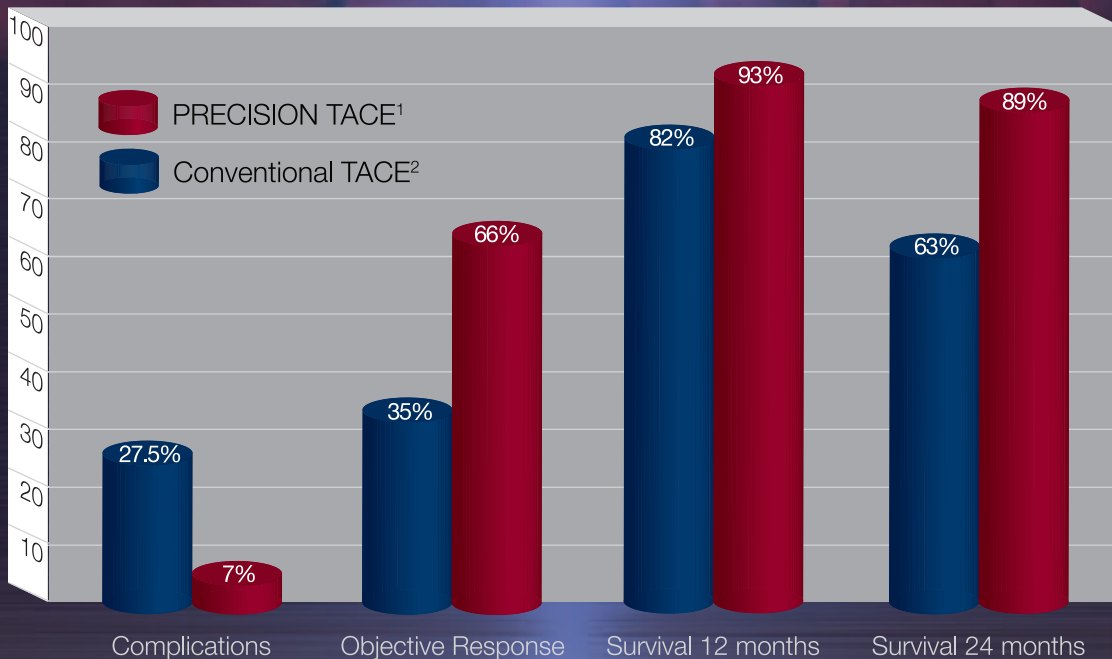
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“ The 1- and 2- year survival is 92.5% and 88.9%, respectively, with a mean follow-up of 27.6 months.¹ ”



“ None of the patients presented alopecia, bone marrow toxicity, dyspnea or pulmonary embolism.¹ ”

“ Chemoembolisation using DEBs is a safe and effective procedure with a favourable pharmacokinetic profile.¹ ”

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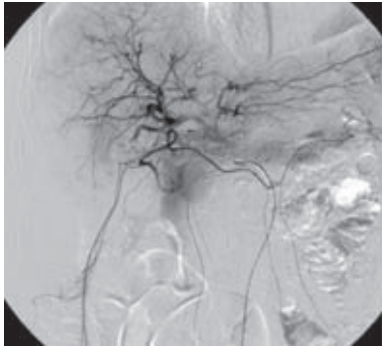
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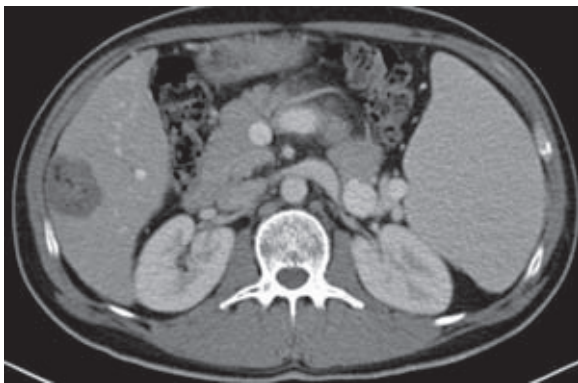


Figure 2c: After Applying the Epirubicin-enriched Particles to the Hepatocellular Carcinomas, the Tumour Is Markedly Devascularised



As embolisation was performed using a microcatheter system, the remaining parts of the liver are well arterialised.

Figure 2d: A Control Computed Tomography Scan One Day After Embolisation Confirms the Tumour to Be Devascularised



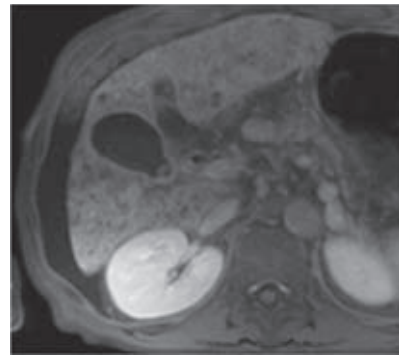
Note the air bubbles inside the tumour, which are due to our method of particle resuspension.

One, air bubbles within the tumour are regular findings following embolisation with DC Beads at our institution because the particles are suspended for a second time prior to embolisation. They do not represent an infectious complication (see *Figure 2d*).

Case Study Three

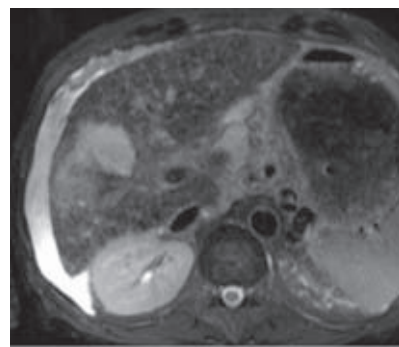
A 58-year-old male patient presented suffering from a diffusely growing HCC predominantly in the right liver lobe (see *Figure 3a*). After three cycles of DC Bead embolisation (each with 2ml of 300–500µ DC Beads enriched with epirubicin 50mg), the patient developed a biliary abscess close to the gall bladder (see *Figures 3b* and *3c*). The abscess was drained percutaneously, and the patient was fine. ■

Figure 3a: CE T1w Flash FS Status Prior to Transarterial Chemoembolisation



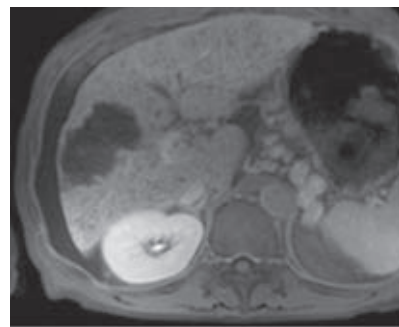
Note the irregular nodules close to the gallbladder.

Figure 3b: T2w TSE FS Status After Three Interventions



Close to the gallbladder there is an area of increased signal intensity in the T2-weighted sequence.

Figure 3c: CE T1w Flash FS Status After Three Interventions



Close to the gallbladder there is an area of low signal intensity comparable to the signal of the gallbladder lumen. Puncture of this area revealed a biliary abscess. CE T1w Flash FS describes the sequence used for magnetic resonance imaging: CE = contrast-enhanced; T1w = T1-weighted; Flash = the gradient echo (GRE) sequence from Siemens; FS = fat suppression.

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