

# Drug-eluting beads: a new opportunity in the treatment of hepatocellular carcinoma

**Key words:** Transarterial chemoembolization (TACE); hepatocellular carcinoma (HCC)

## Katerina Malagari

Associate Professor of Radiology,  
University of Athens, Greece

Address for correspondence:

Dr Katerina Malagari, MD  
2<sup>nd</sup> Department of Radiology  
University of Athens, 19 Monis Kyccou  
15669 Papagou, Athens, Greece  
Tel/Fax: +30-210-651-0340  
Email: kmalag@acn.gr

### Abstract

Drug-eluting beads represent a new technology in selective locoregional treatment. Doxorubicin-eluting beads have been tested *in vitro* and *in vivo* and the first results of clinical series are being released. The safety and efficacy of doxorubicin-loaded beads in the treatment of hepatocellular carcinoma are discussed in detail in this review.

### Introduction

Transarterial chemoembolization (TACE) is the most widely used treatment for hepatocellular carcinoma in non-surgical patients not suitable for radiofrequency ablation. There is no fixed or standard procedure for TACE, but the common denominator is the selective administration of a chemotherapeutic agent in an emulsion with iodized oil, followed by the injection of an embolizing agent into the feeding vessels of the tumour.<sup>1</sup> The procedure aims to induce ischaemic necrosis of the tumour and cell death by the local effect of the chemotherapeutic agent.

TACE variables include the choice of embolizing agent, chemotherapeutic agent(s) and embolization procedure. TACE is a technique widely used in the past 25 years, interest in which has recently increased after landmark studies were reported demonstrating a significant benefit for TACE over systemic chemotherapy or symptomatic supportive treatment.<sup>2-5</sup>

DC Bead™ (Biocompatibles International plc, Surrey, UK) has properties that allow a one-step procedure and assist in the standardisation of TACE. The pharmacokinetics and the antitumour effects of this new treatment are described in this paper.

### DC Bead description

DC Bead is a soft deformable device of spherical shape composed of a polyvinyl alcohol (PVA) and a hydrophilic monomer known as AMPS (2-acrylamido-2-methylpropane sulphonic acid) capable of being loaded with anthracycline drugs such as doxorubicin.<sup>6,7</sup> The microspheres are stored in a phosphate packing solution. During preparation,

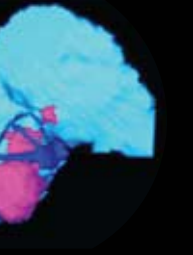
the beads initially increase in diameter with the admixture of water for injection and subsequently shrink again on loading with doxorubicin. Diameter changes are more pronounced with larger beads.<sup>7</sup>

### Elution kinetics

The ideal TACE should result in high levels of doxorubicin in the tumour with low plasma levels to reduce systemic toxicity. Conventional TACE pharmacokinetic studies have shown that plasma concentrations are lower than those observed with systemic chemotherapy and even lower when the agent is administered with lipiodol.<sup>8</sup> However, a significant fluctuation in plasma doxorubicin levels is observed. Johnson *et al.* showed that plasma levels of doxorubicin were identical if the drug is administered alone or in an emulsion with iodized oil.<sup>9</sup>

From a pharmacokinetic standpoint, controlled drug elution with DC Bead occurs only within the tumour and in a gradual fashion since doxorubicin is contained within the beads. Doxorubicin loss on bead suspension and contrast agent mixture is about 0.2%, minimizing the systemic release of doxorubicin and hence the side-effects seen with conventional TACE.<sup>7</sup> In this respect, DC Bead presents an opportunity to standardise and improve TACE. Initial *in vivo* studies in a rabbit Vx-2 model showed that, at concentrations per liver weight planned for clinical trials, the concentration of doxorubicin in the peripheral blood was low and that the fraction of non-viable tumour was higher compared with intra-arterial injection.<sup>10</sup> Additionally, the systemic plasma concentration of doxorubicin was significantly lower than when injected intra-arterially without the DC Bead.<sup>10</sup> From a clinical viewpoint, the first published human study, by Varela *et al.*, showed a 2-log reduction in plasma doxorubicin for the loaded beads compared with conventional TACE.<sup>11</sup>

The rate of elution of doxorubicin follows the Higushi equation and depends on the osmolality of the tumour and the size of the injected beads (the larger the beads, the slower the local release).<sup>7</sup>



**Katerina Malagari** is Associate Professor of Radiology at the University of Athens, Greece. She is part of a research team for the National Referral Center for Liver Diseases and Hepatocellular Carcinoma and a co-investigator in the Precision V multicentre study, a randomised trial comparing doxorubicin-eluting beads with conventional chemoembolization in the treatment of HCC. She has contributed several scientific papers and abstracts to international peer-reviewed journals.

In a study by Lewis *et al.* in Yucatan pigs, doxorubicin peak concentrations were 15 times higher in animals treated with smaller beads.<sup>12</sup>

Other embolizing agents such as gelatine-coated tris-acryl embospheres, PVA or Bead Block™ (Biocompatibles International plc, Surrey, UK), are incapable of being loaded with or transferring doxorubicin molecules and, further, can be unstable: when lipiodol is added to the loaded bead suspension all the doxorubicin may be lost in under 4 hours.<sup>12,13</sup>

### Doxorubicin loading range

Overall, the extent of loading with doxorubicin depends on the osmolality of the bead suspension.<sup>7</sup> The maximum loading capacity of the beads with doxorubicin reaches levels as high as 45 mg/ml of hydrated beads (irrespective of the size of the beads) while still maintaining the capability for controlled local release. The recommended dose range, suggested by the Precision Study,<sup>8</sup> is 25–37.5 mg of doxorubicin per ml of hydrated beads (100–150 mg per patient). These concentrations can be achieved by the preparation of 6 ml of beads with 25 mg/ml of hydrated beads or 4 ml of beads with 37.5 mg of hydrated beads (total 150 mg/patient) or 4 ml of beads with 25 mg/ml of hydrated beads (total 100 mg/patient). This range achieves doses of 50–75 mg/m<sup>2</sup>, which are considered safe treatment levels. The maximum recommended lifetime dose of doxorubicin is 450 mg/m<sup>2</sup> to avoid cardiac toxicity.<sup>14</sup>

### Choice of beads

As a general rule, the choice of bead diameter depends on the size and vascularity of the target lesion. The elution kinetics show that larger beads release doxorubicin more slowly than smaller beads.<sup>7</sup> However, small diameters can be more harmful to the adjacent liver tissue, and a versatile combination of bead diameters for each patient is needed. It has to be noted that larger diameters require longer loading times compared with small diameters.<sup>7</sup>

### Mechanisms of action: antitumoural effect

The induction of tumour ischaemia is an essential mechanism in TACE, whether conventional or with DC Bead. The concept is based on the preferential arterial flow to the tumour compared with the non-malignant liver tissue.<sup>15</sup> Both treatments aim to obliterate the tumour vasculature while preserving afferent arterial branches. Selective or superselective administration of the embolizing agent increases the local ischaemia and preserves adjacent non-malignant liver tissue.

In conventional TACE the effect of ischaemia is augmented by lipiodol, which temporarily obliterates the portal venules and further enhances ischaemia.<sup>6</sup> DC Bead enables a more reproducible procedure since the chemotherapeutic agent is contained within the embolizing bead, the chemical structure of which ensures a local and sustained delivery within the tumour. The toxic effect of doxorubicin is augmented with ischaemia induced by DC Bead that block the lumen of the neoplastic vessels.

Conventional TACE pharmacokinetic studies have shown that the doxorubicin half-life in tumourous liver is two or three times longer, compared with intra-arterial administration,<sup>8</sup> while the total dwell time of the chemotherapeutic agent in the tumour may be up to 1 month after TACE.<sup>17,18</sup> In addition, TACE achieves local drug concentrations at least twice the levels achieved by systemic chemotherapy; Kanematsu *et al.* showed a nine-fold increase in retention of the chemotherapeutic agent within the tumour, compared with adjacent non-malignant liver tissue.<sup>16</sup> The length of dwell time and the increased concentrations of the chemotherapeutic within the tumour augment the effect of tumour ischaemia induced by the embolizing agent.<sup>19</sup> However, the washout from the tumour is, to a certain extent, unpredictable while the mechanical obstruction of the neovascularity varies according to the nature and size of the embolizing agent.

By contrast, with doxorubicin-loaded DC Bead, one sole agent (the loaded bead) with defined characteristics simultaneously induces ischaemia and releases doxorubicin locally within the tumour. Further, the procedure can be performed in a standardised manner. Tumour cell ischaemia causes tumour cell membrane damage, resulting in intracellular retention of the chemotherapeutic drug. Increased retention and sustained release of doxorubicin after embolization with loaded DC Bead has been demonstrated by staining and coloration techniques in Yucatan pigs 28 and 90 days after liver embolization. Results showed that the local level of doxorubicin was sustained for 90 days post embolization,<sup>12</sup> an observation supported in previous *in vitro* studies and in rabbit (Vx-2) models showing half-lives of doxorubicin release between 60 and 100 days.<sup>10</sup> In the Vx-2 rabbit model, Hong *et al.* found that intratumour doxorubicin levels at 72 hours after embolization were about 400% higher than after conventional TACE.<sup>10</sup>

## Drug-eluting beads: a new opportunity in the treatment of hepatocellular carcinoma *continued*

Katerina Malagari

Tumour necrosis was greatest at 7–14 days after treatment and, in this period, almost all cells were damaged or necrotic, while the plasma concentration of doxorubicin was minimal.<sup>9</sup> Comparing these results with necrosis induced in controls through intra-arterial injection of doxorubicin followed by embolization with unloaded DC Bead, there was a statistically significant advantage for the loaded beads.<sup>10</sup>

Histologically, the results observed in animals embolized with doxorubicin-loaded beads have been shown to depend on the size of the beads.<sup>7</sup> Doxorubicin-loaded beads of diameters of 100–300 µm are shown to inflict widespread pan-necrosis of the target and adjacent hepatic tissue, with notable degrees of vasculopathy, neutrophilic inflammation, moderate portal fibrosis and arteriovenous and biliary hyperplasia. The patterns of necrosis in this group tend to radiate outwards centred on clusters of DC Bead, with extensive liquefactive and coagulative necrosis suggesting both ischaemic and toxic causes of cell death. With loaded beads of larger diameters (700–900 µm), necrosis has been shown to be less extensive compared with the smaller doxorubicin-loaded beads, and not radiating outwards.

With non-drug-loaded beads of 100–300 µm (inert), changes were shown to represent mostly non-necrotic vasculopathy without hepatic necrosis.<sup>12</sup> These findings are indicative of the added value of doxorubicin. However, randomized studies are needed to clearly demonstrate the benefit of loaded beads over inert embolization with beads alone.<sup>20,21</sup> The large extent of the necrosis in 100–300 µm loaded beads has been attributed to damage caused by the combination of the small size of the beads (smaller beads lodge more centrally and occlude collateral circulation) and the local actions of doxorubicin.

The induced cellular necrosis further increases the diffusion of doxorubicin that is not carried away by the collateral circulation and is not metabolized by destroyed liver cells.<sup>12,22</sup>

### Clinical application: embolization procedure

The inclusion–exclusion criteria for DC Bead TACE are the same as for conventional TACE.<sup>11</sup> Embolization procedures in the clinical series included selective and superselective embolization. One practical difference with the procedure compared with conventional TACE is that no lipiodol is used with DC Bead. Therefore, there is no morphologic evaluation of the distribution of the preparation within the tumour, as there is with TACE using lipiodol. However, the absence of lipiodol allows a better depiction of the residual tumour or of local recurrence.

### Results of conventional TACE versus DC Bead

Comparison of various series of TACE is not easy because of the variation in different techniques and the heterogeneity of patient and tumour samples. Additionally, there is the difficulty that in some studies sequential embolization is adopted, while in other studies disease progression is the indication to repeat the treatment.

In the first clinical studies of DC Bead, survival was not the primary aim due to the short follow-up time of this new treatment scheme. Apart from survival, these studies also report tumour responses that correlate well with survival rates.<sup>3–5</sup> Varela *et al.*, in the first human trial with doxorubicin-loaded beads, studied 27 patients with cirrhosis-related HCC and observed a response rate of 75% (66.6% on intention-to-treat), while survival rates at 1 and 2 years were 92.5% and 88.9%, respectively.<sup>11</sup>

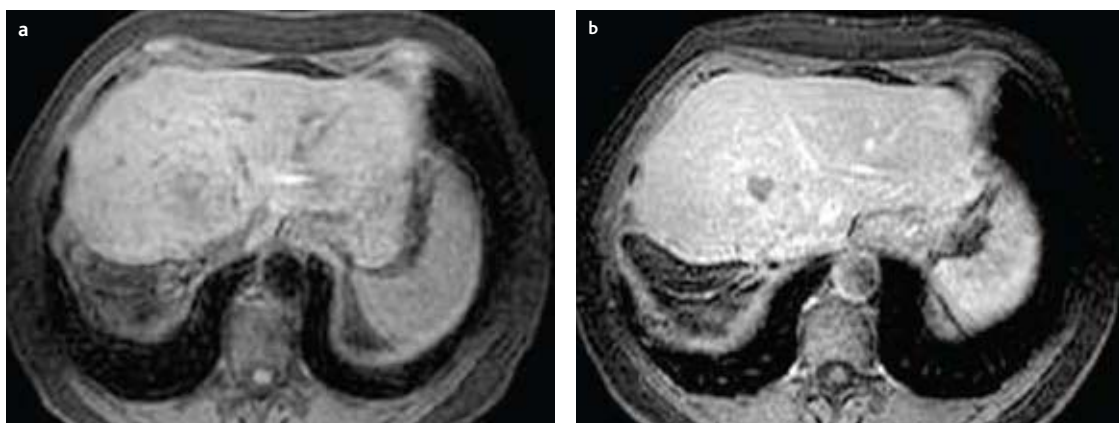


Figure 1. (a) Pre-embolization MR image shows a relatively well defined HCC of 5 cm in diameter near the diaphragm. (b) One month after two superselective embolization sessions with DC Bead, the lesion shows complete necrosis and considerable shrinkage in size.

Overall, TACE achieves a partial response in 15–55% of patients, with a delay in tumour progression, while systemic doxorubicin provides partial response in 10% of cases without proven survival advantages.<sup>2–5,23–25</sup> Llovet *et al.* reported 1- and 2-year survival rates of 82% and 63% with objective response sustained for at least 6 months in 35% of cases and a 3-year survival rate of between 20% and 50%.<sup>24</sup> In addition, in the study arm where TACE was repeated every 2 months, a tumour response of 35% was observed while 1- and 2-year survival rates were 82% and 63%, respectively. In the study by Lo *et al.*, the tumour response rate for conventional TACE was 39% by WHO criteria and the fetoprotein response rate 72%.<sup>4</sup> Malagari *et al.*, in a study of 62 cirrhosis-related-HCC patients who underwent sequential embolization with doxorubicin-loaded DC Bead, observed high rates of tumour necrosis – ranging from 77.4% to 83.9% across three treatment procedures.<sup>26</sup> In the same study, objective response according to European Association for the Study of the Liver (EASL) criteria was observed in 59.6%, 81.8% and in 70.8% of patients across the three treatments (Figure 1). Complete response was observed in 4.8% of patients after the first procedure and 3.6% and 8.3% after the second and third treatments, respectively. Alpha-fetoprotein levels showed a mean decrease of 1,123 ng/ml (95% CI=846, 1,399,  $p=3 \times 10^{-11}$ ) after the first session and remained stable after the second and third embolizations (42 and 70 ng/ml decreases, respectively).<sup>26</sup>

### Liver function

The protection of non-tumourous liver is an important issue since HCC develops on a background of cirrhosis, and patients already have compromised hepatocyte function.

An increase in liver enzymes following TACE is well documented.<sup>27</sup> In a porcine model, increased levels of aspartate aminotransferase were observed until day 14, returning to near or below pretreatment levels by days 28–90 in the groups treated with loaded beads.<sup>10</sup> By contrast, in the group with non-loaded beads, a slight increase was seen but levels returned to normal by day 7. The increase in liver enzymes was greater with the smaller beads compared with the larger ones. Similar patterns of liver enzyme levels were also recorded for alanine transferase and alkaline phosphatase, although these increases were not as marked. The higher elevation of liver enzymes with smaller loaded

beads was attributed to the more distal nature of the embolization and the elimination of collateral flow.<sup>28</sup>

In a recent human study, Varela *et al.* showed that the treatment was well tolerated without impairment of liver function.<sup>11</sup> Similarly Malagari *et al.*<sup>26</sup> observed transient liver enzyme increases with return to baseline at 1 month following each procedure. Bilirubin levels remained relatively constant, with no statistically significant changes compared with baseline.<sup>26</sup>

### Complications

Following embolization, an increase in the polymorphonuclear and leucocyte counts are observed. These have been attributed to the administration of doxorubicin. A postembolization syndrome<sup>14</sup> of variable severity is a common side-effect of TACE. Lo *et al.* recorded episodes of fever in 76% of patients and abdominal pain, with or without vomiting, in 38.5% of patients.<sup>4</sup> Malagari *et al.* observed that all patients suffered from postembolization syndrome, but the maximum duration of pain was 3 days.<sup>26</sup> Fever was observed in 83%, 80% and 95% of patients after the first, second and third procedures, respectively. Apart from the postembolization syndrome, no other effects that affected quality of life were recorded.

Overall, TACE-related mortality is under 4%<sup>1</sup> and Malagari *et al.* reported no procedure-related deaths.<sup>26</sup> The most common serious adverse events of TACE are liver abscesses or infarction and cholecystitis, which each occur in approximately 2% of patients.<sup>1</sup> The 30-day mortality rate of conventional TACE is 1%.<sup>1</sup> Similar rates for these complications were observed in previous clinical series with DC Bead. Varela *et al.* recorded two cases of liver abscess in 27 patients, one of which was fatal.<sup>11</sup> Similarly, Malagari *et al.* observed liver abscesses and cholecystitis in 3.2% of their patients despite antibiotic prophylaxis treatment and the lack of risk factors for abscess formation.<sup>26</sup>

### Conclusion

Clinical results so far show that doxorubicin-eluting DC Bead results in higher necrosis and tumour response rates in short-term follow-up in comparison with TACE. Randomised trials of DC Bead and conventional TACE procedures are ongoing to investigate long-term survival rates, recurrence-free durations and the percentage of new lesions occurring in non-embolized areas of the liver.

# Drug-eluting beads: a new opportunity in the treatment of hepatocellular carcinoma *continued*

Katerina Malagari

## Key Learning

- Drug-eluting beads represent a new technology in selective locoregional treatment of hepatocellular carcinoma
- Controlled drug-elution with DC Bead occurs only within the tumour and in a gradual fashion, the rate of elution following the Higushi equation
- While both conventional TACE and DC Bead act in a similar way (tumour ischaemia), DC Bead permits a more controlled, localised action of the antichemotherapeutic agent compared to TACE
- The early results using DC Bead with doxorubicin are encouraging – higher necrosis and tumour response rates have been observed compared to TACE
- Data from ongoing randomised trials are awaited

## References

1. Brown DB, Geschwind JF, Soulen MC, *et al.* Society of Interventional Radiology position statement on chemoembolization of hepatic malignancies. *J Vasc Interv Radiol* 2006;**17**:217–30.
2. Gamma C, Schepis F, Orlando A, *et al.* Transarterial chemoembolization for unresectable hepatocellular carcinoma: meta-analysis of randomized controlled trials. *Radiology* 2002;**224**:47–54.
3. Llovet JM, Real MI, Montana X, *et al.* Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. *Lancet* 2002;**359**:1734–9.
4. Lo CM, Ngan H, Tso WK, *et al.* Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. *Hepatology* 2002;**35**:1164–71.
5. Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: chemoembolization improves survival. *Hepatology* 2003;**37**:429–42.
6. Gonzalez MV, Lloyd AW, Phillips GJ, *et al.* Drug-eluting beads for embolotherapy: drug loading, distribution and release studies. Presented at the 3<sup>rd</sup> Annual Meeting of the UK Society for Biomaterials, Brighton, UK, 8–9 July 2004: Abstract p19.
7. Lewis AL, Gonzalez MV, Lloyd AW, *et al.* DC Bead: in vitro characterization of a drug-delivery device for transarterial chemoembolization. *J Vasc Interv Radiol* 2006;**17**:335–42.
8. Raoul JL, Heresbach D, Bretagne JF. Chemoembolization of hepatocellular carcinomas. A study of the biodistribution and pharmacokinetics of doxorubicin. *Cancer* 1992;**70**:585–90.
9. Johnson PJ, Kalayci C, Dobbs N, *et al.* Pharmacokinetics and toxicity of intraarterial adriamycin for hepatocellular carcinoma: effect of coadministration of lipiodol. *J Hepatol* 1991;**13**:120–7.
10. Hong K, Khwaja A, Liapi E, *et al.* New intra-arterial drug delivery system for the treatment of liver cancer: preclinical assessment in a rabbit model of liver cancer. *Clin Cancer Res* 2006;**12**:2563–7.
11. Varela M, Real MI, Burrel M, *et al.* Chemoembolization of hepatocellular carcinoma with drug eluting beads: efficacy and doxorubicin pharmacokinetics. *J Hepatol* 2007;**46**:474–81.
12. Lewis AL, Taylor RR, Hall B, *et al.* Pharmacokinetic and safety study of doxorubicin-eluting beads in a porcine model of hepatic arterial embolization. *J Vasc Interv Radiol* 2006;**17**:1335–43.
13. Ball DS, Heckman R, Olenick SW, *et al.* In vitro stability of tris-acryl gelatin microspheres in a multipharmaceutical chemoembolization solution. *J Vasc Interv Radiol* 2003;**14**:83–8.
14. Müller HJ, Port RE, Grubert M, *et al.* The influence of liver metastases on the pharmacokinetics of doxorubicin – a population-based pharmacokinetic project of the CESAR-APOH. *Int J Clin Pharmacol Ther* 2003;**41**:598–9.
15. Bierman HR, Byron RL Jr, Kelley KH, *et al.* Studies on the blood supply of tumors in man. III. Vascular patterns of the liver by hepatic arteriography in vivo. *J Natl Cancer Inst* 1951;**12**:107–31.
16. Kanematsu T, Furuta T, Tkemada K, *et al.* A 5-year experience of lipiodolization: selective regional chemotherapy for 200 patients with hepatocellular carcinoma. *Hepatology* 1989;**10**:98–102.
17. Nakamura H, Hashimoto T, Oi H, *et al.* Transcatheter oily chemoembolization of hepatocellular carcinoma. *Radiology* 1989;**170**:783–6.
18. Sasaki Y, Imaoka S, Kasugai H, *et al.* A new approach to chemoembolization therapy for hepatoma using ethiodized oil, cisplatin, and gelatin sponge. *Cancer* 1987;**60**:1194–203.
19. Charnsangavej C. Chemoembolization of liver tumors. *Semin Invest Radiol* 1993;**10**:150–60.
20. Ramsey DE, Kernagis LY, Soulen MC, *et al.* Chemoembolization of hepatocellular carcinoma. *J Vasc Interv Radiol* 2002;**13**(Suppl):S211–21.
21. Li X, Feng GS, Zheng CS, *et al.* Expression of plasma vascular endothelial growth factor in patients with hepatocellular carcinoma and effect of transcatheter arterial chemoembolization therapy on plasma vascular endothelial growth factor level. *World J Gastroenterol* 2004;**10**:2878–82.
22. Go J, Qian F, Szymanski-Exner A, *et al.* In vivo drug distribution in thermoablated and normal rabbit livers from biodegradable polymers. *J Biomed Mater Res* 2002;**62**:308–14.
23. Bruix J, Llovet JM, Castells A, *et al.* Transarterial embolization versus symptomatic treatment in patients with advanced hepatocellular carcinoma: results of a randomized, controlled trial in a single institution. *Hepatology* 1998;**27**:1578–83.
24. Llovet JMM, Fuster J, Bruix J. Prognosis of hepatocellular carcinoma. *Hepatogastroenterology* 2002;**49**:7–11.
25. Pelletier G, Ducreux M, Gay F, *et al.* Treatment of unresectable hepatocellular carcinoma with lipiodol chemoembolization: a multicenter randomized trial. *J Hepatol* 1998;**29**:129–34.
26. Malagari K, Chatzimichael K, Alexopoulou E, *et al.* Transarterial chemoembolisation of unresectable hepatocellular carcinoma (HCC) with drug eluting beads (DEB); results of an open label study of 62 patients. *Cardiovasc Intervent Radiol* 2007; Nov 13 [Epub ahead of print].
27. Wigmore SJ, Redhead DN, Thomson BN, *et al.* Postchemoembolization syndrome: tumour necrosis or hepatocyte injury? *Br J Cancer* 2003;**89**:1423–7.
28. Pelage JP, Laurent A, Wassef M, *et al.* Uterine artery embolization in sheep: comparison of acute effects with polyvinyl alcohol particles and calibrated microspheres. *Radiology* 2002;**224**:436–45.