The Effect of Doxorubicin Loading on Response and Toxicity with Drug-eluting Embolization in Resectable Hepatoma: A Dose Escalation Study

DARREN KLASS[1], DAVID OWEN[2], ANDREZJ BUCZKOWSKI[3], STEPHEN W. CHUNG[3], CHARLES H. SCUDAMORE[3], ALAN A. WEISS[4], ERIC M. YOSHIDA[4], JO-ANN E. FORD[4], STEPHEN HO[1] and DAVID M. LIU[1]

Departments of [1]Interventional Radiology, [2]Pathology, [3]Hepatobiliary Surgery, University of British Columbia, Faculty of Medicine, Vancouver General Hospital, Vancouver, BC, Canada; [4]Division of Gastroenterology, University of British Columbia, Faculty of Medicine, BC Cancer Agency, Vancouver, BC, Canada

Abstract. *Aim: The dose–response relationship between doxorubicin and superabsorbent drug-eluting microspheres has not been established. In this study, we investigated the relationships between dose and delivery parameters as they pertain to toxicity and response in surgically resectable hepatocellular carcinoma (HCC). Patients and Methods: Twenty-five patients with resectable HCC were randomly assigned and divided into four groups, each receiving either bland, 25 mg, 50 mg or 75 mg of doxorubicin loaded Super Absorbent Polymer microspheres, with 24 patients undergoing surgical resection. Response Evaluation and Criteria in Solid Tumors (RECIST) 1.0 and European Association for the Study of the Liver (EASL)-based volumetric response was performed at one month and surgical resection of the reference tumor was performed at two months. Adverse events were collected at regular intervals. Results: Fifty-six percent of patients demonstrated complete response according to EASL criteria as opposed to 0% according to RECIST (v1.0) criteria. Residual tumor was identified in all groups (0 mg: 35%±28.5%; 25 mg: 42%±30.4%; 50 mg: 3.6%±3.3%; and 75 mg: 49.29%±32.6%. A total of 112 adverse events of grades 1-3 occurred (average 5.1 per patient), with no grade 4 or 5. No difference was noted between bland embolic and drug-loaded groups. Subset analysis did demonstrate a significantly increased degree of necrosis in the 50 mg-loaded group (p=0.018). Strong correlation existed between arterial phase Computer Tomography EASL-based response and histopathology (r=0.81; p<0.0001). All groups had residual tumor. Conclusion: Histology correlates strongly with one-month post-procedural imaging and response optimized at 50 mg of loading per vial. Adverse events were a reflection of embolization, with no relationship between loading dose or administered dose of doxorubicin.*

Doxorubicin is an anthracycline chemotherapeutic and one of the most commonly used chemotherapies in ethiodol-based (lipiodol ultra-fluide, Guerbet, France) chemoembolization (1). The use of ethiodol in the setting of chemoembolization however, remains controversial despite its widespread adaptation, for no significant benefit has been established when compared to other chemoembolization techniques (1, 2). Furthermore, doxorubicin itself has been associated with nephrotoxicity and cardiotoxicity, which is directly related to total systemic dose, area under the plasma concentration–time curve (AUC) and maximum plasma drug concentration (C_{max}). In addition, ethiodol emulsions created with doxorubicin, designed theoretically to slow systemic release rates and increase tumoral drug concentration, have been associated with significant passage of the doxorubicin into the systemic circulation. Thus, a predictable and controlled release of the drug (with maximum concentration at the tumor site for therapy) theoretically could result in fewer complications and severe adverse reactions associated with systemic exposure.

The development of polyvinyl alcohol-based (PVA) drug-eluting microspheres (DEMS) with slow, predictable elution characteristics has the potential to increase the intensity and duration of local tumor ischemia while enhancing drug delivery to the tumor (3). Super-absorbent polymer (amine-acrylate) microspheres (SAP-MS) (Hepasphere/Quadrasphere;

Correspondence to: Dr. David Liu, Department of Interventional Radiology, University of British Columbia, Vancouver General Hospital, Vancouver, V5Z 1M9, Canada. Tel: +1 6048754111, Fax: +1 6048754111, e-mail: david.liu@vch.ca

Key Words: Hepatocellular carcinoma, lipiodol, chemoembolization, drug eluting beads, microsphere, pathology, response, imaging.

Table I. *Inclusion criteria. Summary of the inclusion and exclusion criteria for the prospective study.*

Inclusion criteria	Exclusion criteria
1. Surgically-resectable tumor, amenable to embolotherapy, no predefined size criteria	1. Infiltration of liver >70%
2. Anticipated surgical resection of hepatic lesion (through resection or transplant) in 4-8 weeks following embolization.	2. Portal vein embolization required prior to surgical resection
3. Child-Pugh score A or early B	3. Child-Pugh score C
4. No evidence of cardiotoxicity or cardiomyopathy.	4. Encephalopathy

Merit Medical, South Jordan, UT, USA) have demonstrated utility in the treatment of hepatocellular carcinoma (HCC) as a bland embolic (4). Due to the nature of the matrix, the polymer exhibits a net negative charge, which has been shown both *in vivo* and *in vitro* to allow sustained, predicable local chemotherapy delivery (4), resulting in a DEMS embolization platform that is well-tolerated and associated with few complications and favorable outcomes compared to lipiodol-based chemoembolization (5-9). The aim of the present study was to determine whether a potential benefit may exist in loading (SAP-MS) with doxorubicin utilizing a dose-escalation strategy (0, 25, 50 and 75 mg) for surgically resectable HCC in an open-label format.

Patients and Methods

Approval was obtained from the University of British Columbia Clinical Ethics Review Board for this prospective study (ClinicalTrials.gov Identifier: NCT01116635).

Informed consent was obtained from each patient. Inclusion and exclusion criteria are listed in Table I. Following informed consent; patients were enrolled into the study and randomised to a group receiving 0, 25, 50 or 75 mg doxorubicin loaded onto SAP-MS (Hepasphere/Quadrasphere™; Merit Medical). Each patient underwent super-selective transarterial embolization of SAP-MS utilizing a microcatheter to achieve optimal delivery to the target lesion with defined endpoint as the complete delivery of drug or endpoint of stasis, with exception of the bland embolic group (0 mg) receiving administration of bland embolic to terminal stasis. Post-procedural protocol included a triple-phase computer tomographic (CT) study at least one month following the completion of the treatment session and prior to a surgical resection of the affected lesion. Following resection, the specimen was examined histologically for tumor response, SAP-MS distribution and these were correlated with imaging response and parameters relating to the administration.

SAP-MS preparation. The sterile preparation of the SAP-MS (50-100 μm) was conducted in our pharmacy under a biohazard hood. The loading has been described in previous publications, applying a two-step loading technique (5). In brief, lyophilized doxorubicin hydrochloride (25, 50 or 75 mg) was reconstituted with 10 ml of normal saline and injected into a sterile empty 30 ml vial. An additional 10 ml of 0.9% saline was then added to the vial containing the doxorubicin and mixed, making the total solution 20 ml. A volume of 10 ml of this solution was then added to a vial of dry SAP-MS and incubated at 37˚C with manual agitation every minute for 10 minutes. The resultant microsphere suspension was then combined with the remaining 10 ml of doxorubicin hydrochloride solution in the 30 ml vial and incubated for 120 minutes at 37˚C. The resulting suspension in its entirety was then transported to the interventional radiology suite for injection, where the loaded SAP-MS were drawn into a sterile syringe on the operative field, and the diluent expunged, with SAP-MS resuspended with dilute contrast.

Embolization/chemoembolization procedure. Informed consent for the technical procedure was obtained from each patient prior to embolization/chemoembolization session. Arterial access was obtained *via* an ultrasound-guided puncture of the right common femoral artery. A 5 Fr arterial sheath was inserted and selective cannulation performed of the common hepatic artery using a Simmons 1 reverse curve catheter (Cook Medical, Bloomington, IN, USA) with microcatheter super-selection utilizing a variety of high flow microcatheters. The SAP-MS (50-100 μm dry) loaded with 0, 25, 50 or 75 mg of doxorubicin were then withdrawn from the vial prepared in the pharmacy into a 20 ml syringe on the sterile field (as described above). Superselective catheterization and delivery of drug-loaded chemoembolization with SAP-MS was then performed with the endpoint defined as 100% of the anticipated doxorubicin dose administered or until stasis was achieved. In the case of the bland embolic-treated group, administration of bland SAP-MS was performed to stasis.

Imaging. Each patient underwent a triple-phase (non-contrast, early arterial and late portal venous phase) CT scan prior to treatment and at one-month post treatment. Images were acquired using one of two department CT scanners (Siemens 64; Siemens Healthcare, Erlangen, Germany; and GE Lightspeed 8, GE Healthcare, Waukesha, WI, USA). Imaging of the upper abdomen was obtained using the standard institutional protocol [6-mm collimation; 5-mm/s table speed (pitch, 1.0) during a single breath-hold helical for each phase of image acquisition; and a 3-mm slice thickness with 1.5 mm reconstruction interval]. Non-contrast, hepatic arterial and portal venous phases were performed at 0, 35 and 70 s respectively after initiation of an injection of non-ionic iodinated contrast medium (Optiray 320, Ioversol 68%); Covidien Pharmaceuticals, Hazelwood, MO, USA), *via* a peripheral vein at a rate of 4 ml/s by power injector, followed by a 30 ml flush of normal saline. Images and tumor volumes were analyzed with a Vitrea workstation (Toshiba

Table II. *Response criteria. Summary of the definitions for response criteria for European Association for the Study of the Liver (EASL) and Response Evaluation In Solid Tumors (RECIST).*

Response	RECIST	EASL
Complete (CR)	No tumor visible	No enhancing tumor visible
Partial (PR)	30% Decrease in tumor size	50% Decrease in tumor enhancement
Stable (SD)	Neither CR or PR met	Neither CR or PR met
Progressive (PD)	20% Increase in lesions or new lesions	25% Increase in lesion enhancement or new lesions

Medical Systems, Tokyo, Japan). The volumetric analysis of tumors was assessed according to European Association for the Study of the Liver (EASL) and Response Evaluation In Solid Tumors (RECIST) (Table II) criteria and graded accordingly (10).

Toxicities. Toxicity profiles were reported as per Common Terminology for Adverse Events (CTCAE) v4.0 standard for GI and constitutional, neurological and gastrointestinal events. Documentation of adverse events (AEs) was performed immediately prior to procedure, 24 hours post-procedure and at one-week and one-month follow-up appointments (11).

Surgical resection. Surgical techniques for laparoscopic liver resection and open liver resection were similar (12), apart from abdominal access, and were adapted from procedures as previously described (13, 14). In both types of resection, the Pringle manoeuvre (15), tissue sealants and drains were not used.

Histopathology. Following surgical resection, the resected specimen was placed in 10% formalin and transported to the Pathology Department. The specimen was marked and fixed for 24 hours in preparation for gross pathological and histological examination. The Department sectioned and stained with hematoxylin and eosin and prepared on slides for histopathological analysis. The degree of tumor necrosis, residual tumor, as well as the position of SAP-MS within tissue and number of SAP-MS per section was noted.

Statistical analysis. Descriptive and analytic statistics were utilized. Regression analysis was performed on the data using statistical software SAS 9.4 (SAS Institute Inc, Cary, NC, USA). Adverse events were analyzed using multinomial logistic regression analysis. Values are presented as the mean±0.95 confidence interval (CI); an alpha level of significance of 0.05 for a two-tailed test ($p<0.05$) was regarded as statistically significant.

Results

Twenty-five patents in total underwent either chemoembolization with SAP-MS or bland embolization with SAP-MS. Out of these patients, one patient was excluded from the study due to technical failure at the time of embolization; the catheter became clogged resulting in failure to deliver, with subsequent lipiodol-based chemoembolization being performed. A second patient underwent successful embolization but died a month after the procedure, prior to surgical resection. Postmortem study did not reveal the cause to be related to the embolization procedure. A total of 23 patients were therefore included in the final data analysis. Twenty males and three females with a mean age of 59 years (range=48-73 years) were treated. The etiologies of chronic liver disease included hepatitis B (n=10) and hepatitis C (n=13); Child-Pugh scores range from 5 to 7. All the patients underwent successful embolization and were discharged from hospital the same day.

Table III. *Adverse events according to the Common Terminology for Adverse Events (CTCAE) v4.0 standard for GI and constitutional, neurological and gastrointestinal events.*

Adverse event	Number of adverse events
Abdominal or flank pain	15
Fatigue, weakness or sleepiness	13
Nausea or intermittent nausea	8
Dizziness	5
Decreased appetite or anorexia	5
Vomiting or intermittent vomiting	4
Constipation	4
Insomnia	4

A total of 112 AEs of grades 1-3 occurred (average 5.1 AEs per patient) (Table III), with no grade 4 or 5 AEs (Table IV). The mean time between the procedure and AEs was 4±2 days, with average duration of AE of six days; 27 out of 112 AEs had not resolved at end of the 30-day treatment period (Figure 1). One patient developed a groin hematoma post-embolization at the site of arterial puncture; resulting in hospitalization and subsequent surgical intervention.

Under an assumption of grade 1 events modeled statistically to give adjusted odds ratio of 1.0, adjusted odds ratio for a grade 2 AE was 1.006 (95% CI=0.970-1.043; $p=0.751$) and for a grade 3 AE was 1.033 (9502 CI=0.970-1.101; $p=0.311$), no association was found between higher grade of AE and dose of doxorubicin administered. Of particular note, the likelihood of developing a grade 1, 2 or 3 AE was the same amongst all patients at all doxorubicin-loading concentrations and dose-administration levels.

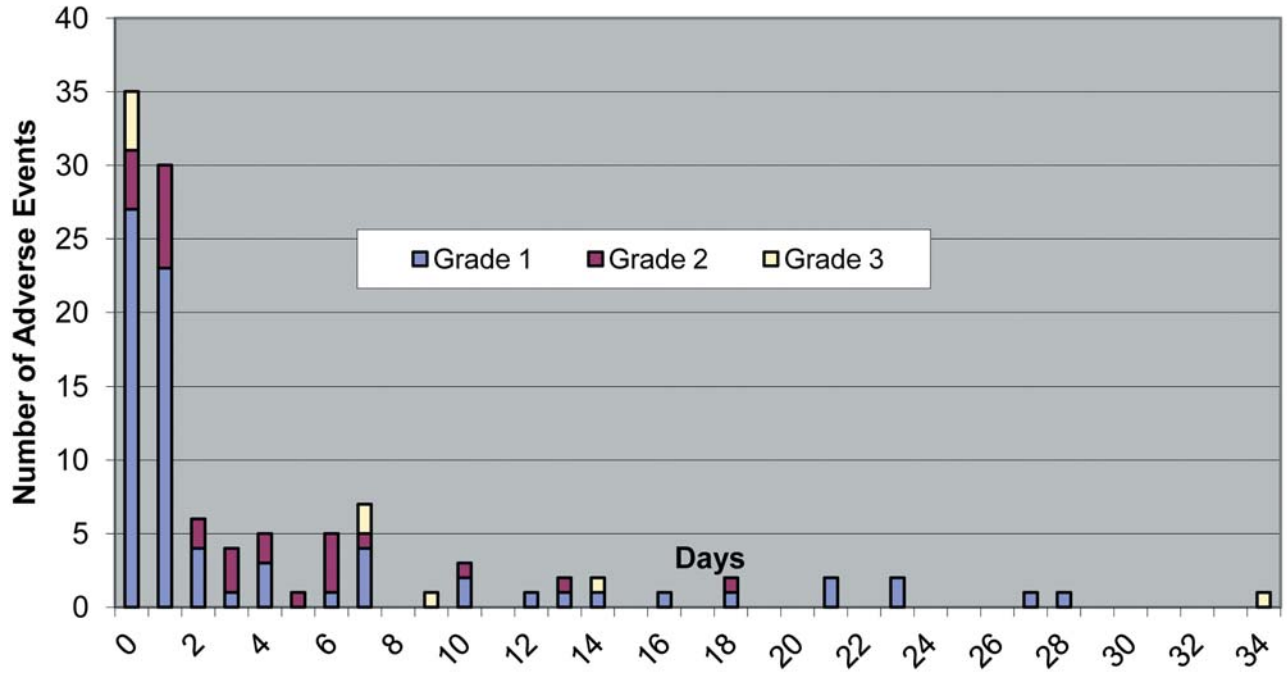

Figure 1. *Days between embolization and adverse event.*

Table IV. *Correlation of adverse events and dose of doxorubicin delivered.*

Adverse event grade	No. of adverse events	No. of patients with adverse events	Average no. of events per patient	Average dose delivered
Grade 1	76	25	3.4	36 mg
Grade 2	27	1	1.2	38 mg
Grade 3	9*	5	0.4	38 mg
Grade 4	0	0	0	
Grade 5	0	0	0	

Note: *Three of the grade 3 events were in a single patient with groin puncture complications.

The reference tumor volume was calculated on the pre-treatment imaging and the one-month post-treatment imaging and assessed in a volumetric fashion according to RECIST and EASL principles (Table V). In terms of drug delivery, 16.7% (n=3) of the patients in the chemoembolization groups received 100% of the intended doxorubicin dose (all receiving 75 mg of doxorubicin).

Lack of complete dose administration was due to complete embolization of second- and third-order vessels during the procedure. Dose administration percentage is detailed in Table V.

The mean tumor volume decreased from 81.72 cm^3±20.79 to 45.7 cm^3±16.35, with no significant difference between the control group and the treatment groups combined (p=0.27) according to RECIST criteria.

Each post treatment scan was then evaluated and the volume of enhancing tumor was calculated according to volumetric EASL and RECIST criteria for comparison to histology. Overall the mean residual volume of enhancing tumour was 12.4 cm^3±4.1, with no difference between the control group (bland embolization) and treatment groups combined (p=0.0861). Statistical comparison of the groups treated with the highest and lowest amount of drug (25 mg, p=0.0730; and 75 mg, p=0.091) did not demonstrate a significant difference in the amount of necrosis compared to the control group; however, significantly more necrosis (p=0.0005) was found for the 50 mg group when compared to the control group.

The overall response rate by RECIST criteria was 100%, and 100% by EASL criteria (Table VI). Subset analysis of this data demonstrated that of the 12 tumors deemed Partial

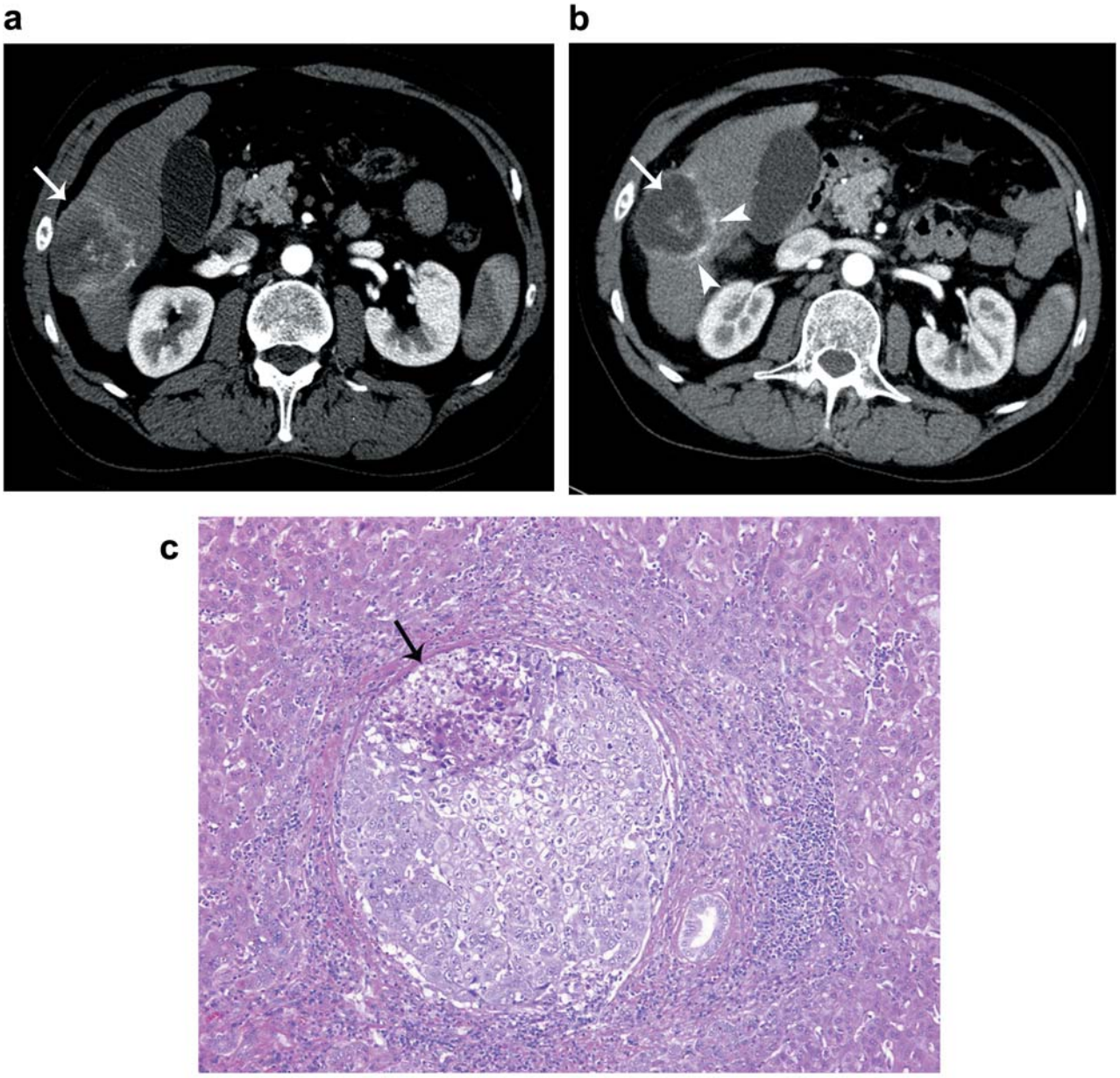

Figure 2. *Patient with hepatocellular carcinoma in segment VI following chemoembolization (75 mg doxorubicin). a: computer tomography study prior to treatment demonstrating mixed attenuation tumor with areas of low attenuation and high attenuation (arrow). The areas of high attenuation correspond to hypervascular HCC and the areas of low attenuation corresponding to necrotic tumor. b: CT at one month post treatment demonstrating extensive devascularization of the tumor (arrow) with peripheral rim of enhancement suspicious for tumor within vessels (arrowhead). c: Hematoxylin and eosin staining histopathology specimen demonstrating tumor within a hepatic vein (arrow), corresponding to the CT image (×100 magnification).*

Response (PR) according to RECIST criteria, eight were deemed Complete Response (CR) and four Partial Response (PR) according to EASL criteria. For those patients deemed to have Stable Disease (SD) (n=11), six tumors demonstrated Complete Response (CR), four Partial Response (PR) and one tumor Stable Disease (SD) by EASL criteria (Table VI).

Following histological analysis, the overall percentage residual disease in the resected lesions was 32.7%±14.4% for all groups combined, with a comparative 25.9%±13.28% residual enhancing tumor on radiological analysis, with strong correlation between histology and arterial enhancement (r=0.81, $p<0.0001$) (Table V, Figures 2 and 3).

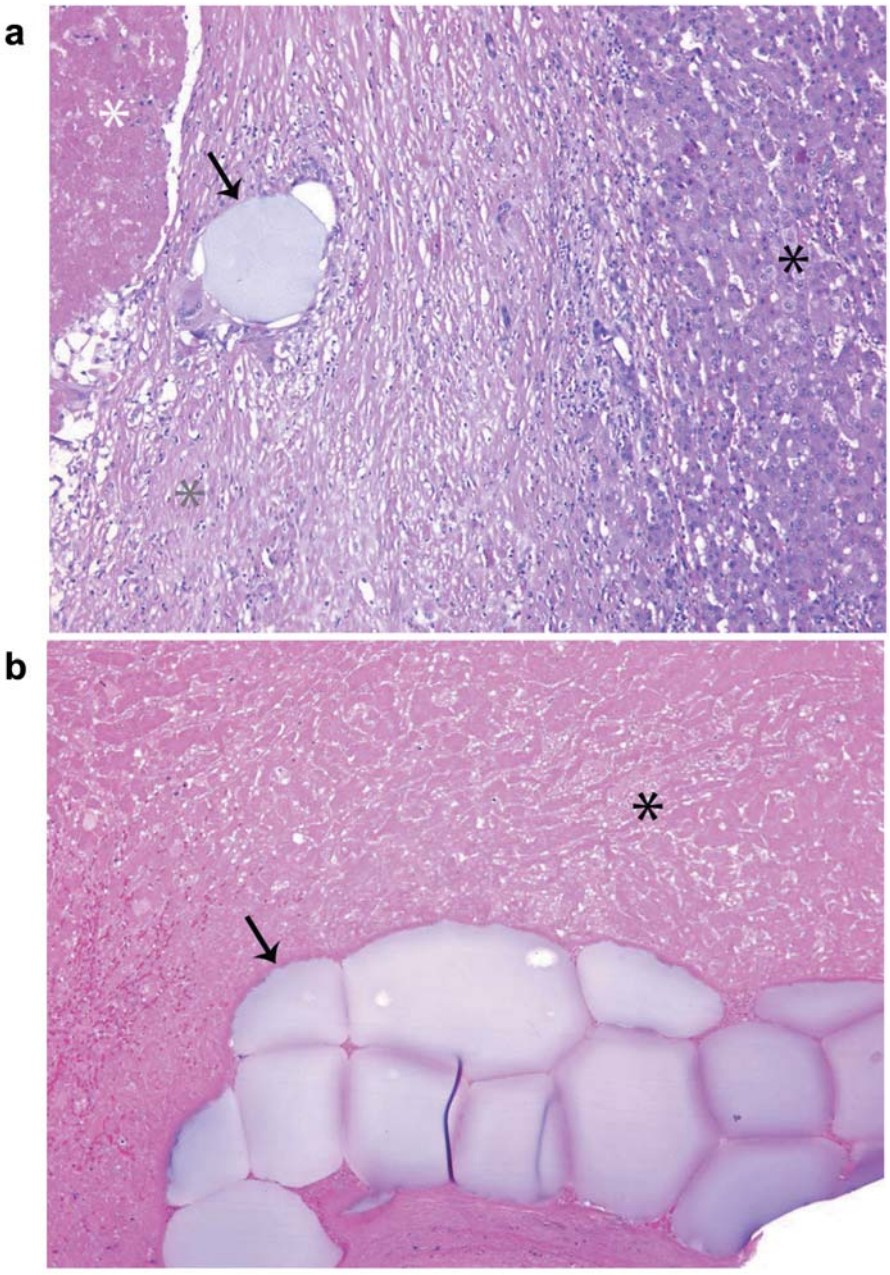

Figure 3. *Heematoxylin and eosin staining histopathology specimen demonstrating single Hepasphere bead (arrow) within a rim of fibrosis (grey asterisk), with necrotic tissue downstream (white asterisk) and residual Hepatocellular Carcinoma upstream (black asterisk) (×100 magnification) (a), and the presence of compressible beads within vessels (black arrow) (×100 magnification) (b).*

No statistical difference was observed between the degree of histological response of the control group (0 mg doxorubicin) and the treatment groups (all doses of doxorubicin loading) combined (p=0.4917). Analysis of the percentage of tumor response based on the RECIST criteria is extrapolated in Figure 4; the figure demonstrates the random pattern of tumor response independent of the dose of doxorubicin loaded onto the microspheres. Subset analysis demonstrated no difference between the control group and the 25 mg (p=0.6058) and the 75 mg (p=0.8631) groups; however, there was a significant difference compared to the 50-mg group, with the 50-mg group demonstrating greater necrosis (p=0.0181). Comparative assessments of residual enhancing tumor on radiological imaging at one month

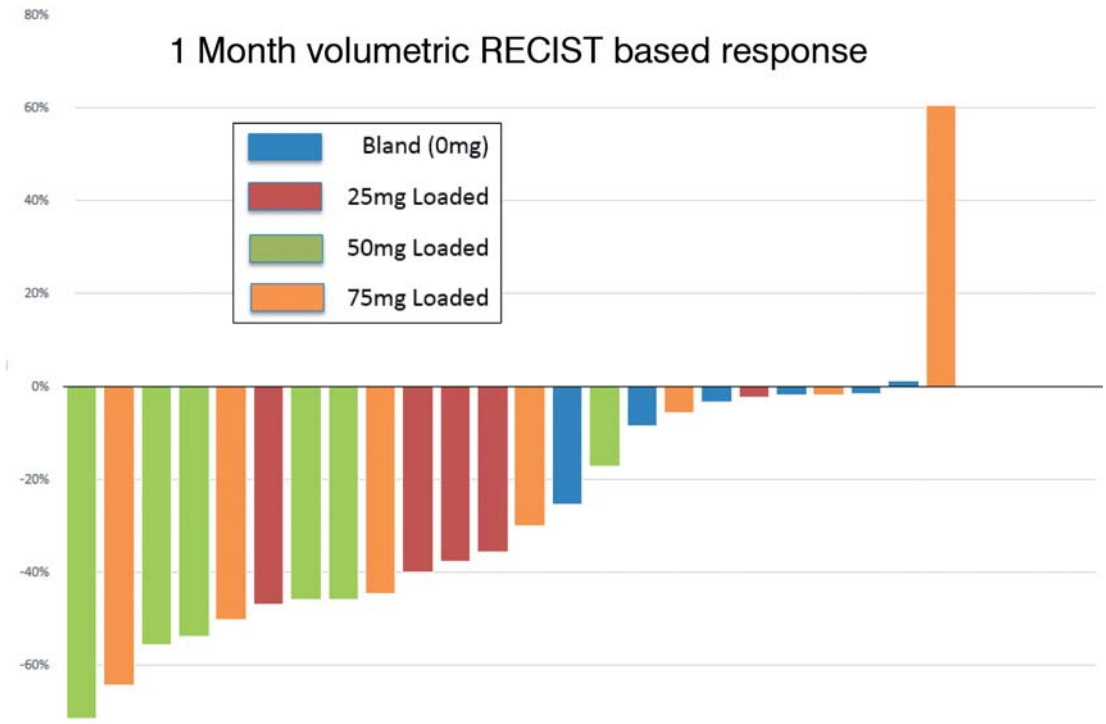

Figure 4. *Waterfall chart of volumetric response according to dose of doxorubicin administered and loading dose based on Response Evaluation In Solid Tumors (RECIST) The data is partitioned in descending order of response, with the corresponding color coding of the bars representing loading dose of particles. The Y-axis denotes the percentage of tumor response, with the negative axis showing the degree of tumor necrosis.*

Table V. *Tumoral response summary detailing the response according to European Association for the Study of the Liver (EASL) and Response Evaluation In Solid Tumors (RECIST) with dose–response correlation.*

Intended dose (mg)	Dose injected (%)	Actual dose injected (mg)	Pre volume (cm^3)	RECIST Post volume (cm^3)	EASL Residual volume (cm^3)	Residual tumor	
						Histology	Radiology
0	0	0	95.6±68.5	92.72±70	49.56±65.1	35±28.5	27±19
25	51	12.85±5.12	37.42±29.7	24.46±20.8	5.14±8.31	42±30.4	38±28
50	54	27.1±8.24	68.03±16	35.04±12	0±0	3.6±3.3	1.7±3.3
75	78.6	58.93±14.8	44.12±35	27.88±23.6	0.93±1.1	49.29±32.6	37.25±32.6

demonstrates an overall residual enhancing tumor percentage of 25.9%±13.3% on imaging. Correlation between the histological assessment of response and the radiological assessment overall was highly significant ($p<0.0001$).

Discussion

Worldwide, primary HCC is one of the 10 most common types of cancer (16). Liver transplantation is currently considered to be the only potential curative treatment for small tumors (17) as it eliminates both the tumor and the underlying cirrhosis – thus preventing new tumors from developing, however, transplantation is available to only a small group of patients. Despite surgical resection being an established treatment modality with the potential for cure for HCC (18, 19), the potential for malignant transformation of the underlying cirrhotic/inflamed liver parenchyma persists. Systemic chemotherapy and biological agents may provide improvement in median survival time for some patients at a cost of significant systemic toxicity (20). Unfortunately, patients who have advanced disease not suitable for resection rarely survive beyond 5 years (21). Tumor progression and co-morbidities often associated with HCC often prevents patients from undergoing transplantation or resection, thus necessitating a

Table VI. *Summary of response rates (n) by volumetric European Association for the Study of the Liver (EASL) and Response Evaluation In Solid Tumors (RECIST) criteria.*

	PR	SD	CR
RECIST	12	11	0
EASL	8	1	14

PR: Partial Response; SD: stable disease; CR: complete response.

less invasive, repeatable, but effective treatment.

For those patients with advanced, large volume or multi-focal disease, transarterial chemo-embolization (TACE) (22-26) remains one of the few modalities allowing disease control. The increased incidence of HCC (27) and the inconsistent nature of lipiodol-based chemoembolization, both in it its *in vitro* characteristics (28) and clinical application (29), has necessitated improved regional intra-arterial infusion techniques delivering a more reliable dose of chemotherapeutic to tumors. Embolization of the hepatic artery was initially described in the early 1980s (24), however, it has transitioned to become targeted, highly concentrated local therapy.

The administration of doxorubicin-ethiodized oil-based emulsion followed by gelatin sponge or PVC particles is widely accepted and referred to as conventional TACE (9). The administration of this combination is not standardized by chemotherapeutic agent, method of administration or use of gelatin sponge or PVA particles. The technique has been shown to induce a variable response, with tumor progression and partial response reported consistently in a large retrospective survey (1). The limitations of lipiodol-based TACE have been well established (28, 30-32). Lipiodol-based TACE involves the emulsification of a chemotherapeutic agent in an oily medium (the drug carrier), which is delivered directly to the tumor *via* the trans-arterial route, thus maximising the antiangiogenic effect of the drug. Despite evidence of some early clinical success with TACE, recently, the use of lipiodol or indeed chemotherapy and embolization, has been questioned (2, 29, 33) due to the continued controversy surrounding the elution and biodistribution of injected chemotherapeutic. Ideally, the sequestration of chemotherapeutic should be facilitated through gradually elution to avoid systemic toxicity, while minimizing systemic toxicities and exposure (through a low maximum peak concentration and area under the curve). In the case of lipiodol carrier-based TACE, the unpredictable nature of first-pass extraction within the tumor results in erratic and unpredictable systemic exposure and pharmacokinetic profile. Despite this, TACE still offers a survival benefit to patients with HCC who are not suitable for resection or locoregional ablation therapy or serves as a bridging procedure to transplant (30).

Our study evaluated the relationship between doxorubicin dose loaded onto SAP-MS microspheres and tumor response utilizing histopathological and radiological correlation. In standard clinical trial execution, the individual contributions of the chemotherapeutic and embolic carrier are difficult to separate; in this study, three doses of doxorubicin (25, 50 and 75 mg) were loaded onto the SAP-MS, and compared to the use of the SAP-MS without drug loading, with correlative studies performed at one-month post treatment, to determine the tumor response. A benefit of SAP-MS TACE is the ability to interpret the post treatment follow-up imaging without the confounding imaging artefacts caused by lipiodol (Figure 2). This provides a significant benefit for patient care and allows for early intervention for residual tumor. The radiological and histopathological correlation was highly significant in this study; demonstrating that CT imaging is an accurate surrogate of tumor response, with accurate correlation of imaging findings and histology (Figure 2). Of all the groups, only the 50 mg drug-loaded group (27.1 mg actual dose) demonstrated a significant difference in tumor response compared to the control group (p=0.005). Although 50 mg dose loading may seem unusual, as confirmed by ex vivo experiments, delivery of SAP-MS has been demonstrated to be optimal at the 50 mg per vial loading range due to handling characteristics and stability of the ionic binding of the molecule with SAP-MS substrate (5). Furthermore, the subset of patients in the 75mg population receiving 100% of dose (and not achieving stasis, as no bland embolic was used) had demonstrated more residual tumor, further supporting the practice of utilization of additional embolic to stasis when using DEMS.

Currently, doxorubicin remains one of the most commonly used chemotherapeutic agents for lipiodol chemoembolization. Due to its unique characteristics, the popularity of this tumoricidal agent will continue, especially with the increased popularity of drug-eluting microsphere platforms due to the ability to load and release doxorubicin in a suspended solution under a number of conditions (5). Chemoembolization with DEMS combines the chemotherapeutic agent with a mechanical embolic carrier; using the embolic carrier to reduce blood flow to the tumour and simultaneously allowing elution of the chemotherapeutic agent bound to the carrier into the tumor. SAP-MS has been shown to be safe and effective in treating unresectable HCC when used as a bland embolic agent (34, 35) but not with drug loading. In our study however, the degree of necrosis in the groups of patients receiving chemotherapy with drug was higher only in the group receiving 50 mg doxorubicin (p=0.005).

The side-effect profile was similar to other abdominal embolization procedures, with abdominal pain, fatigue-like symptoms, and nausea being the most common adverse events,

however, patients experienced minimal post-embolization syndrome, which was not statistically correlated with the amount of doxorubicin administered. Based on incidence and distribution of AEs, the toxicities relating to SAP-MS delivery likely result from the embolic effect as opposed to dose response related to the use of doxorubicin.

The small patient population poses a major limitation to this study protocol; however, despite the small groups, the histological findings and statistical analysis suggest a trend for therapeutic benefit of chemotherapy with 50 mg-loaded SAP-MS. SAP-MS appears to offer a more reliable, predictable and sustained release of chemoembolic than conventional TACE (36), with the added benefit of the more favorable handling characteristics and stability of the microspheres prior to administration, which from a technical standpoint make this platform an extremely viable alternative to oil-based carriers.

Tumor extension, although present, is not apparent on early imaging due to the lack of visible viable enhancing tumor and the inability to visualize microvascular invasion. In spite of this common knowledge, our study demonstrates a close correlation between the imaging at one month post embolization and the histological appearances in all groups ($p<0.0001$).

Review of imaging response revealed discordance between RECIST- and EASL-based criteria in 67%. In those patients determined to have SD (n=11) according to RECIST criteria, 55% (n=6) were deemed to have CR, 36% (n=4) and only one patient SD. This finding again highlights the importance of assessment of the residual enhancing tissue as a surrogate of response rather than the tumor as a whole when assessing treatment response following locoregional therapy (37). A further notable observation made during this study was the lack of necrosis of the tumor upstream of the embolic endpoint of the SAP-MS (Figure 3a). Furthermore, in spite of extensive review, no evidence of hepatic parenchymal damage secondary to the embolization procedure was identified in any sample, suggesting SAP-MS are compressible and therefore pack in vessels, adding to a probable synergistic chemotherapeutic effect and hypoxia within the dense aberrant vasculature of the tumor without effecting non cancerous tissue (Figure 3b). The correlation between imaging response and histological response in this study is similar to the published literature, despite the lower dose of doxorubicin (in addition to the introduction of the bland embolic arm) (38).

In summary, we conclude that use of SAP-MS is reproducible and can be standardized as a treatment platform, providing a sound and reproducible assessment of histopathological response based on one-month multi-phase CT at all drug loading levels. A trend for response suggests that 50 mg loading may result in increased response, both radiographically and histologically. Further validation of this observation could be attained through a larger cohort study.

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Received February 17, 2014
Revised May 16, 2014
Accepted May 20, 2014