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Authors
Lam, A
Fernando, D
Sirlin, CC
et al.

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Value of the portal venous phase in evaluation of treated hepatocellular carcinoma following transcatheter arterial chemoembolisation

A. Lam[a,*], **D. Fernando**[a], **C.C. Sirlin**[b], **M. Nayyar**[a], **S.C. Goodwin**[a], **D.K. Imagawa**[c], and **C. Lall**[a]

[a]Department of Radiological Sciences, Irvine School of Medicine, University of California, 101 The City Drive South, Orange, CA 92868, USA

[b]Department of Radiology, University of California, San Diego Medical Center, 200 West Arbor Drive, San Diego, CA 92103, USA

[c]Department of Surgery, Irvine School of Medicine, University of California, 101 The City Drive South, Orange, CA 92868, USA

Abstract

AIM—To evaluate the utility of the portal venous phase on multiphasic computed tomography (CT) after treatment of hepatocellular carcinoma (HCC) with trans-arterial chemoembolisation (TACE).

MATERIALS AND METHODS—This was a retrospective review of patients who underwent TACE for HCC between 1 April 2012 and 21 December 2014, with appropriate multiphasic, pre- and post-procedural CT examinations. The maximum non-contrast, arterial phase, and portal venous phase attenuation values of the tumour and tumour bed were evaluated within a region of interest (ROI), with values adjusted against background hepatic parenchyma. Linear regression analyses were performed for both the arterial and venous phases, to assess the level of enhancement and to determine if the venous phase had additional value in this setting.

RESULTS—A total of 86 cases from 51 patients were reviewed. All pre-procedural CT examinations of lesions demonstrated arterial phase enhancement with portal venous and delayed phase washout compatible with HCC. The post-procedural CT examinations following TACE revealed expected decreased arterial enhancement. Sixty-five cases (76%) showed persistent non-enhancement on the portal venous phase following embolisation therapy. A total of 21 cases (24%), however, demonstrated progressive portal venous hyper enhancement. Linear regression analysis demonstrated a statistical significance between the difference in maximal arterial and portal venous enhancement in these cases.

CONCLUSION—Following TACE, the treated lesion may demonstrate portal venous phase hyper-enhancement within the tumour bed. As such, full attention should be given to these images for comprehensive evaluation of tumour response following treatment.

[*]Guarantor and correspondent: A. Lam, Department of Radiological Sciences, University of California, Irvine, 101 The City Drive South, Orange, CA 92697, USA. Tel.: +1 714 456 7890; fax: +1 714 456 7864. ahlam@uci.edu (A. Lam).

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer in the world, with an incidence that is rising in Western nations.[1,2] Hepatic carcinogenesis is a complex process and is classically described as a gradual transition from low- and high-grade dysplastic nodules to early- and late-stage invasive tumour, following the accumulation of numerous epigenetic and genetic mutations. Among the many histopathological changes that take place, the most radiologically significant alterations arise from the angiogenesis of unpaired arteries and sinusoidal capillaries and gradual disappearance of hepatic venous outflow, which results in near-complete neo-arterialisation of the tumour bed.[1,3,4] This translates to avid enhancement on arterial phase imaging.[5] The second hallmark of HCC imaging is rapid washout of contrast medium in the portal venous and delayed phases, with sensitivities and specificities approaching 89% and 96% in the literature, respectively.[5] The mechanism behind this phenomenon is still widely debated; however, the prevailing theory suggests rapid drainage of contrast medium from the tumour via the portal system.[6,7]

Because of this arterial preponderance, catheter-based, minimally-invasive, and selective therapeutic approaches have been developed by interventional radiologists to provide locoregional treatment to patients. Trans-catheter arterial drug-eluting chemoembolisation (TACE) has grown in recent years as an integral treatment modality for unresectable HCC. Drug-eluting chemoembolisation is typically recommended for patients with intermediate-stage HCC, especially those with multifocal disease and no vascular invasion or extrahepatic spread.[8–11] The procedure is also often offered to patients who are poor candidates for surgical resection or percutaneous ablation. The therapeutic effect stems from the tumour-directed administration of chemotherapy agents and the embolisation of the parasitised arterial supply and or neoangiogenesis, resulting in stagnant trans-tumour flow and prolonged residence of chemotherapy within the tumour bed.

Embolisation directly alters the haemodynamics of the HCC tumour bed. As haemodynamic properties are responsible for the characteristic enhancement patterns of HCC on multiphasic CT examinations, changes in these patterns can be expected after the haemodynamic alterations caused by embolisation. Prior authors have correlated changes in arterial enhancement with pathological necrosis.[8–11] This study focuses on the interval change of tumour enhancement separate from the typical HCC pattern identified on routine follow-up imaging at a single institution with emphasis on the portal venous phase. In addition to an expected decrease in arterial enhancement within the tumour bed, the investigators hypothesise that decreased arterial flow from embolisation may result in persistence of contrast medium within the portal system. In turn, this translates into increased enhancement during the portal venous phase, and may potentially provide insight into the presence of residual tumour or recurrence.

Materials and methods

This is an institutional review board (IRB)-approved, single institution, retrospective review of patients who underwent TACE with drug-eluting beads for HCC between 1 April 2012 and 21 December 2014. Inclusion criteria included histopathology or imaging and serology

proven HCC and appropriate multiphasic, pre- and post-procedural CT examinations to evaluate treatment planning and response. Exclusion criteria included conventional TACE with Lipiodol, concurrent sorafenib therapy, or treatment with prior ablations.

All multiphasic CT examinations were performed using a Philips 256-slice Brilliance iCT system (Philips Healthcare, Amsterdam, Netherlands). All CT examinations were performed using a tri-phasic protocol, including a non-enhanced acquisition. The contrast-enhanced images were acquired with 100 ml iopamidol intravenous contrast medium (370 mg iodine/ml; Isovue 370, Bracco Diagnostics, Milan, Italy) injected at a rate of 3 ml/s with a section thickness of 3 mm. The arterial phase images were timed to trigger when the descending aorta reached 150 HU by bolus tracking. The portal venous phase images were acquired following a 65–70 second delay following injection. Sagittal and coronal reconstructions were performed at an independent workstation and uploaded to the picture archiving and communication system (PACS) server.

Each TACE procedure was performed in accordance with recommendations from multidisciplinary tumour board. As per the institutional protocol, patients with limited disease as defined by the Milan criteria for liver transplantation were treated with 25–100 mg doxorubicin loaded onto 100–300 μm LC beads (BTG International, London, UK) depending on the severity of the tumour burden. Following femoral artery catheterisation under local anaesthesia, a coaxial microcatheter system was used to sub-select third-and fourth-order arterial branches supplying the tumour. The target lesions were then embolised under fluoroscopic guidance with a mixture of beads and iodinated contrast material. Adequate pruning of the neo-arterialised vessels on digital subtraction angiography (DSA) was considered the procedural end-point. Details from the report, including arterial sub-selection, success of embolisation, and endpoint were reviewed with the imaging on PACS.

Each CT examination was reviewed on an IMPAX 6.5.1.144 workstation (Agfa Healthcare, Mortsel, Belgium) by two independent, blinded, fellowship-trained abdominal radiologists. The region of interest (ROI) for each series of CT examinations was identified following evaluation of the target lesion on the procedural DSA. If multiple lesions were treated, the ROI was placed on the largest lesion. Each circular ROI measured approximately 100 mm^2, with a variance of approximately ±10 mm^2. The maximum raw attenuation of the tumour was obtained on each phase on the pre- and post-procedural images. The attenuation of the background liver was measured on the same image and phase to correct for enhancement of the normal hepatic parenchyma through subtraction.

Results

The initial PACS query yielded 109 TACE procedures from 74 patients with HCC. After excluding patients that did not have appropriate pre- and post-procedural, multiphasic CT examinations within 30 days of the TACE, 86 cases from 51 patients remained (35 patients received two treatments and 16 patients received one). Of these patients, 32 (63%) were male and 19 (37%) were female. The average age was 67 years for the entire cohort, with a range of 44–81 years. For men, the average age was 64 years. For women, the average age was 71 years. HCC was initially diagnosed in patients via liver biopsy or alternatively by

multiphasic CT imaging demonstrating a mass lesion with the expected enhancement on arterial phase and portal venous washout against a background of cirrhosis as defined by Liver Imaging-Reporting and Data System (LI-RADS) version 2014. Patients who underwent prior treatments were excluded. Ninety-one percent of patients had viral and/or alcoholic hepatitis, 2% non-alcoholic steatohepatitis, and 7% cryptogenic cirrhosis.

All pre-procedural CT examinations demonstrated arterial phase enhancement and portal venous washout compatible with HCC. Mean tumoural arterial attenuation for all cases averaged 95 HU, with a range of 65–150 HU. Correcting for intrinsic hepatic parenchymal enhancement, the average tumoural enhancement during arterial phase was 32 HU. No appreciable enhancement greater than background was identified on portal venous phase, with an average attenuation value of 67 HU for all cases.

The arterial parenchymal enhancement on post-procedural CT examination measured 78 HU, with a range of 18–125 HU. Mean arterial tumoural enhancement on post-procedural CT examination for all cases measured 59 HU, with a range of 22–167 HU. Mean portal venous parenchymal enhancement measured 84 HU, with a range of 33–132 HU. Mean portal venous tumoural enhancement on post-procedural CT examination for all cases measured 61 HU, with a range of 16–226 HU. Twenty-one cases (24%) demonstrated portal venous enhancement above arterial phase enhancement, with an average attenuation value of 122 HU, ranging between 45–226 HU. The mean attenuation of the surrounding hepatic parenchymal attenuation measured 79 HU, with a range between 42–112 HU. The mean relative tumoural enhancement on portal venous phase measured 43 HU. Sixty-five cases (76%) showed expected hypo-enhancement relative to hepatic parenchyma on portal venous phase imaging. Linear regression analysis demonstrated statistical significance between the difference in maximal arterial and portal venous enhancement (Fig 1).

Discussion

Multiphasic CT examination is the test of choice to evaluate treatment response following TACE. In a subset of patients in the present series, arterial embolisation resulted in an increase in portal venous enhancement within the tumour bed. This was identified in nearly 25% of the patients, many of whom demonstrated more prominent nodular areas of enhancement within the tumour bed on the venous phase when compared to the arterial phase, which is the classic phase to assess for residual HCC. Thus, the authors surmise that a thorough assessment of the portal venous phase is warranted to fully evaluate the possibility and volume of recurrence or residual tumour, which may often be overlooked when applying standard HCC treatment assessment criteria if only the arterial phase images are reviewed.

The liver is a large organ, constituting approximately 2.5% of the body weight and receiving approximately 25% of the cardiac output via two major inflows, namely the proper hepatic artery and the portal vein.[12,13] In normal hepatic physiology, the hepatic artery accounts for approximately 20–25% of the total blood flow to the liver, with the other 75–80% being contributed by the portal vein.[14] The portal vein is a valve-less confluence of efferent vessels that drain several visceral organs including the intestine, pancreas, and spleen. The portal vein drains directly into portal sinusoids, prior to draining into the hepatic vein. The hepatic

artery, after a number of divisions, branches into four major communications between the hepatic arterial and terminal portal venules: the peribiliary plexus, terminal arteriosus twigs that connect the arterioles to the origin of the sinusoids, the vasa vasora of the portal vein, and the direct arterioportal anastomosis.[15] The peribiliary plexus and terminal arteriosus twigs drain into the sinusoids, while the portal vein vasa vasora and arterioportal anastomoses drain directly into the portal vein.

This normal hepatic microcirculation experiences a number of changes during progression from normal liver parenchyma, to dysplastic nodules, and ultimately, HCC. The dedifferentiation process towards HCC is initially accompanied by a steady, gradual loss of the portal venous inflow and hepatic arterial flow, resulting in a period of relative hypovascularity in relation to the underlying normal hepatic parenchyma.[16–18] Through increases in vascular endothelial growth factors, the progressive neovascularisation and establishment of non-triadal arteries associated with HCC shifts the vascular inflow to become increasingly arterial in nature, with a minimal or nonexistent portal venous component.[3,4,15,16,19–21] This increase in arterial vasculature has been pathologically correlated with increases in arterial phase enhancement characteristic of HCC.[17,22] Brisk arterial enhancement is immediately followed by avid washout on portal venous and delayed imaging. The mechanism underlying portal venous washout continues to be poorly understood; however, the conventional theory favours a decrease in nodular portal blood supply, and partially through impedance of portal venule flow by high arterial pressures and hepatic carcinogenesis.[6,15] Interventional radiologists have leveraged this unique pathologic alteration in blood flow to preferentially deliver chemotherapy and radiotherapy-based embolic agents directly to the tumour and its surrounding vascular supply via hepatic artery sub-selection.

Prior research has demonstrated changes to the hepatic microcirculation following embolisation of the hepatic artery mediated by significant upregulation of angiogenic growth factors.[23–28] These microcirculatory changes following TACE may also manifest in increased enhancement on portal venous imaging within the tumour bed through increased portal venous supply to the tumour, suggesting the possibility of residual tumour. This is the first study to establish alterations in contrast enhancement in the portal venous phase of multiphasic CT imaging following embolisation.

The literature suggests that an uncertain amount of arterial flow travels initially to the sinusoids and portal venules via the peribiliary plexi and arteriovenous twigs.[12,13] The amount of embolic material that follows this course, however, has yet to be fully elucidated. Given its size, the particulate embolic material probably fails to enter the tumour microvasculature.[15] Nonetheless, some authors have observed reversal of blood flow within the sinusoids of mice models following embolisation of the terminal portal venules with 30–35 μm plastic beads.[15,29] Such flow reversal was accompanied by collateralisation proximal to the embolised vessel, their adjacent branches, and neighbouring terminal portal venules. In some instances, this occurred within 5 days of occlusion.[15,30] Prior authors have proposed that a steady increase in angiogenic growth factors, such as vascular endothelial growth factor (VEGF), over 6 days following hepatic artery embolisation, is the primary driver for

the development of collateral circulation via vascular neoangiogenesis following embolisation.[3,23,31,32]

Following embolisation and subsequent collateral formation, ischaemia–reperfusion injury to liver tissue has been known to incite an inflammatory response via mediators, such as tumour necrosis factor-alpha and reactive oxygen species, leading to recruitment of circulating leukocytes to the sinusoids.[33,34] In animal models, the leukocytes accumulate and adhere within the microvasculature and establish sinusoidal plugging and stagnation of flow without complete cessation in the sinusoids.[12,35–38] The reduction in inflow has been theorised to result in diminished outflow of blood and blood products.[13,39] As a corollary, the stagnation of flow may manifest at multiphasic imaging as reduced apparent washout of contrast material in the portal venous and delayed phases. Moreover, sub-endothelial capillary oedema following injury further narrows the sinusoids, leading to vasoconstriction and reduced perfusion gradient, most pronounced in the periportal segment of the sinusoids.[12,40] Similar to stagnation of flow, the reduced perfusion gradient decreases blood flow and promotes the persistence of contrast material within the portal system. In addition to stagnation of flow and increased collateralisation to the portal system, direct alterations to the arterial flow found in advanced HCC following embolisation also likely contribute to increased portal venous enhancement. The high-pressure hepatic arterial low in advanced HCC has been linked to impedance of the physiological portal venules, leading to the classic portal venous washout. By eliminating hepatic low via embolisation, this resistance is significantly decreased, allowing for contrast medium enhancement within the portal system to persist.[15] These multiple changes initiate the cascade that promotes an increase and/or persistence of contrast medium within the portal system reflected in increased portal venous enhancement (Figs 2–4).

The present study is limited by a relatively small, disproportionate sample size given the low number of patients and examinations, limiting the analysis. In addition, the study has a limited extended follow-up period of approximately 1 month, reducing the ability to generalise the results. Moreover, the data surrounding the postoperative period of approximately 57 days are rather limited, restricting the conclusions that can be drawn concerning the temporality of the microhaemodynamic alterations. Lastly, histopathological correlation is lacking in a number of the studies, preventing definite conclusions concerning the underlying aetiology.

It is important to note that further studies are undoubtedly warranted to elucidate the significance of increased venous enhancement following TACE and its implications on tumour response, tumour progression, and residual or recurrent tumour viability. Future comparisons with concurrent DSA and quantitative imaging parameters, such as those offered with diffusion- and perfusion-weighted imaging, may potentially be used to illustrate viability within the tumour bed, and possibly correlate with survival outcomes. This information may eventually be used to stratify patients and target those who would benefit from retreatment or further surgical management. Additionally, studies evaluating changes in imaging following TACE therapy with concurrent anti-angiogenic medications such as sorafenib should be considered to further clarify the role of angiogenesis in increasing portal venous phase enhancement.

In conclusion, the often overlooked, portal venous phase in a multiphasic CT examination following TACE for HCC is valuable as it may demonstrate increased enhancement within the tumour bed and a more precise volume of residual tumour. This finding is likely multifactorial in aetiology and dependent on microhaemodynamic reactive changes in the tumour bed. Regardless, full attention should be given to the portal venous phase in a multiphasic CT study to evaluate tumour response to treatment comprehensively and accurately following chemoembolisation. Further studies are warranted to elucidate the clinical significant of portal venous enhancement following embolisation in a larger multicentre setting.

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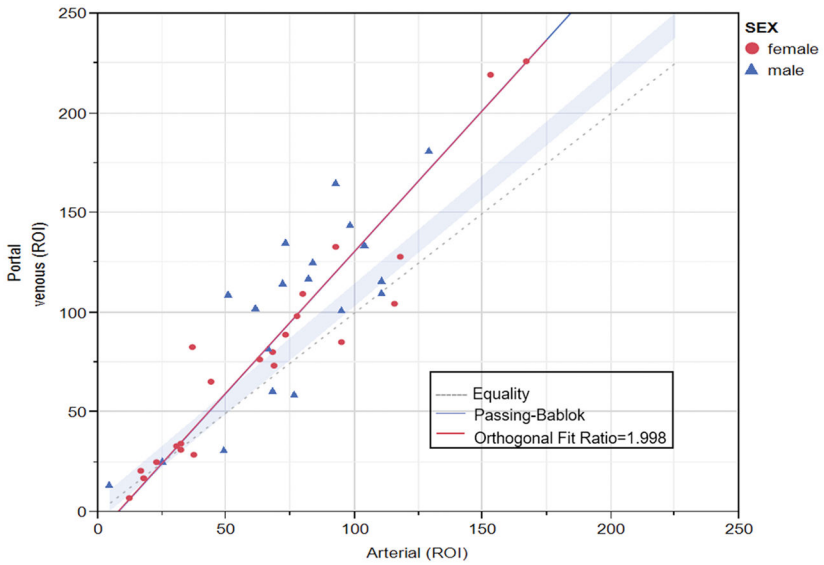

Figure 1.

Bivariate fit of portal venous (ROI) by arterial (ROI). The attached graph shows the slope of the regression line to be 1.41 (with a 95% confidence interval of 1.215–1.644 and correlation coefficient of 0.9073). This indicates that there is a statistically significant increase in enhancement on venous phase relative to arterial phase ROI. In other words, venous phase ROI is approximately 41% higher (given that slope of line is 1.41) than arterial phase on these cases. Additionally, there is high correlation (91%) between venous and arterial ROIs.

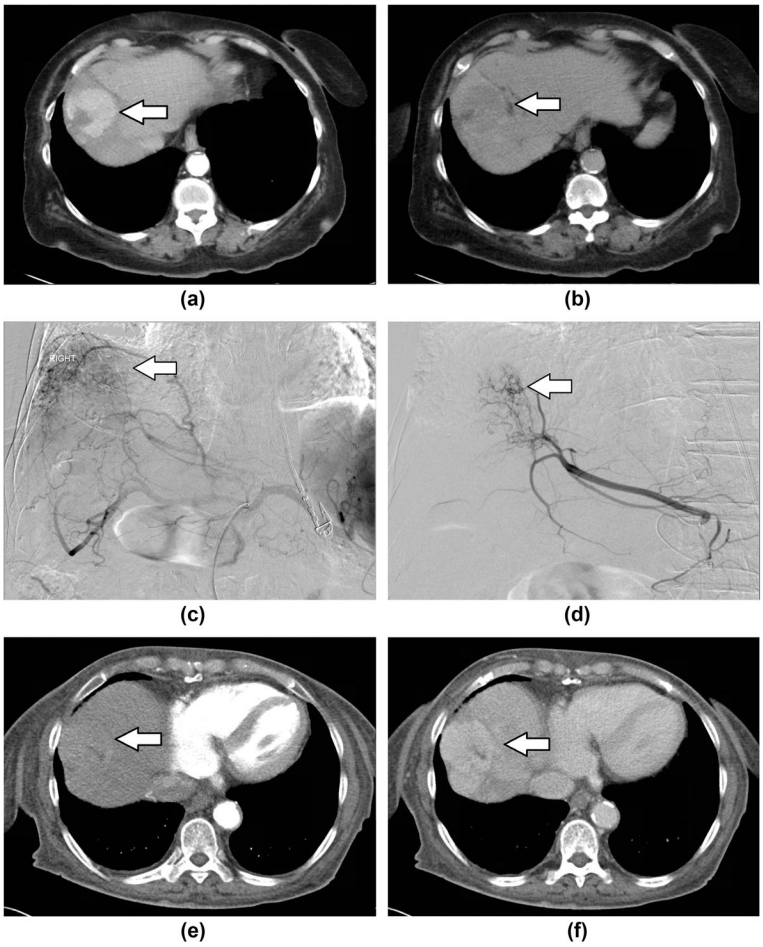

Figure 2.

A 72-year-old woman with a history of hepatitis C with biopsy-proven HCC. (a) Pre-procedural axial multidetector CT image during arterial phase demonstrates heterogeneous enhancement of a circumscribed mass centred at the hepatic dome (white arrow). (b) Pre-procedural CT image during the portal venous phase shows washout of contrast medium from the HCC as evidenced by relative hypo-attenuation in relation to background hepatic parenchyma (white arrow). (c) DSA images, with selection of the proper hepatic artery, shows focal, circumscribed tumour “blush” corresponding to hypervascularity and supply from the right hepatic artery. (d) Post-procedural DSA with selection of the right hepatic artery, shows a significant reduction in the contrast blush, consistent with adequate “pruning” of the tumour’s vascular supply. (e) Post-procedural axial CT images during the arterial phase 1 month following the procedure demonstrating a significant reduction of enhancement within the tumour bed when compared to the pre-procedural scans. (f) Post-procedural axial multidetector CT images during the portal venous phase show lobular, interrupted, peripheral enhancement, not seen on the pre-procedural venous phase images.

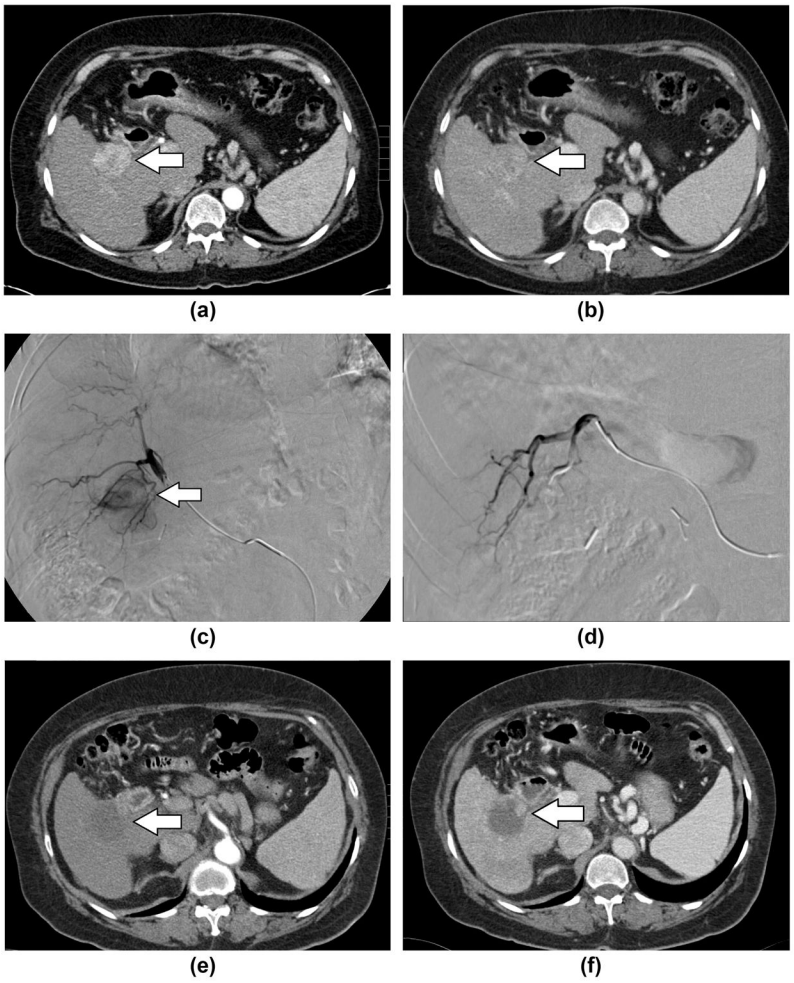

Figure 3.

A 65-year-old woman with a history of hepatitis C and biopsy-proven HCC. (a) Pre-procedural axial multidetector CT image during the arterial phase demonstrating nodular, heterogeneous enhancement of a well-circumscribed mass in segment V of the liver (white arrow). (b) Subsequent portal venous phase images with expected washout of the previously enhancing lesion, compatible with known HCC (white arrow). (c) Anterior–posterior projection of a selective proper hepatic DSA demonstrating a focal, well-circumscribed "blush" of contrast medium in the region of the tumour corresponding to the expected tumour hypervascularity, with innumerable vessels branching from the right hepatic artery (white arrow). (d) Post-procedural DSA with selection of the right hepatic artery showing a significant reduction in the contrast blush, consistent with adequate "pruning" of the tumour hypervascularity. € Immediate post-procedural, arterial phase axial multidetector CT image exhibiting a significant reduction in enhancement of the tumour bed as compared to the pre-procedural images. (f) Subsequent portal venous images with interval development of peripheral, nodular enhancement.

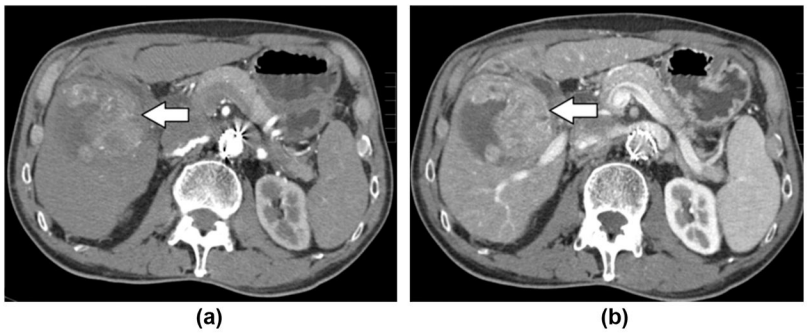

Figure 4.

(a) Post-procedural arterial and (b) portal venous phase MDCT images of a 68-year-old patient with known history of hepatitis B and biopsy-proven HCC. Following TACE, the portal venous phase images (b) demonstrate interval development of lobular enhancement within the tumour bed greater than the pre-procedural images and the corresponding arterial phase image (a).