

Tumor response criteria for hepatocellular carcinoma treated by transarterial chemoembolization - a radiologist's point-of-view

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ABSTRACT

Hepatocellular carcinoma is a common malignancy which, in specific stages, benefits from transarterial chemoembolization. The survival of treated patients depends on the accurate interpretation of follow-up studies after the procedure, with focus on the early detection of residual tumor or tumor recurrence. Dynamical contrast enhanced CT and MRI are sensitive methods in evaluating tumor response, although diffusion weighted imaging and other new modalities can improve the diagnostic role of these tests. A strong knowledge of common and rare imaging signs of neoplastic tissue in a chemoembolized nodule can lead to a prompt and effective complementary treatment. Some lesions related to the endovascular intervention mimic tumor behavior and should always be sought and correctly identified, in order to avoid unnecessary treatment and impacts in the patient's quality of life.

Key words: Transarterial chemoembolization, tumor response criteria, hepatocellular carcinoma, medical imaging, imaging signs, pseudolesions.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most common malignancy in the world, and third most common cause of cancer-related deaths by most studies (1, 2). One of the distinctive features of HCC is its onset in patients with chronic liver disease, most commonly an underlying cirrhosis, which is seen in 4 out of 5 HCC patients (3).

Early diagnosis is demonstrated to improve survival of patients at risk (4), and thus screening and surveillance can prove effective in this case, although an optimal protocol is still to be agreed upon (5). Most studies recommend using serum alpha-fetoprotein levels and abdominal ultrasound at 6- to 12 month intervals (6).

Positive diagnosis should be set on CT or MRI, and all patients with liver nodules larger than 1 cm detected on ultrasound should be referred to one of these two superior diagnostic procedures. Biopsy is usually performed only for non-typical HCC imaging findings, though the specific risks should be considered (7).

There is no consensus as to which staging system is most useful, though Barcelona Clinic Liver Cancer (BCLC), the Okuda system, CLIP score and TNM system are the most commonly used (8). Surgical treatment is preferred for early stages depending on tumor size and location, and liver function, while liver transplantation is the most viable surgical option for non-operable patients (9).

Transarterial chemoembolization (TACE)

Patients with multifocal HCC or surgically incompatible lesions are candidates for TACE. This procedure is generally recommended for BCLC stage B multinodular asymptomatic tumors confined to the liver (10). This minimal invasive procedure has a dual function, of directly introducing a strong chemotherapeutic drug directly into the tumor while eliminating the tumor blood supply by administering embolic material into the feeding arteries. The resulting vessel occlusion causes necrosis which is considered a positive response and minimal systemic toxicity (11).

This procedure can be applied in different technological methods, which hold specific imaging findings, depending on the drug and carrier being used, as described in the following.

“Classical” transarterial chemoembolization

The procedure introduced in the late 1970s by Yamada et al, which uses chemotherapeutic agents with or without iodized oil, followed by Gelfoam (12). The expected result is to prevent wash-out of the therapeutic drug from the tumoral nodule, and to obtain ischemic necrosis. There is no standard protocol for this procedure, though a very common feature in most centers is the use of iodized oil, because it has been demonstrated that it is selectively absorbed into the tumor vascular structure (13).

Transarterial chemoembolization using drug-eluting microspheres

A new procedure of drug-delivery, which uses polyvinyl alcohol-based microspheres to absorb a specific drug, and then introducing them transarterially to the tumor site (14). Specific properties of microspheres include a stable and sustained drug-release and a greater uptake by the tumor when compared to

conventional TACE (15). Typically, doxorubicin-capable beads (DC beads) are used to charge up to 25 mg/mL doxorubicin in a maximum of 120 minutes (16), but copolymer microspheres (QuadraSphere) also loaded with doxorubicin have also shown efficient chemotherapeutic properties (17).

Other transcatheter embolization procedures include a hybrid method of using micron-sized particles loaded with a radioisotope (Yttrium-90) which can deliver up to 150 Gy at the tumor site without the systemic complications of external beam irradiation (18). Although some studies showed good tumor response, the low availability of the isotope, specific handling regimen and generally low experience with this method limit its usage (19).

Imaging findings in treated HCC

Surveillance of a treated HCC is routinely performed by either computed tomography (CT) or magnetic resonance imaging (MRI), but contrast-enhanced ultrasound (CEUS) has also proven effective in the management of these patients (20).

Role of CT in treated HCC

Usually performed 1 to 3 months after the TACE procedure, is the most commonly used imaging modality in this cases, because of its accessibility and ability to analyze the microcirculation by perfusion CT (21).

Our center uses a GE Optima CT660 64 slice computed tomography machine with an Advantage Workstation, as well as a Siemens Somatom Emotion 16 slice CT with a Syngo Workstation (22); images in this paper were obtained on these machines.

The scanning protocol should include an unenhanced scan which objectifies the presence, morphology and distribution of the iodized oil, in the case of classical TACE (23). A mid-arterial and a portal phase, usually at around 30 – 40 seconds and 80 – 90 seconds respectively after the injection of the iodine contrast should be employed. A late phase at around 180 – 210 seconds is most helpful in describing contrast wash-out from viable tumoral areas (24). Fine reconstructions of 1.5 mm thickness with 1 mm increment aid the image analysis.

Imaging findings of a successful treatment with classical TACE should include a homogenous iodized oil retention at an interval longer than 4 weeks (*figure 1 a,b,c*), being indicative of a complete necrosis (25).

When microspheres are used, complete necrosis is suggestive of a successful procedure, the embolized nodule appearing as a homogenous non-enhancing hypodense lesion (*figure 1 d,e,f*) (26, 27).

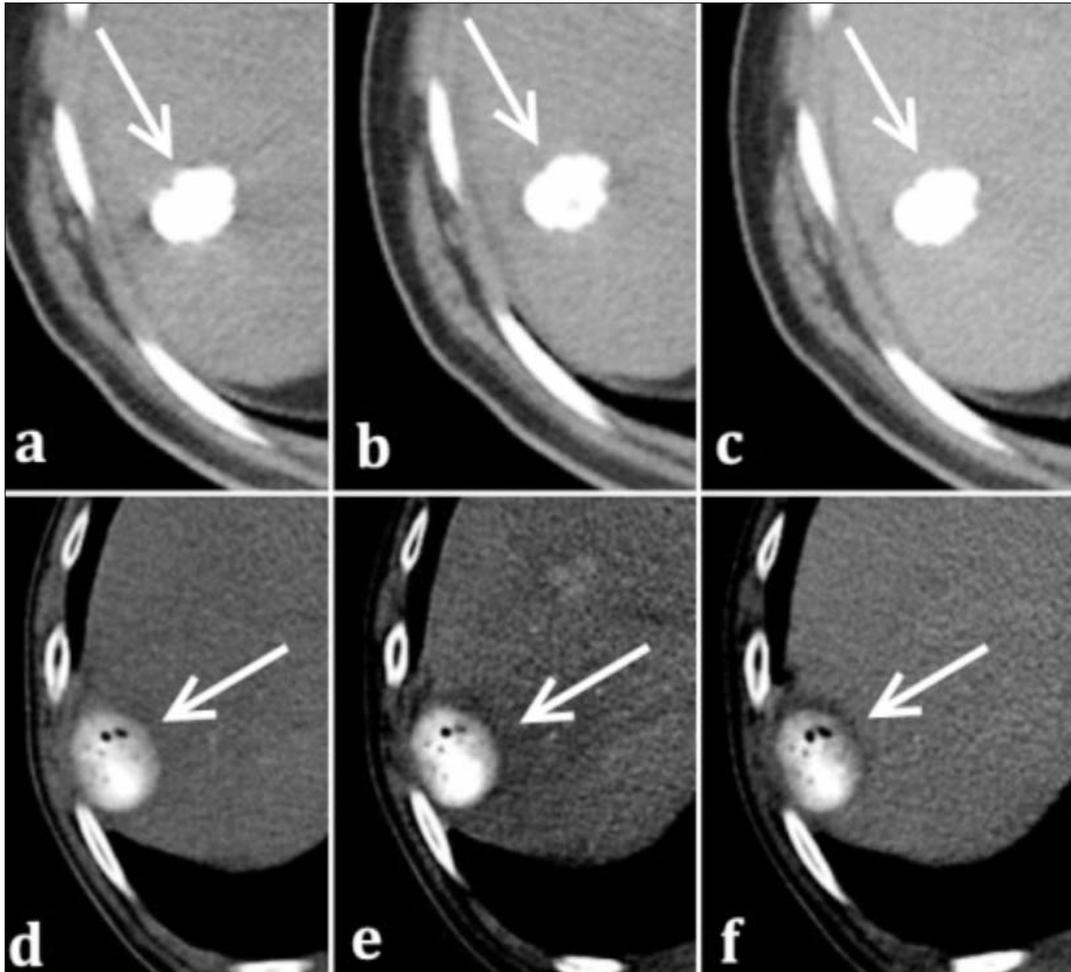


Figure 1 - Conventional TACE - Iodized oil mass on CT in different phases of contrast administration: unenhanced (a), arterial (b) and portal (c). DC-bead TACE 24 hours after the procedure with iodine contrast still visible inside the nodule on CT, and small air bubbles due to tumor necrosis: unenhanced (d), arterial (e) and portal (f) phases

Role of MRI in treated HCC

MRI is generally considered superior to CT in the evaluation on HCC treated by TACE due to the higher contrast resolution and variety of acquired sequences (28). Also, iodized oil deposits do not interfere with signal intensity in T1- and T2-weighted images (29).

Our department uses a Toshiba Vantage Titan 1.5T machine and as well as a GE Sygna Excite 1.5T MR installation, both used to capture the images in this article. Although some authors note higher resolution or other improvements in image detection at higher field MR machines, the specific limitations due to increased artifacts and image inhomogeneity at 3T still represent a challenge, and the final role of 3T scanners in the imaging of the treated hepatocellular carcinoma is yet to be demonstrated (30).

The routine follow-up protocol should include axial

T1 WI, T2 WI, T2* GRE and T1 dual-echo images, which should respect the same parameters in regard to slice thickness, spacing and positioning, to aid the interpretation of imaging findings in all sequences. Dynamic administration of hepatocyte-specific contrast media (Gd-BOPTA or Gd-EOB-DTPA) is mandatory, with arterial, portal and late acquisitions, as well as in so-called hepatobiliary phase performed at 60 to 120 minutes after the Gd-BOPTA iv. injection or at 15-20 minutes after GD-EOB-DTPA iv. injection. Long echo-time T2 WI can better delineate fluid areas associated with necrosis.

Diffusion-weighted imaging (DWI) can show the restriction of free water movement commonly identified in hypercellular areas such as tumoral nodules. Multiple b-values should be used when available, commonly including three values as follows: first b-value between 0 and 50 s/mm², second b-value between 400

and 600 s/mm^2 and the third between 800 and 1000 s/mm^2 or higher, depending on field strength and machine capabilities (31, 32). The current challenges that DWI is facing are due to its high susceptibility especially in the liver dome, liver edges in contact with the gastro-intestinal tube or liver areas below the heart. Calculation of the apparent diffusion coefficient (ADC) doesn't seem to provide additional diagnostic criteria (33).

A successful TACE procedure induces liquefaction necrosis in the tumor, with no enhancement on dynamic contrast administration (*figure 2 a,b,c*). Although this method is applied in a similar fashion on CT, MRI is demonstrated to be more sensitive than CT for lesions smaller than 2 cm (34).

On DWI, the cellular necrosis associates increased membranous permeability which translates to a reduced restriction on DWI and hyperintensity on the ADC map (*figure 2 d,e*). Some authors consider DWI to be more valuable than dynamic contrast enhancement (DCE) MRI after TACE (35).

Imaging signs of tumor viability after TACE

Areas of nodular or crescent-shaped enhancement in connection with the treated nodule

Some authors classify crescent or incomplete ring enhancement as nodular enhancement (36). Necrotic tissue has no contrast media uptake, enhancement being observed in residual tumor tissue (*figure 3a*).

In classical TACE, image analysis on CT can be difficult due to the beam-hardening artifacts produced by iodized oil; in this case, MRI can prove to be superior, although microscopically residual areas of tumor cells in the capsule can be missed because the tumor capsule can appear as a hyperintense ring in T1 WI, with early and/or late enhancement (37). Another possible solution to counter the iodized oil artifacts on CT is to use image subtraction, though breath-in asymmetry and various software limitations can lead to suboptimal results (*figure 3b*).

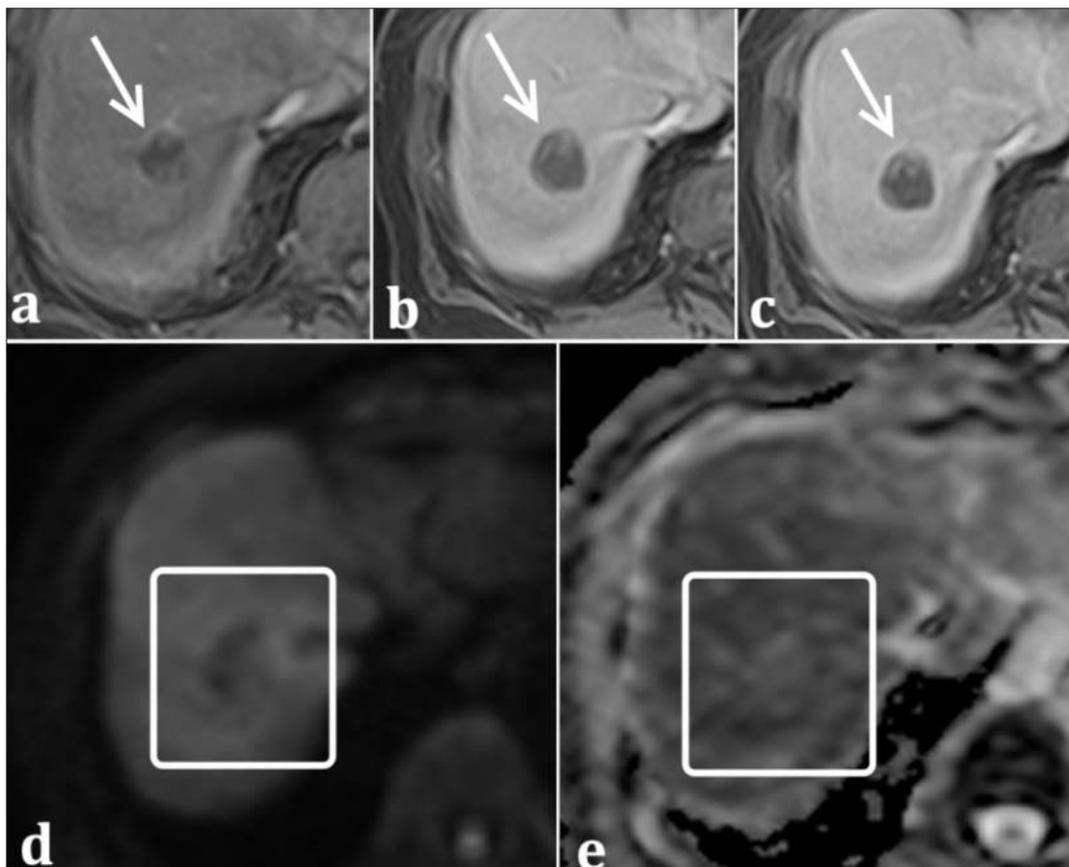


Figure 2 - MRI follow-up of a TACE-treated nodule with complete necrosis. DCE with unenhanced (a), arterial (b) and portal (c) phases show no enhancing lesions while DWI (d) and corresponding ADC map (e) show no restricted diffusion

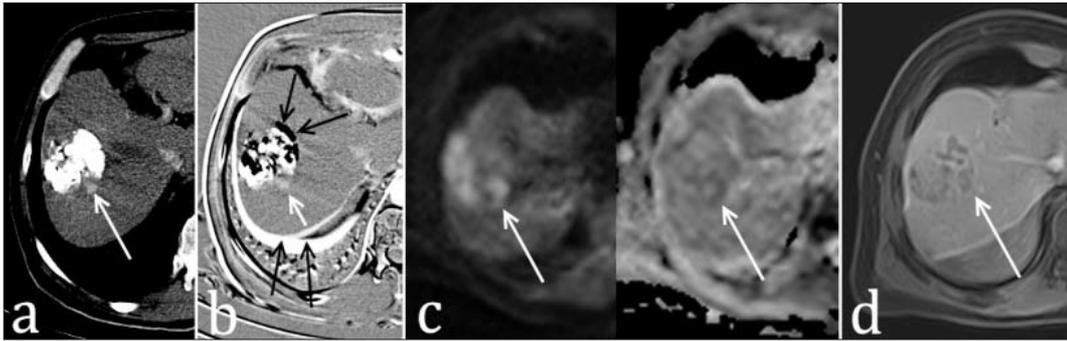


Figure 3 - HCC treated by conventional TACE. Enhancing nodule in contact with the iodized oil mass on arterial phase CT (a), also analyzed on subtracted images (b), with good visualization of the lesion (white arrow), despite obvious artifacts due to unequal breath-hold between phases (black arrows). MRI shows small areas with restricted diffusion on DWI and ADC map (c), and late hepatobiliary phase with hepatocyte-specific contrast media shows hypointensity of the small tumoral areas with restricted diffusion into the nodule

Nodular enhancing areas often correlate with hyperintense areas on DWI, and corresponding low ADC values (*figure 3c*). Studies show that breath-hold DWI in conjunction with DCE-MRI has superior sensitivity in tumoral detection than DCE-MRI alone, especially in very small lesions (38).

A hepatobiliary phase study after the administration of hepatocyte-specific contrast media should demonstrate complete washout of the nodular area, while normal liver cells in the vicinity show normal contrast concentration (*figure 3d*).

Peripheral enhancement with washout in the equilibrium phase

Washout in peripheral areas of the treated nodule is characteristic of viable tumor tissue in most cases, on both CT and MRI (*figure 4*) (39). Hypervascularity and hypercellularity of the HCC are key factors in this imaging finding. Because inflammatory changes around the embolized nodule can also show these features, analyzing the hepatobiliary phase images when using liver-specific contrast media on MRI can help delineate between the two (40).

A correct scanning protocol plays a major role in obtaining optimal timings in regard to contrast bolus flow in the specific anatomical compartments.

Focal defect / washout in the mass with iodized oil

Best interpreted on DCE-CT, this imaging sign of tumor viability is caused by partial iodized oil retention and subsequent incomplete necrosis (*figure 5*). The accumulation patterns of iodized oil on CT should be known, as they can help establish the therapeutic

effectiveness of TACE and the probability of malignancy (41). A focal defect or washout in a iodized oil mass is commonly regarded as the presence of tumoral tissue and the need for additional treatment (42). Even an homogenous iodized oil nodule can hold a minute probability of viable tumoral tissue, so pre- and post-treatment images should always be analyzed side-by-side (26). Also, using the same modality to assess the treated nodule before and after TACE is ideal to obtain a maximum comparability (23). Suspicious or indeterminate imaging features on CT should be further analyzed by MRI (43).

Increase in size on follow-up studies

Due to the heterogeneity of imaging features of the treated nodule, size increase between consecutive studies is proven to be one of the most reliable signs of tumor viability and disease progression, thus being the most important criteria used in modern target lesion response criteria guidelines (*figure 6*) (44).

An increase the lesion size between the treatment start and current investigation of more than 20% in the sum of the diameters is an indicator of progressive disease according to RECIST 1.1 and mRECIST, while WHO and EASL criteria use an dimensional increment of 25% in the sum of the diameters between investigations (45).

The tumor response criteria use the nodule size increase independently and regardless of other imaging signs. For the best results in comparing tumoral nodules at different moments in time, using the same technique, machine and perhaps investigating doctor can be ideal.

A three dimensional quantitative tumor response

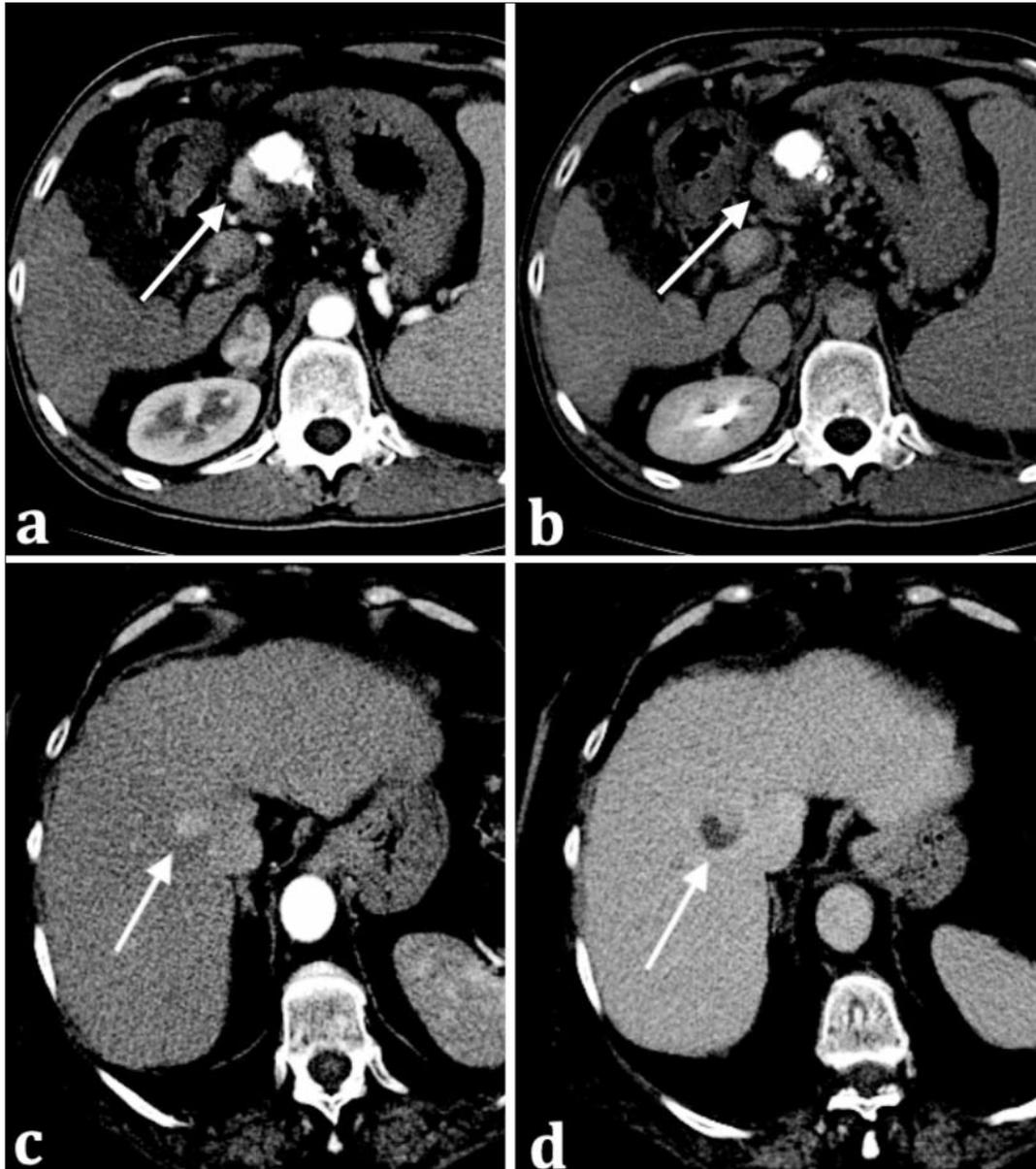


Figure 4 - HCC treated with conventional TACE. Enhancing lesion in connection with the iodized oil mass, with important arterial flash (a) and portal washout (b). HCC treated with DC beads TACE. Nodule connected with the necrotic area of the tumor, with arterial enhancement (c) and portal washout (d) of the contrast (white arrow)

assessment provides a more accurate analysis, though it requires a special software platform, and is not yet validated by major randomized trials (46).

Pseudolesions mimicking tumor viability after TACE

Enhancing peripheral ring

A common feature of nodules treated by radio-frequency ablation, a complete arterial-phase enhanc-

ing peripheral ring or rim appears as an inflammatory response due to thermal necrosis (47). This rim can also appear in some cases in DC Bead embolization, with similar features: early thin peripheral ring enhancement with no washout on the portal venous phase (figure 7) (48).

Wedge-like peripheral enhancement

Sometimes difficult to differentiate from nodular peripheral enhancement, this pseudolesion translates

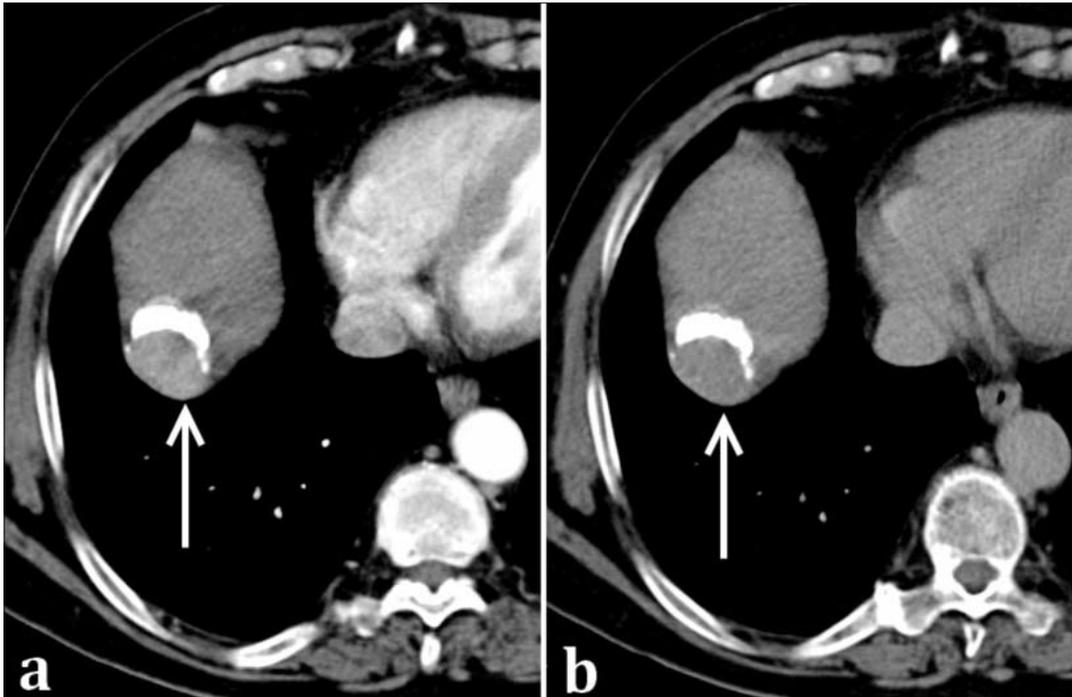


Figure 5 - Iodized oil focal defect in a HCC of the liver dome treated with conventional TACE. Tumoral tissue with visible contrast uptake in the arterial phase(a), and subsequent wash-out in the late phase (b)

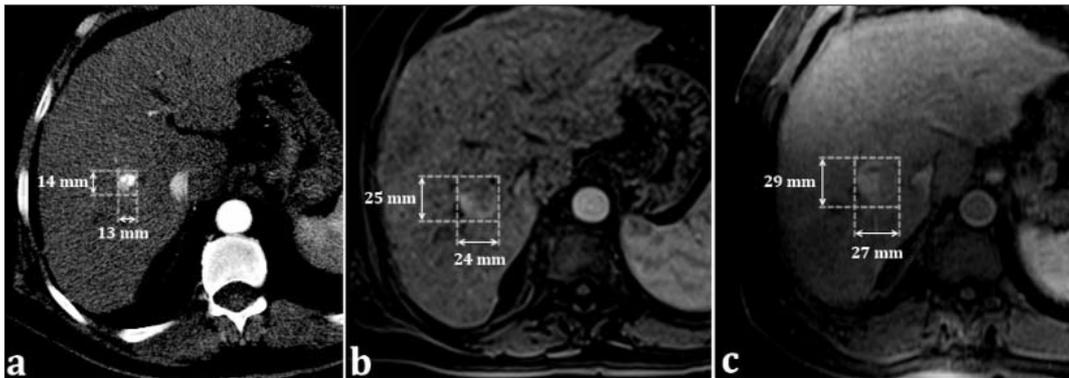


Figure 6 - Serial evaluation of a nodule treated by conventional TACE. Initial post-procedural CT evaluation in May 2014 (a), with significant size progression on subsequent MRI investigations in October 2014 (b) and December 2014 (c)

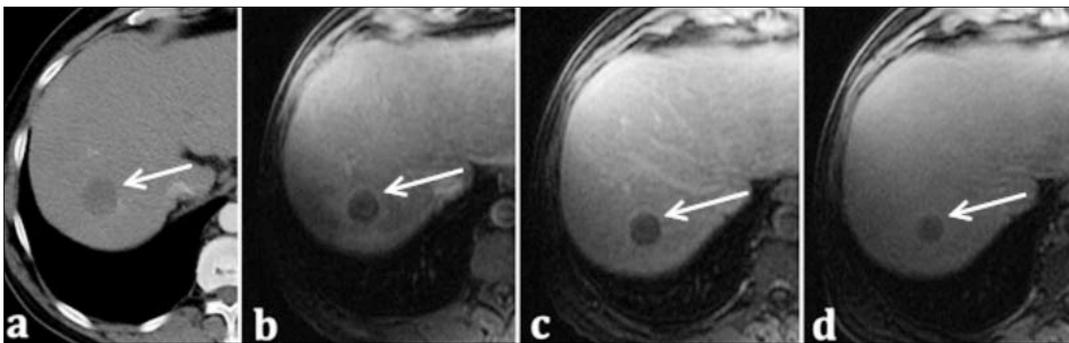


Figure 7 - Peripheral rim in a HCC nodule after TACE. Similar findings in CT (a), as well as arterial (b), portal (c) and late (d) phases of MRI scan

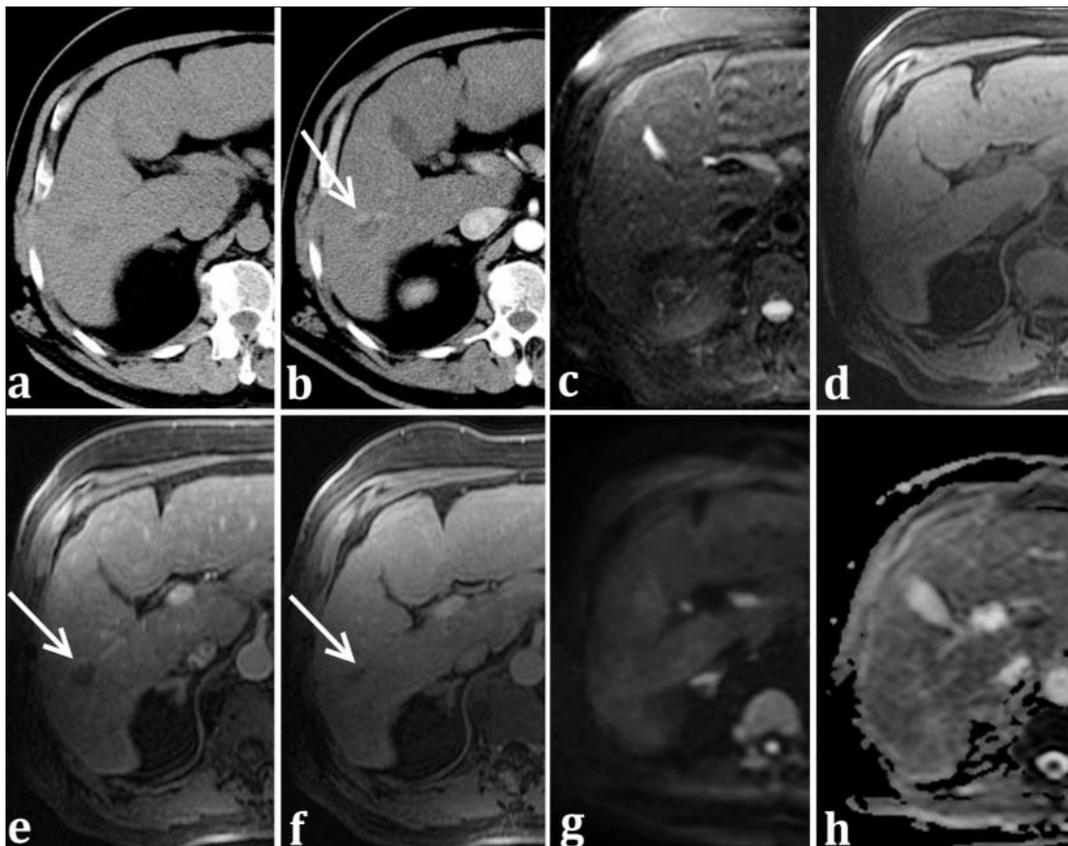


Figure 8 - Wedge like enhancing lesion on the anterior side of a TACE-treated nodule. Unenhanced studies CT (a) and MRI T2 (c) and T1 sequences (d) show no focal heterodense lesions and no signal anomalies, respectively, around the treated nodule. Arterial phase on CT (b) and MRI (e) shows wedge like enhancing lesion with no washout (f) and no restricted diffusion (g,h)

small arterio-portal shunts often caused by the toxic effects of iodized oil on small hepatic arteries (*figure 8*) (49). This sign is also commonly found in RF ablation of tumoral nodules, more frequently on the trajectory of the needle (50).

Focal washout of iodized oil in specific areas of the liver

TACE relies on the principle that up to 85% of the tumoral tissue blood supply is derived from the hepatic artery, thus selective catheterism and administration of chemotherapeutic drugs holds good results. An important aspect of liver vascularization is that specific areas of the liver usually have collateral arterial supply, which can feed tumoral nodules in these areas. These areas are the bare area of the liver (which has secondary arterial supply from the inferior phrenic artery), the area near the falciform ligament (with arterial sources from the internal mammary artery) and the anterolateral subcapsular areas (with arterial omental branches)(51). In

this case, a focal washout of iodized oil can point to the presence of collateral vessels, but not necessarily to viable tumoral tissue (*figure 9*). Supplementary caution should be exerted during TACE procedure in these areas, in order to correctly identify all arterial blood sources of the liver nodule (52).

CONCLUSIONS

Sectional imaging plays a main role in the investigation of hepatocellular carcinoma treated by transarterial chemoembolization. DCE CT or MRI are the most sensitive methods to diagnose therapeutic efficacy, although DWI and other emerging techniques can improve the sensitivity of these tests. Although there is no consensus as to the optimal timing and method for imaging follow-up, the key features of tumor viability or recurrence should be well-known, and any suspicion of malignancy remnants should be sanctioned by a subsequent TACE procedure or specific treatment according

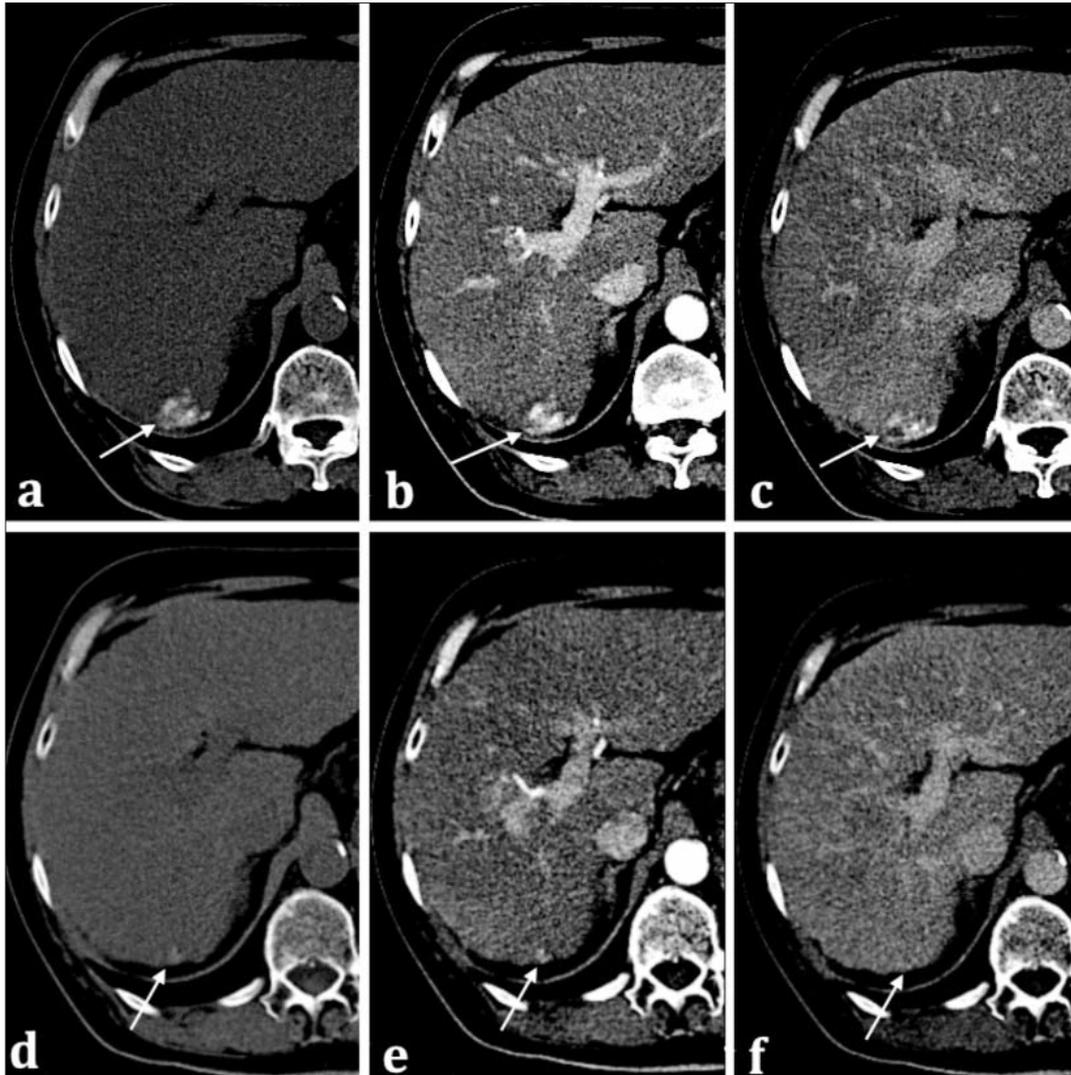


Figure 9 - Subcapsular HCC in treated with conventional TACE (segment VII). Unenhanced CT shows heterogeneous iodized oil spots in (a), with some arterial enhancing small zones (b) with washout in the portal phase (c). Patient follow-up after 19 months shows iodized oil clearance in the unenhanced study (d), but no signs of tumor recurrence on contrast administration in arterial and portal phases (e and f, respectively). New HCC nodule adjacent to the right portal vein (d, e and f)

to the disease stage at that moment. Pseudolesions can mimic disease and can erroneously expose the patient to the administration of unnecessary toxic drugs and/or submittal to irradiating and sometimes risk-bearing procedures.

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