Post-locoregional Therapy Imaging of the Liver

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Introduction

Primary and secondary hepatic malignancies constitute an increasing healthcare problem with the progressive rise of hepatitis and obesity, as well as the high incidence of colorectal carcinoma and associated metastatic involvement of the liver [1]. Ideally, treatment strategies involve tumor resection or hepatic transplantation; unfortunately, many patients have advanced stage or multifocal tumor at the time of presentation and, therefore, are not candidates for these treatment options [2]. In these cases, alternative locoregional therapy (LRT) is employed to treat the disease with promising results reported in experienced hands [3].

The use of LRT in treating hepatic malignancies has markedly increased over the past decade, highlighting the emphasis on improving peri- and post-LRT imaging [3]. Varying techniques can be utilized in the treatment of small primary and secondary hepatic malignancies with the ultimate goal being tumor cell death [4]. Tumor ablation is defined as the directed application of chemicals or energy to achieve tumor "destruction" [4]. LRT is achieved most commonly by chemical, thermal, or radiation techniques with novel techniques focused on cytostatic or delayed cytotoxic effects [5–7]. Appropriate imaging methods need to be employed that can adequately evaluate the specific LRT technique being utilized. Due to complexities in therapeutic approach, the imaging evaluation of post-LRT of primary and secondary hepatic malignancies is of paramount importance in assessing the effectiveness of these treatment options. Evaluation for treatment response, treatment margins, and tumor recurrence is essential in assessing therapies and directing the need for future treatment [8]. The following discussion focuses on peri- and post-LRT imaging evaluation utilizing CT, PET, US, and MR.

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Imaging Evaluation of Locoregional Therapies

Imaging Considerations

Multiple challenges exist when evaluating peri- and post-LRT. The effectiveness of the tumor destruction is assessed by the change in number and/or function of neoplastic cells in response to treatment [11]. In the peri-LRT setting, monitoring must be able to assess and quantify the response to therapy as well as determine the completeness of the therapy and whether further intervention is necessary [8–10]. On follow-up post-LRT monitoring, assessment of treatment effectiveness and residual disease as well as evaluation for tumor recurrence and metastatic involvement must be made [12]. Therefore, the ideal monitoring method should be optimized to detect an immediate response for a specific tumor by a specific LRT technique while being reliable and repeatable for subsequent follow-up evaluation. Although tissue sampling is the gold standard in determining effectiveness, it is invasive and not practical for each case; therefore, surrogate imaging biomarkers are utilized to assess response to treatment [13]. Various imaging modalities and techniques are utilized to obtain these anatomic, functional, and molecular biomarkers that are then used to determine the effectiveness of the LRT.

Peri-LRT/Procedure Evaluation

Periprocedural evaluation of transcatheter therapies such as TACE or Y90 radioembolization can be challenging as the index tumor may have a variable blood supply. Identification of the vessels that perfuse the tumor is essential in directing

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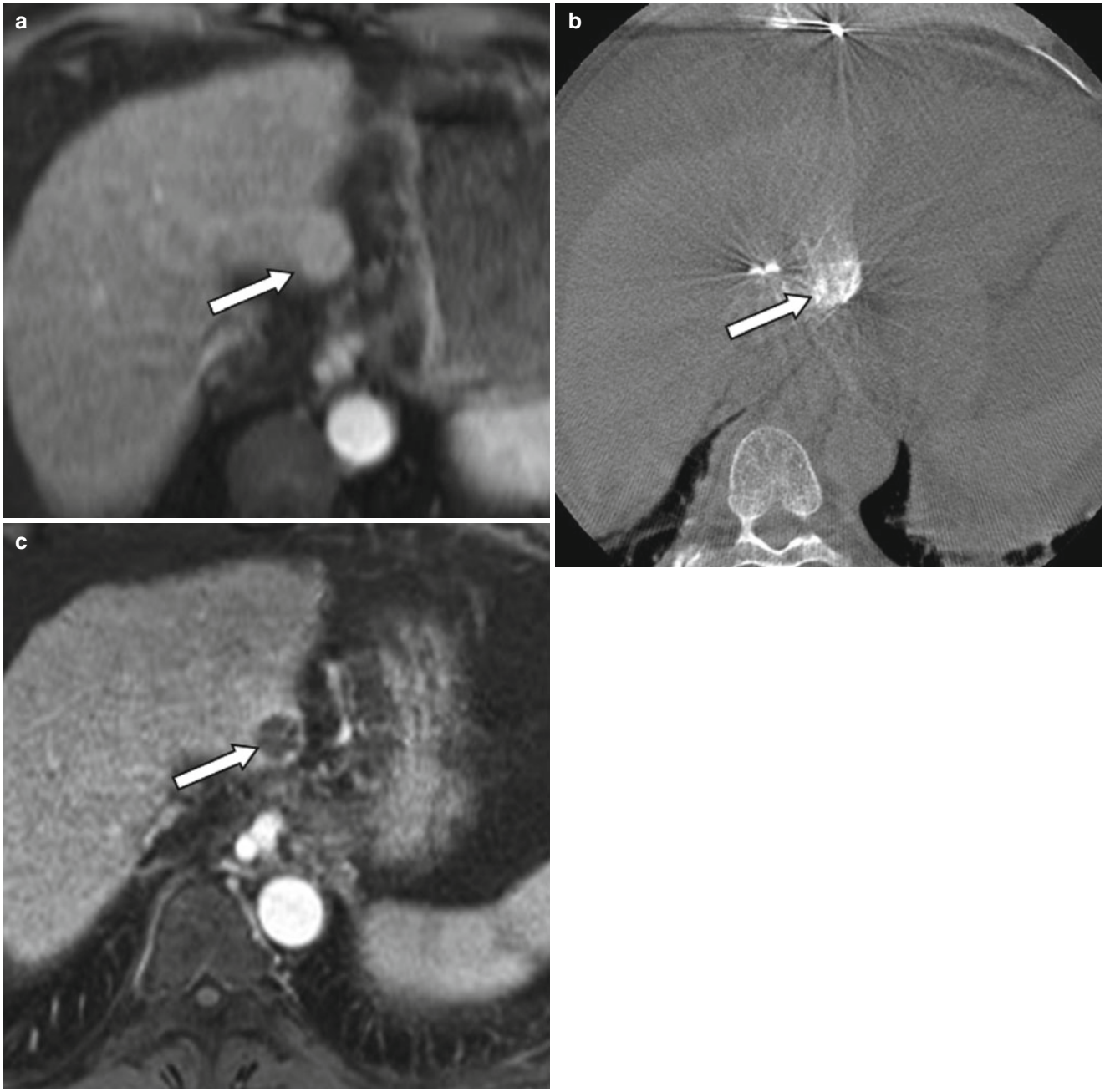

Fig. 4.1 A 64-year-old male with unresectable HCC. The segment II lesion (*arrow*) demonstrates hyperenhancement on the contrast-enhanced gradient echo MRI images before treatment (**a**). Immediately after administration of radioembolization particles, DynaCT shows distribution of therapy throughout the lesion (**b**). Follow-up MRI demonstrates loss of enhancement compatible with a complete response to therapy (**c**)

the catheter-directed therapy and to ensure that an adequate therapy response is achieved with minimal collateral damage [14]. Conventional digital subtraction angiography (DSA) is limited in assessing the variable vascular supply to a tumor and also in determining therapeutic end points [15]. C-arm cone-beam computed tomography (CACT) offers reconstructed CT-like images from a flat panel C-arm during the LRT allowing visualization of the liver tumor and feeding vessel (Fig. 4.1) [14]. Additionally, the distribution of the therapeutic particles and associated embolic materials such as ethiodized oil can be evaluated during the procedure, and catheter position can be modified accordingly (Fig. 4.2). In

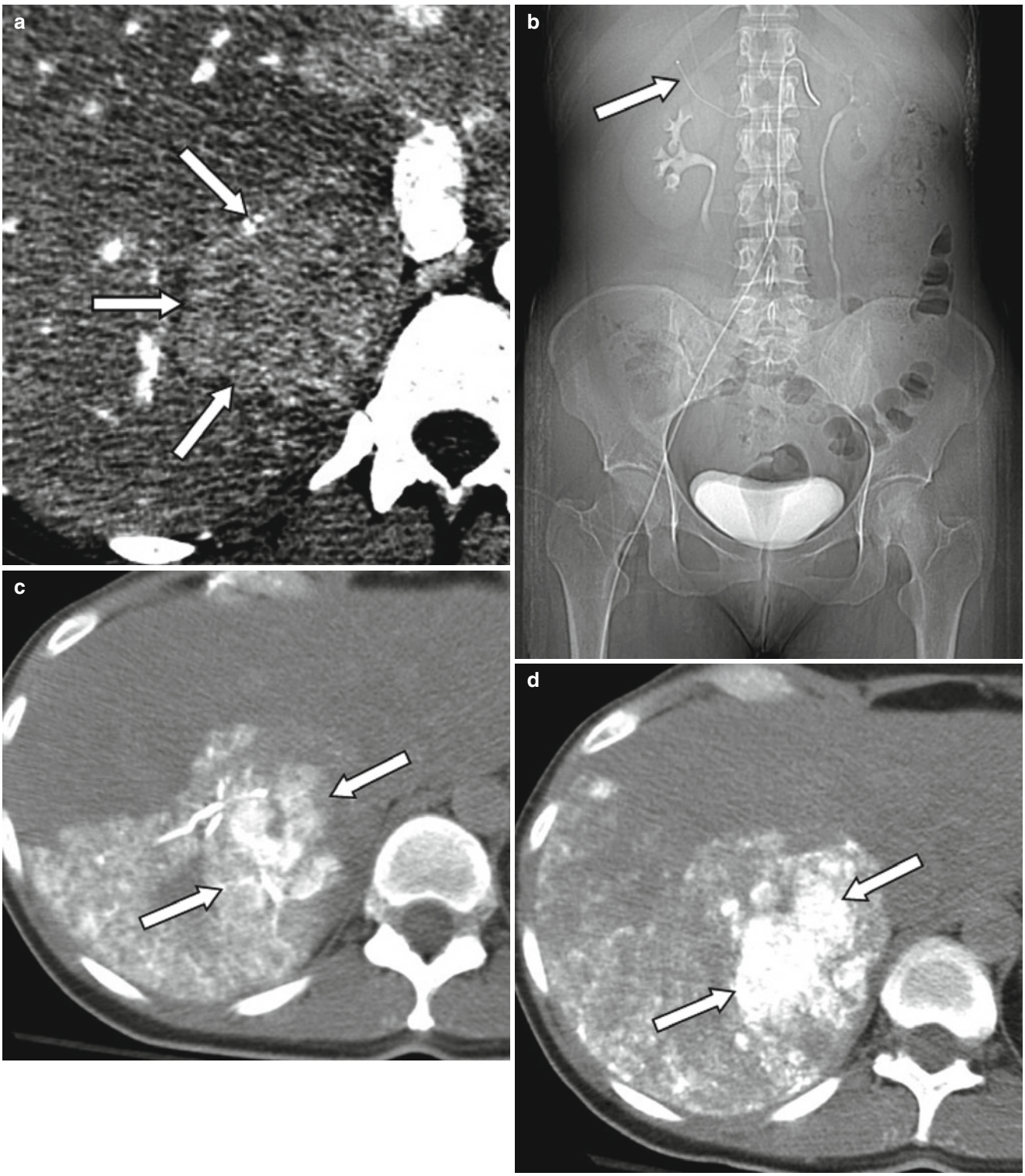

Fig. 4.2 A 48-year-old female patient with ocular melanoma metastasis to liver. Pre-treatment contrast enhanced CT demonstrates a large mass in the right lobe posterior segment of the liver (*arrows*) (**a**). Patient subsequently received TACE treatment (**b**–**d**) with superselective catheterization of the posterior branch of the right hepatic artery as seen on the scout CT image (*arrow*) (**b**). In order to assess ethiodized oil retention within the tumor, patient was evaluated with CT right after administration of ethiodized oil (**c**). Since there was insufficient treatment of tumor, additional chemoembolization material was administered, and sufficient therapy was confirmed with a second CT examination performed 2 h after the procedure (**d**)

one study, CACT modified the catheter position in 39 % of patients and improved diagnostic confidence in 79 % of cases [14].

Currently, there is no consensus in angiographic end points for transcatheter therapies. Stasis or substasis to antegrade flow on DSA evaluation is typically the goal of therapy with substasis postulated as being more efficacious as excessive embolization may be counterproductive and harmful for the patient [15]. Relatively newer techniques such as transcatheter intraarterial perfusion (TRIP) MR offer direct intraprocedure verification of therapy as well as an assessment of tumor perfusion after embolization to help guide therapeutic end points (Fig. 4.3) [15]. The ability to objectively quantify perfusion changes during therapy may serve as a functional imaging biomarker in the optimization of transcatheter therapies.

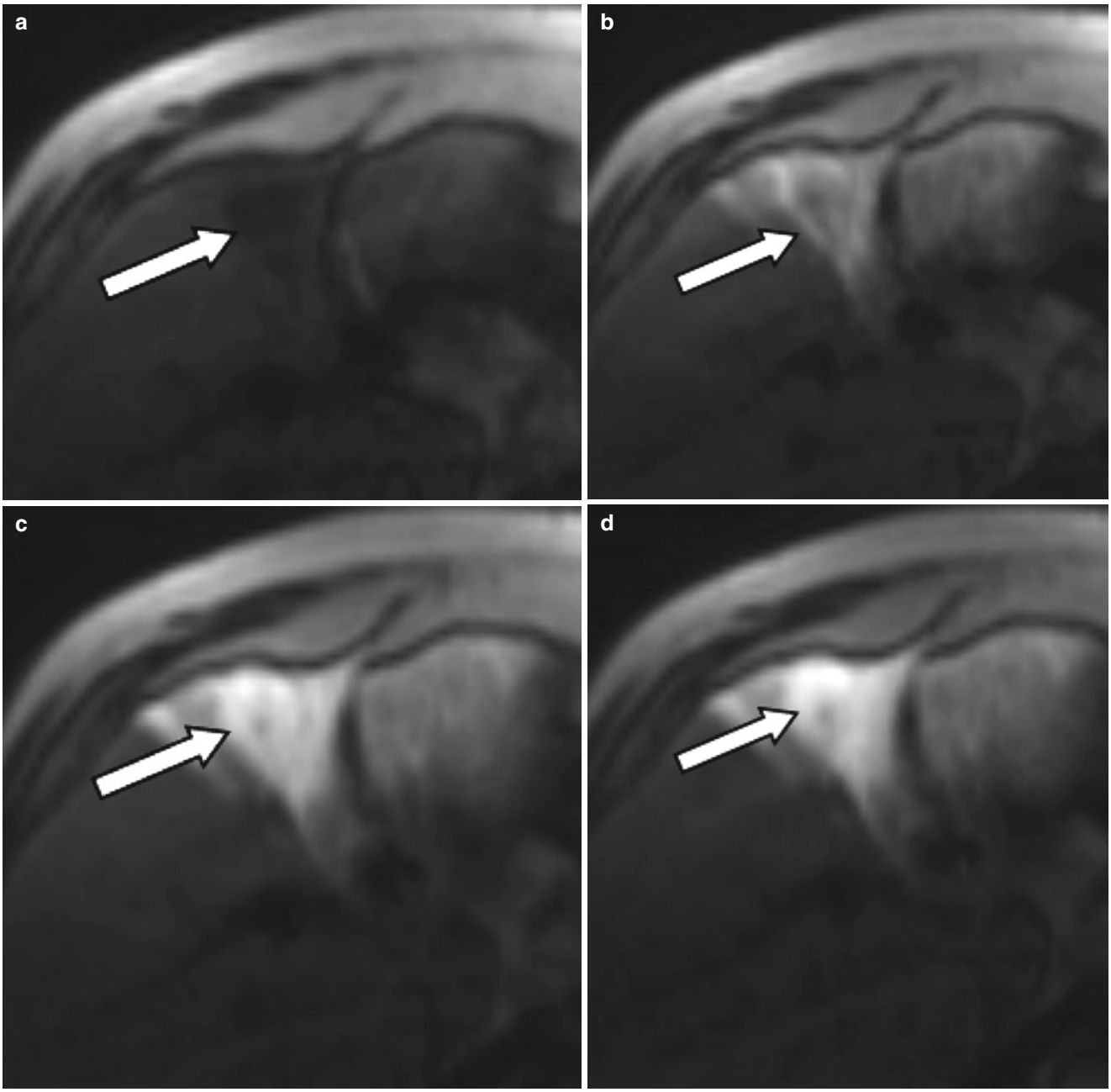

Fig. 4.3 A 54-year-old male patient with an HCC lesion involving segment 4b of the liver (*arrow*) for treatment with radioembolization. After selective catheterization of the right hepatic artery, patient was transferred to the MR suit to obtain TRIP MRI images before treatment. Serial dynamic MRI images were obtained by administration of contrast agent through intra-arterial catheter (**a**–**f**) confirming the therapeutic site

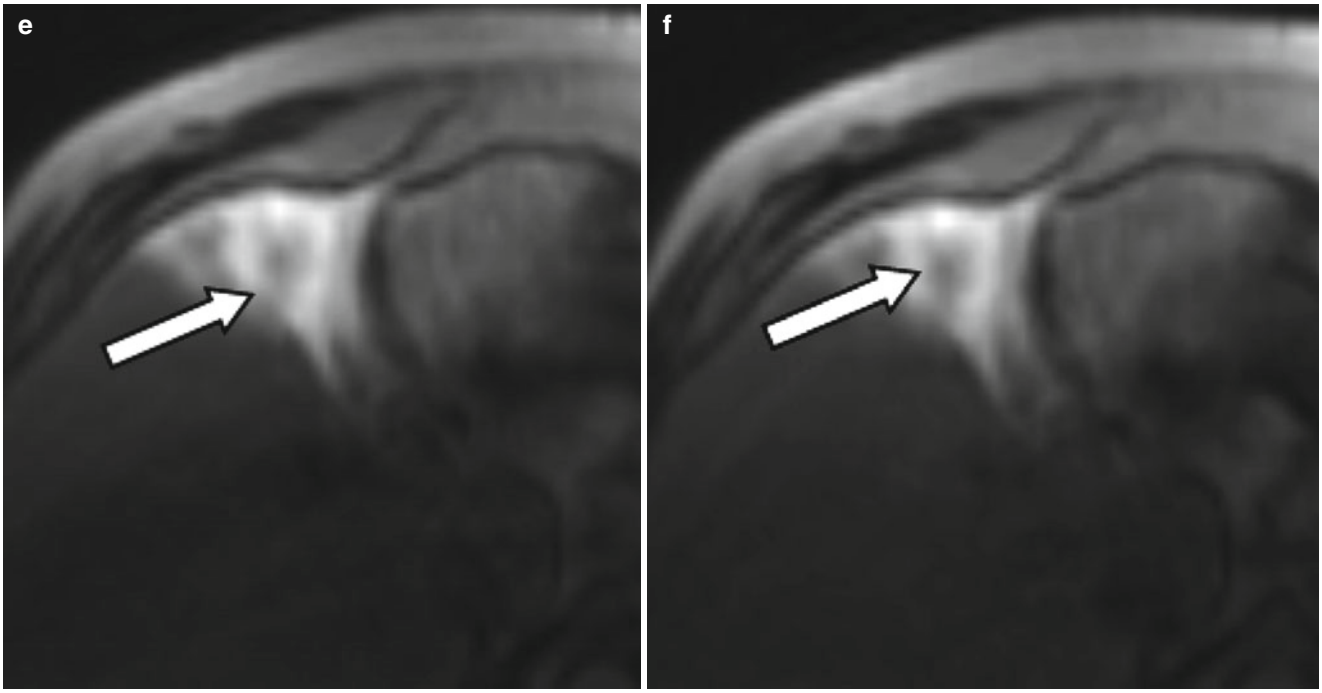

Fig. 4.3 (continued)

In the immediate post-LRT setting, for example, within 24 h after thermal ablation, a multiphase contrast-enhanced CT in the arterial, portal, and equilibrium phase may be performed to evaluate the effectiveness and extent of the therapy [12]. In centers utilizing contrast-enhanced US, evaluation of a well-delineated single tumor using this modality may be an option given the comfort and experience of the ultrasound operator [16].

With thermal ablation, a successful treatment is defined as a non-enhancing ablation zone encompassing the entire index tumor with ablative *safety margins of at least 5 mm* of the non-tumor hepatic parenchyma [17]. Safety margin should be evaluated in all three orthogonal planes. Evaluation of the safety margin can be performed by the image fusion of the pre- and post-thermal ablation CT [12]. As the zone of ablation may not be spherical due to causes such as a "heat sink" effect, evaluation can be challenging, and reliance on the multiplanar capabilities of reformatted CT images is essential in determining the safety margins of the entire ablative zone [18]. Although a safety margin of 5 mm is not always possible, the presence of unablated tumor within the ablative bed is clearly a technical failure, and additional treatment is required [12].

Nodular or thick enhancing areas along the margin of the treated zone are consistent with residual tumor in cases of hypervascular lesions, such as HCC or neuroendocrine metastasis [12]. In cases of hypovascular metastasis, evaluation can be difficult with low-attenuation nodular protrusions along the treatment margin being suspect for tumor recurrence [4]. In challenging cases, the FDG avidity of the tumor can be utilized to evaluate the tumor margin on PET imaging [4]. Alternatively, contrast-enhanced US may be beneficial with the advantage of immediate re-treatment [16]. However, in inconclusive cases short-term follow-up in 3 months or sooner may be necessary to assess the manifestation/progression of residual disease along the therapy margin.

Transient hyperemia manifested by a thin uniform enhancement of the ablation zone is an expected finding in the peri-ablative setting and although challenging should be differentiated from residual malignancy (Fig. 4.4) [5]. The hyperemia represents a transient physiologic response to thermal injury to the hepatic parenchyma [4]. Typically the transient enhancement resolves within 1 month on follow-up imaging but may last for several months [5]. However, a small amount of residual tumor may be obscured by the transient hyperemia, and careful evaluation of the ablative safety margin and close attention for persistent enhancement on short-term follow-up should be performed to determine whether further invasive treatment is needed [4].

A central hyperdense area is often seen within the treated site in the location of the electrode and should not be confused for an area of persistent enhancement. The hyperdense area is felt to represent an area of coagulative

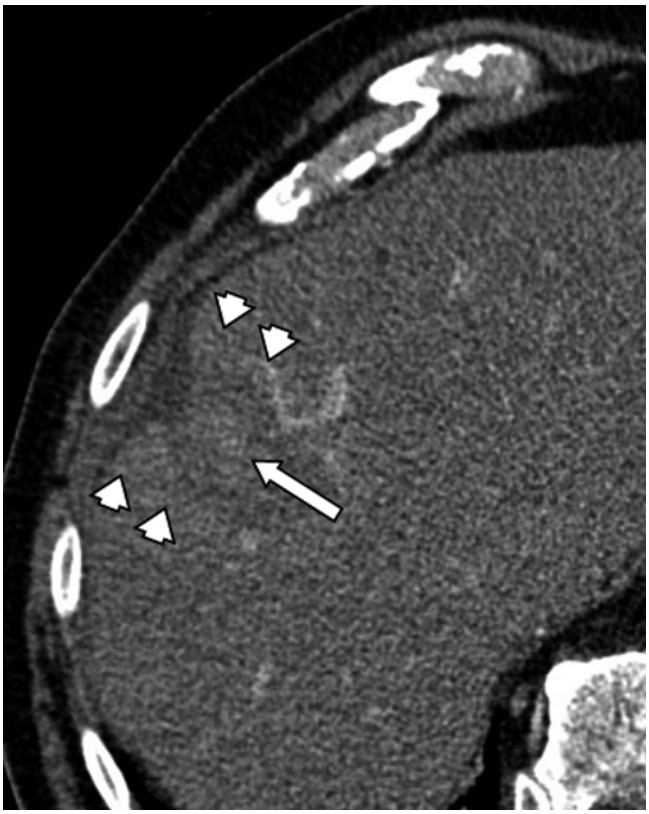

Fig. 4.4 A 74-year-old male patient with HCC. CT image 2 h after RFA procedure demonstrates central hyperdensity within the ablation cavity (*arrow*) consistent with hemorrhagic necrosis. Please note the enhancement of peri-ablative liver indicating transient hyperemia (*arrowheads*)

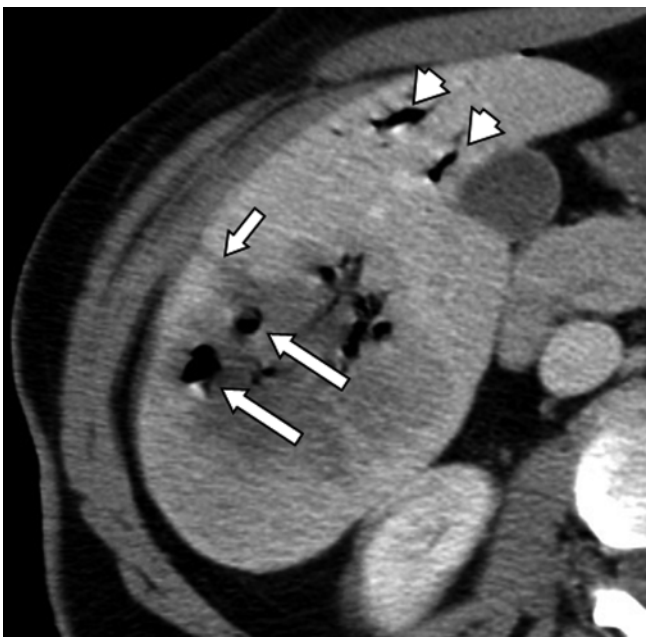

Fig. 4.5 A 42-year-old female patient with metastatic melanoma to the liver. Immediate post-procedure CT image after RFA demonstrates multiple air bubbles secondary to necrosis induced by RFA (*large arrows*). Note the needle tract extending from the ablation zone to the liver capsule (*small arrow*). There is also air in the biliary system secondary to the intervention (*arrowheads*)

necrosis and typically resolves on subsequent follow-up imaging (Fig. 4.4) [5]. This coagulative necrosis will result in hyperdense attenuation within the treated area on CT and hyperintense signal on T1-weighted MRI, limiting assessment of residual tumor enhancement when comparing unenhanced and contrast-enhanced images. Arterial-portal shunts can be seen after thermal injury to small vessels in the hepatic parenchyma with resolution on follow-up evaluation [19]. Additionally, tiny air bubbles that result from the boiling of tissue can be seen in the immediate post-procedure setting and typically resolve within 1 month follow-up (Fig. 4.5) [12]. The air bubbles should be distinguished from the mottled persistent air densities seen with a hepatic abscess or the arborizing air densities seen within a peripheral wedge-shape defect of a hepatic infarct [12].

Subsequent Follow-up Imaging Evaluation

In general, follow-up post-LRT evaluation is performed initially 3–4 weeks after treatment and then subsequently every 3–4 months with contrast-enhanced dynamic CT or MR imaging being the preferred modality [20]. Objective evaluation of the effectiveness of LRT can serve as a surrogate imaging marker for treatment response. Conventionally, oncologic imaging focused on anatomic biomarkers to assess tumor response to a therapy. The World Health Organization (WHO), incorporating bidimensional perpendicular measurements, and the Response Evaluation Criteria in Solid Tumors (RECIST), incorporating unidimensional measurements, guidelines were intended to evaluate change in tumor size and number for systemic treatments over months to years [21, 22]. The emphasis being on size with no regard to the extent or degree of necrosis produced, which is the primary goal of LRT. In fact, a treated lesion can increase in size secondary to intratumoral edema, hemorrhage, necrosis, or ablative margins [20]. For example, a non-enhancing RFA-treated tumor with a 5 mm safety margin will initially be larger than the index tumor and therefore by anatomic biomarkers alone would imply treatment failure (Fig. 4.6). Additionally, the guidelines assume tumors are spherical in shape, and thus high interobserver variability of 5–28 % has been noted in the measurement of ill-defined/irregular lesions [23]. Volumetric evaluation of the treated tumor eliminates this variability and when available offers the most comprehensive anatomic biomarker for determining treatment response [24].

Functional imaging biomarkers provide information on the viability, cellularity, vascularity, and metabolism of a tumor [25]. These biomarkers can detect response earlier than anatomic changes and are more applicable in assessing treatment response for LRT. The reduction in viable

tumor volume is felt to be the optimal method in assessing local response to LRT [13]. The European Association for the Study of the Liver (EASL) criteria evaluate local treatment response by determining the degree of necrosis in two dimensions (Table 4.1), whereas the more recently introduced modified RECIST (mRECIST) evaluates the

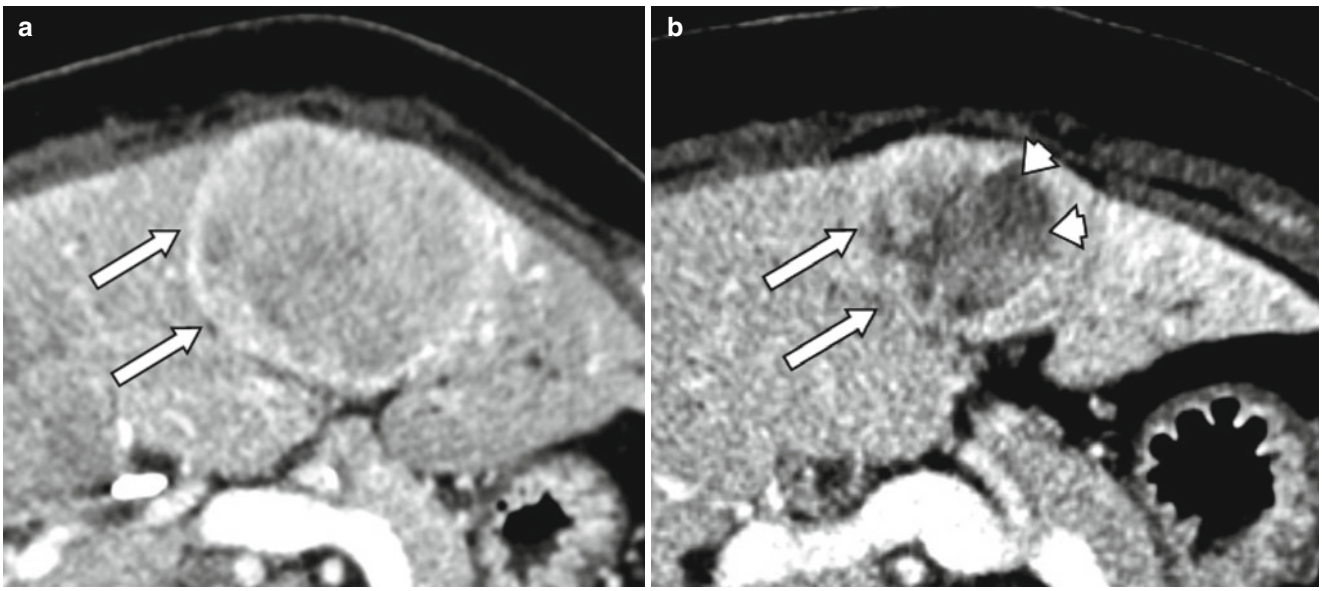

Fig. 4.6 A 52-year-old male with carcinoid metastases to liver (*arrows*, **a**). After treatment with radioembolization, the tumor has decreased in size. Also, the lesions shows central necrosis (*arrowheads*) consistent with partial response per mRECIST criteria (**b**)

Table 4.1 Comparison of EASL and mRECIST criteria

		EASL	mRECIST
Definition of target lesions	Previously untreated lesions	NA	1. The lesion can be classified as a RECIST measurable lesion (i.e., the lesion can be accurately measured in at least one dimension as 1 cm or more) 2. The lesion is suitable for repeat measurement 3. The lesion shows intratumoral arterial enhancement on contrast-enhanced CT or MRI
	Previously treated lesions	NA	The lesion shows a well-delineated area of viable tumor that is at least 1 cm in longest diameter
	Number of lesions to be evaluated[a]	NA	NA
Imaging modality		CT or MRI	CT or MRI
Phase of contrast enhancement		NA	Arterial phase
Method for measurement		Bidimensional	Unidimensional
Response categories	Complete response	Complete disappearance of all known disease and no new lesions determined by two observations not less than 4 weeks apart	Disappearance of any intratumoral arterial enhancement in all target lesions
	Partial response	>50 % reduction in total tumor load of all measurable lesions determined by two observations not less than 4 weeks apart	At least 30 % decrease in the sum of diameters of viable target lesions
	Stable disease	Any cases that do not qualify for either partial response or progressive disease	Any cases that do not qualify for either partial response or progressive disease
	Progressive disease	>25 % increase in size of one or more measurable lesions or the appearance of new lesions	An increase of at least 20 % in the sum of the diameters of viable target lesions recorded since the treatment started

[a]Depends on the mode of treatment

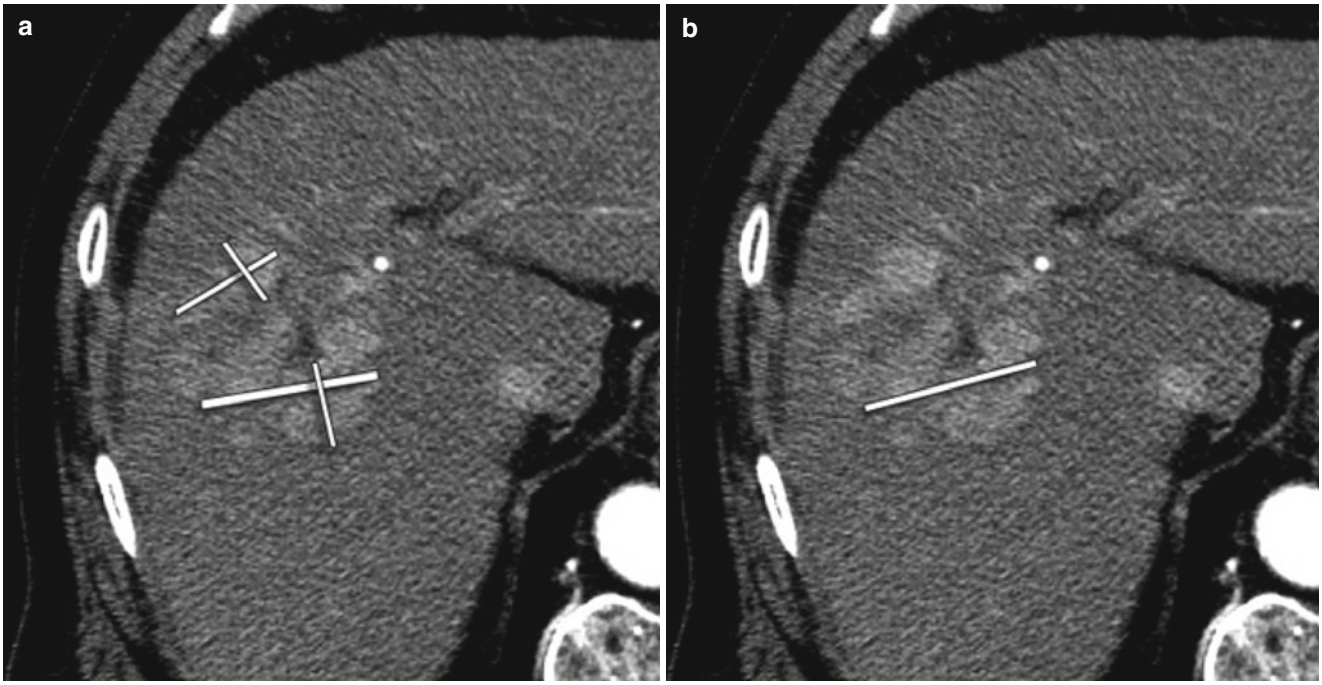

Fig. 4.7 A 64-year-old male with HCC treated with radioembolization. (**a**) EASL requires assessment of the sum of all viable tissue area using bidimensional measurements. (**b**) mRECIST requires measurement of the longest axial diameter of the enhancing tumoral tissue without comprising any necrotic tissue

decrease in intratumoral arterial enhancement (Table 4.1) using the single largest diameter (Fig. 4.7) [26, 27]. However, these measurements are again only estimates of the tumor volume and are prone to interobserver measurement variability (Fig. 4.8). Volumetric quantification of necrosis has been found to be a more reproducible method of assessing necrosis compared to two-dimensional measurements [24]. Additionally, volumetric quantification is particularly helpful in cases where necrosis is heterogeneously distributed.

Assessing change in metabolic activity for secondary hepatic malignancies has been proven to be more effective in predicting treatment response than anatomic biomarkers [28]. For example, a rapid decline in the standardized uptake value (SUV) of FDG for a tumor can be used to distinguish responders from nonresponders and thus direct treatment options. Definition for metabolic response to a treatment by FDG-PET has been categorized by the European Organization for Research and Treatment of Cancer [29]. Although FDG-PET utilization has increased,

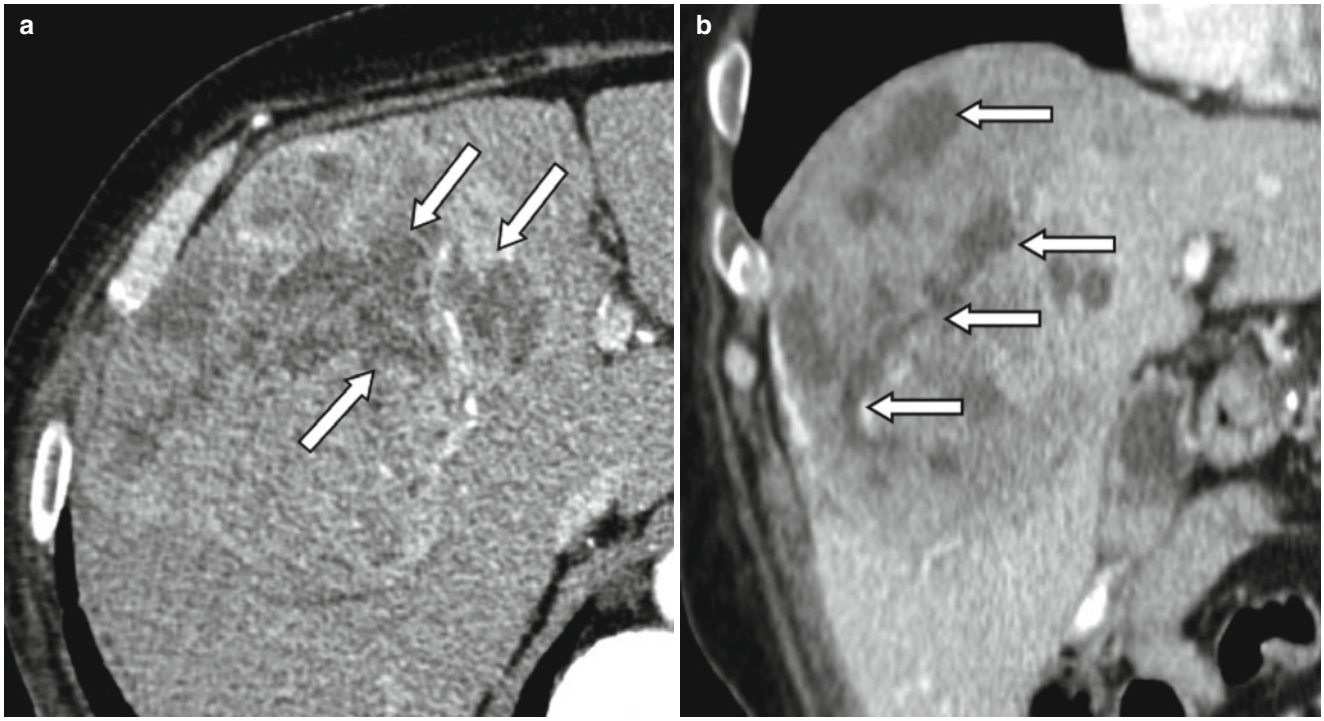

Fig. 4.8 Contrast-enhanced CT of a 67-year-old male patient with HCC treated with radioembolization. (**a**) The percentage of necrosis after treatment on the axial slices can be measured differently depending on which level it was measured. (**b**) Coronal view shows the heterogeneous distribution of necrosis within the tumor. *Arrows* indicate necrotic portion of the tumor on the axial (**a**) and coronal (**b**) planes

it is still not widely available and has a limited role in evaluating HCC. The use of decreasing CT attenuation in assessing treatment response has demonstrated positive results in colon and gastrointestinal stromal tumor metastasis [30]. A 15 % decrease in attenuation of the metastatic liver lesion after treatment combined with minimal change in tumor size demonstrated 97 % sensitivity and 100 % specificity in identifying FDG-PET responders for gastrointestinal stromal tumors [30].

Contrast-enhanced dynamic MR with diffusion-weighting imaging (DWI) can be advantageous in assessing functional treatment related changes and has been shown to be superior to CT in evaluating ethiodized oil-based TACE therapies (Fig. 4.9) [31]. The beam-hardening effects of the high-attenuation ethiodized oil on CT may obscure small enhancing tumors. However, ethiodized oil does not adversely affect MR signal characteristics allowing for small tumors to be detected on postcontrast evaluation [31]. Lesions treated

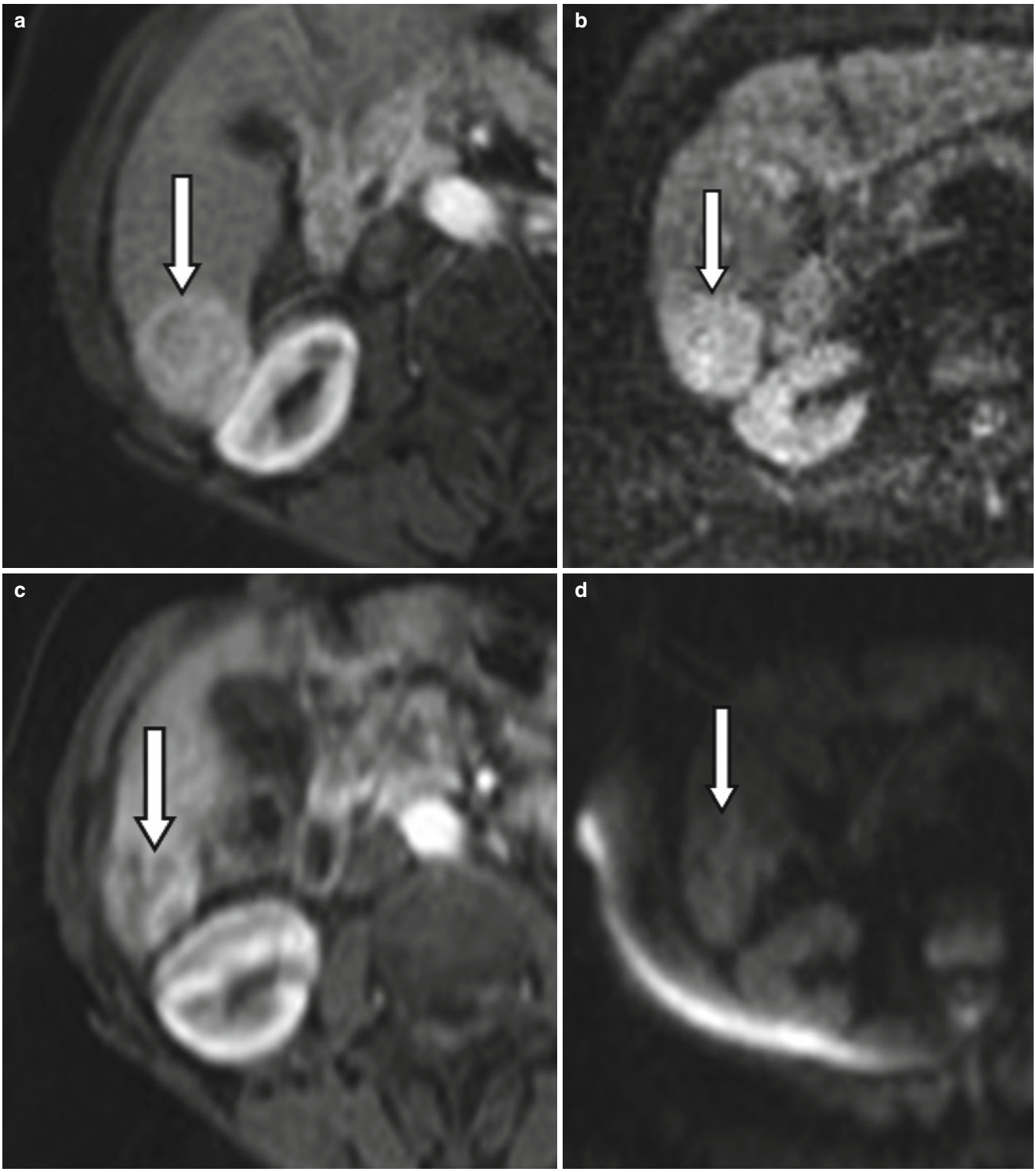

Fig. 4.9 A 65-year-old female patient with unresectable HCC. The lesion in segment VI of the liver (*arrow*) was treated with radioembolization. Before treatment the lesion is hyperintense on contrast-enhanced fat-saturated gradient echo imaging indicating enhancement (**a**) and hyperintense on diffusion-weighted (b800) MR images indicating restricted diffusion (**b**). After treatment, necrosis is evident by loss of internal enhancement (**c**), and improving restricted diffusion (**d**)

with RFA typically undergo coagulative hemorrhagic necrosis that appears hyperintense on precontrast T1-weighted sequences making postcontrast evaluation difficult. MRI subtraction techniques may be beneficial in depicting true enhancement (Fig. 4.10) [32]. However, correlation with other sequences is essential when using this technique so that post-LRT rim enhancement is not overdiagnosed as tumor recurrence.

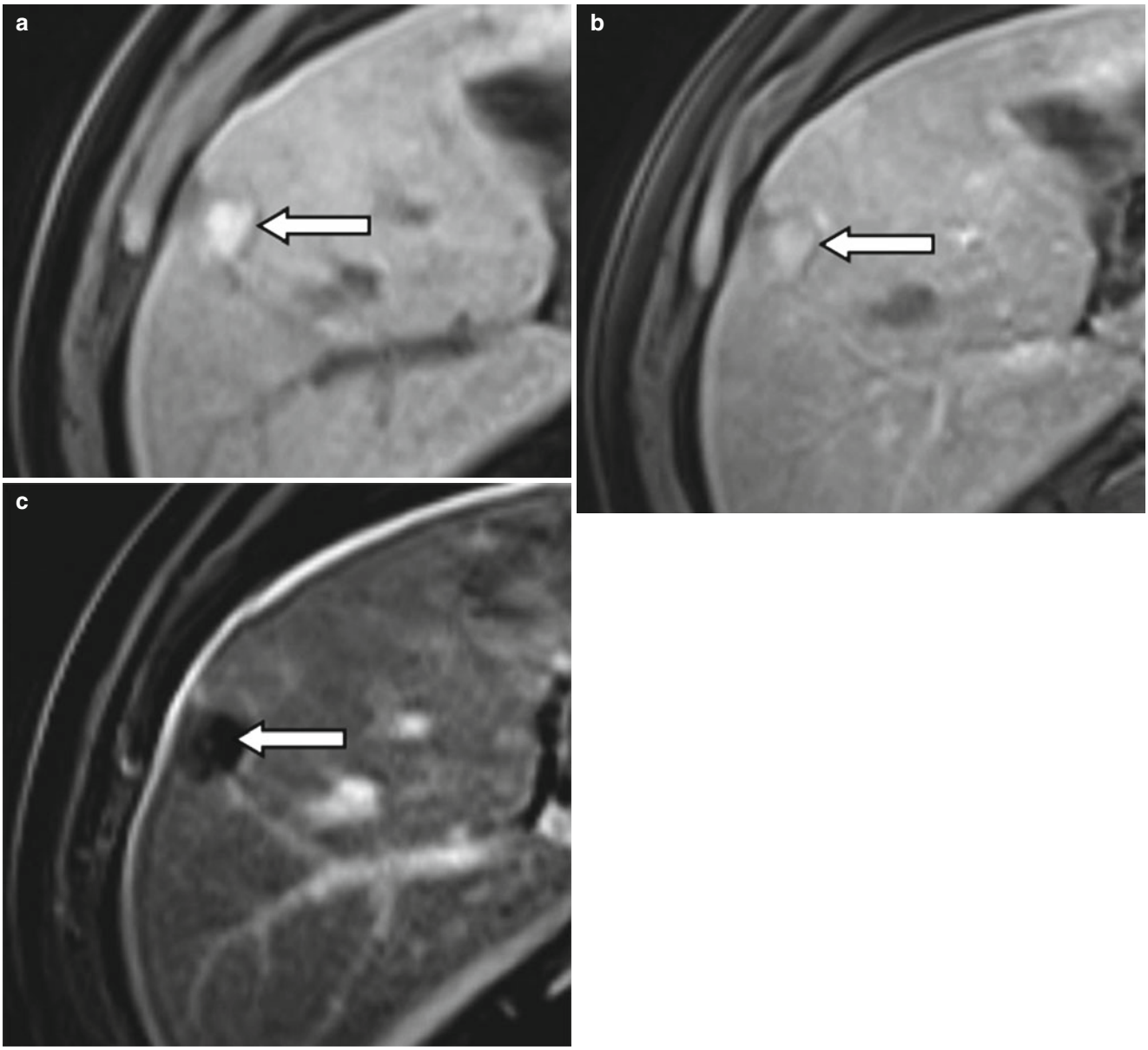

Fig. 4.10 A 48-year-old male patient with HCC. After treatment with RF ablation, the lesion (*arrow*) is hyperintense on unenhanced fat-saturated T1-weighted gradient echo MR image (**a**). After contrast administration, it is difficult to assess enhancement due to the intrinsic hyperintense signal of the lesion (**b**). Subtraction MRI is useful by demonstrating no intra-lesional enhancement indicating a complete response to treatment (**c**)

Additionally, newer hepatocyte-specific contrast agents may aid in differentiating small areas of viable tumor from arterial enhancing pseudolesions by utilizing the lack of functioning hepatocytes and the resultant relative washout of contrast on the equilibrium/hepatobiliary phase of imaging [8]. The use of DWI in combination with conventional MRI shows promising results in increasing the sensitivity for detecting viable tumor [31]. Diffusion hyperintensity with low ADC values suggest viable tumor cells that restrict the Brownian motion of water molecules.

Dynamic contrast-enhanced imaging or perfusion imaging assess the change in perfusion and vascularity of a lesion after LRT. Additionally, novel antiangiogenic agents are thought to induce an anti-permeability effect, while arterial embolization reduces tumor blood volume [33]. These effects result in a significant decrease in hepatic arterial fraction, perfusion, and volume in tumors effectively treated by LRT. Total liver volume CT perfusion is a feasible method in the early detection and localization of treatment-site recurrence after RFA [34]. However, the high radiation dose associated with CT perfusion is a limitation.

Additionally, precision of quantification, proper modeling, and validation of MR perfusion techniques have yet to be established [33].

Newer techniques such as dual-energy CT may add additional tools in evaluating post-LRT changes. Dual-energy CT utilizes the variation in photon absorption at different photon energies to differentiate material composition [35]. The linear blending of 140 kVp and 80 kVp images can create virtual non-contrast images and iodine map images [35]. This may be beneficial in objectively assessing the safety margin between the tumor and the ablation zone after RFA [35].

Conclusion

The evaluation of tumor response after LRT is essential in directing management for primary and secondary hepatic malignancies. The evaluation of tumor response should not include only anatomic imaging biomarkers such as reduction in tumor size/volume. Functional imaging biomarkers should be employed as they assess the viability, cellularity, vascularity, and metabolism of a tumor and thus allow for earlier detection of treatment response. Furthermore, an understanding of the various LRT strategies and their peri-/post-therapy imaging appearance is essential in accurately assessing treatment response.

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