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REVIEW

Radiological findings in non-surgical recurrent hepatocellular carcinoma: From locoregional treatments to immunotherapy

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Abstract

Since hepatocellular carcinoma (HCC) represents an important cause of mortality and morbidity all over the world. Currently, it is fundamental not only to achieve a curative treatment but also to manage in the best way any possible recurrence. Even if the latest update of the Barcelona Clinic Liver Cancer guidelines for HCC treatment has introduced new locoregional techniques and confirmed others as well-established clinical practices, there is still no consensus about the treatment of recurrent HCC (RHCC). Locoregional treatments and medical therapy represent two of the most widely accepted approaches for disease control, especially in the advanced stage of liver disease. Different medical treatments are now approved, and others are under investigation. On this basis, radiology plays a central role in the diagnosis of RHCC and the assessment of response to locoregional treatments and medical therapy for RHCC. This review summarized the actual clinical practice by underlining the importance of the radiological approach both in the diagnosis and treatment of RHCC.

Key Words: Carcinoma; Hepatocellular; Liver; Ablation; Catheter; Radio frequency ablation; Ablation techniques; Medication therapy management; RECIST

Core Tip: During the follow-up of patients affected by hepatocellular carcinoma (HCC), radiology is considered the key to the diagnosis of recurrence, by taking advantage of cross-sectional imaging with a special focus on computed tomography and magnetic resonance imaging. As in the case of active surveillance in a patient with mild to moderate risk for developing HCC, cross-section imaging can help in the quick identification of signs of recurrence. Moreover, radiology plays a key role in the evaluation of treatment response during medical therapy for HCC, recently approved in the revised version of the Barcelona Clinic Liver Cancer staging.

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INTRODUCTION

Hepatocellular carcinoma (HCC) represents the sixth-leading cause of cancer-related deaths worldwide, and it is the most frequent primary liver tumor, accounting for about 85% of primary liver malignancies. Cirrhosis is the histological substrate on which 80% of HCCs arise[1]. According to the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases, all patients with a high risk of developing HCC should undergo a surveillance program[2,3]. Treatment options with curative intent are liver resection (LR), locoregional treatments (LRT), or orthotopic liver transplantation (OLT), and the choice of treatment is influenced by intrinsic features of the lesion, aspects related to the patient, and medical and economic resources available in each center[4,5].

Many HCCs are detected at an intermediate or advanced stage, which are not eligible, at least in the first instance, for curative treatment. In such cases, several treatment options are available, which can also be used in a combined or sequential manner including local termoablation [radiofrequency ablation (RFA), microwave ablation (MWA)], traditional transarterial embolization with traditional chemotherapy or microparticles [transcatheter arterial embolization, transarterial chemoembolization (TACE), TACE with drug-eluting beads (DEB-TACE)], transarterial radioembolization (TARE), and stereotactic ablative radiotherapy[6]. Finally, in cases of metastatic disease, the most common and widely used and approved approach remains systemic therapy with sorafenib, a tyrosine kinase inhibitor drug implicated in several pathogenetic mechanisms[7].

However, even if the primary goal is to have a curative intent, recurrence rate after transplantation is between 8% and 21% despite the use of new predictive models[8]. By contrast to OLT, both LRT and LR suffer from a high recurrence rate (60%-80%). When occurring, tumor recurrence may be considered non-transplantable if it exceeds the transplantation criteria such as those defined by the alpha-fetoprotein or Milan/up-to-seven criteria. Non-transplantable recurrence is a major cause of precluding salvage OLT, which showed comparable overall survival (OS) to primary OLT in patients with HCC with compensated cirrhosis[9].

Even if the latest update of the Barcelona Clinic Liver Cancer (BCLC) guidelines[10] for HCC treatment has introduced new locoregional techniques and confirmed others as well-established clinical practices, there is still no consensus about the treatment of recurrent HCC (RHCC)[11]. For these reasons, the multidisciplinary approach should be considered to define the best option for each RHCC patient[12]. On this basis, this review summarized the actual clinical practice by underlining the importance of the radiological approach both in the diagnosis and treatment of RHCC.

LRT

To date, the available options for RHCC were similar to naïve-HCC options and include LR, OLT, and LRT for patients with liver-only recurrence, TACE, TARE, and stereotactic ablative radiotherapy for patients with unresectable disease, and systemic therapies or enrollment in clinical trials for patients with extrahepatic disease recurrence[13-15].

Ablative treatments

Since only 15%-30% of patients with RHCC are suitable for an LR due to progressive liver dysfunction,

presence of multiple nodules, tumor location, or donor shortage for LT, the ablative treatments play a crucial role in early-stage RHCC[16]. RFA for RHCC is a safe and feasible technique, offering no significant difference in OS compared to RFA for primary HCC[17]. As both RFA and LR are indicated in RHCC tumors with similar features, many studies have compared the two treatments.

Three interesting and recent meta-analyses[13,18] established that LR provided better outcomes than RFA, especially in long-term survival outcomes. RFA is associated with a decreased risk of major complications and requires shorter hospitalization time, a more cost-effective approach in comparison with LR. Moreover, in well-selected patients, RFA may be an optimal choice for RHCC with similar outcomes of LR, notably for a single lesion < 3 cm or in patients with three or fewer nodules, following the guidelines for primary HCC[10]. Also, other studies, including one randomized controlled trial[19], confirmed the same results[20-22].

RFA performances are found to be worse than LR in disease free-survival (DFS), because the LR may ensure removal of the tumor-bearing portal territory where micrometastases and microscopic vascular invasion are present and usually impossible to detect through external ultrasonography[13].

To overcome the shortcomings of RFA, MWA has been assessed in the treatment of HCC, as it produces significantly larger areas of necrosis, faster ablation times, higher intratumor temperature, less tumor seeding risk, and less susceptibility to heat-sink effect over RFA[15,23] (Figure 1). However, there are few studies about percutaneous MWA performance in RHCC. Only one has compared surgical MWA and LR for RHCC showing the safety and feasibility of surgical MWA for RHCC within 3 cm in size and no more than three nodules[24]. Nevertheless, MWA was proven to be superior to RFA[25] and competing with LR when the tumor is > 3 cm and < 5 cm and close to the large vessels[26]. During treatment of very early and early HCC, RFA, MWA, and cryoablation have substantially similar outcomes[23].

A multicentric randomized controlled trial comparing RFA with cryoablation in HCC < 4 cm reported no differences in terms of OS and DFS but found differences regarding local tumor control in favor of cryoablation (7.7% *vs* 18.2%, $P = 0.04$)[27]. While another study conducted on 3239 patients showed a significant advantage in liver cancer-specific survival for RFA[28]. Therefore, the results regarding cryoablation are still unclear[29]. However, data are currently lacking concerning outcomes following the use of cryoablation in RHCC, and future studies should be focused on these aspects.

TACE

TACE is the most common treatment modality used for RHCC following initial resection[16,17]. However, as with LR, appropriate candidates for TACE should be carefully chosen based on their hepatic reserve[16,30] (Figure 2). However, there may exist a significant risk of worsened liver dysfunction following TACE among patients who have undergone prior hepatectomy[15,16,30]. Scores such as up-to-seven criteria or biomarkers such as Mac-2 binding protein glycosylation isomer to assess liver fibrosis can be used to identify patients who tolerate TACE less[16,30].

Regarding TACE in RHCC, Zu *et al*[31] demonstrated that the 1-, 2-, and 3-year OS rates after TACE were 73%, 52%, and 32%, respectively, while the number of resected HCC nodules (≥ 2), size (> 5 cm) of the RHCCs, and the number of TACE sessions (≤ 3) are independent risk factors for poor outcomes after TACE for recurrent HCC. Comparing TACE in naïve-HCC and RHCC, Liu *et al*[32] showed that RHCC treated with TACE accomplished acceptable results. After the propensity score matching analysis, there were no statistically significant differences between the naïve-HCC group and RHCC group in objective tumor regression and disease control rate. On the other side, the RHCC group had a shorter median OS (24 mo *vs* 33 mo) and PFS (10 mo *vs* 12 mo) in comparison with the naïve-HCC group.

Since it is a non-curative treatment, a recent meta-analysis demonstrated that TACE had worse outcomes (OS and DFS) than liver transplantation, LR, and RFA in RHCC patients[33]. Even comparing the two LRTs, Gou *et al*[34] showed that RFA had better short-term and long-term OS than TACE. Conversely, TACE may improve survival in patients with inoperable tumors, with large lesions or multifocal RHCC (beyond the Milan Criteria), and early (< 1 year) recurrence[35,36]. Interestingly, TACE proved to be a more effective option than LR/RFA in RHCC of BCLC stage 0 or A with microvascular invasion, especially in those that recur early after curative resection[37].

Among transarterial procedures, DEB-TACE, which uses doxorubicin, and TARE, using yttrium-90-labeled spheres, have been developed[12]. Even if it has been demonstrated that DEB-TACE facilitates higher concentrations of drugs within the target tumor and lower systemic concentrations with fewer adverse events than conventional-TACE in the management of HCC, especially on RHCC, there is no strong evidence showing the superiority of DEB-TACE over conventional TACE[38,39]. There are a lack of studies considering DEB-TACE as monotherapy for RHCC.

TARE may be an option for intermediate or advanced-stage HCC. It could also be used as an alternative to TACE especially for patients with portal vein thrombosis or for patients with earlier stages who are not eligible for curative procedures[16]. It is a safe and effective procedure for RHCC following LR, with satisfactory outcomes (median time-to-progression and OS were 11.3 mo and 22.1 mo, respectively)[40].

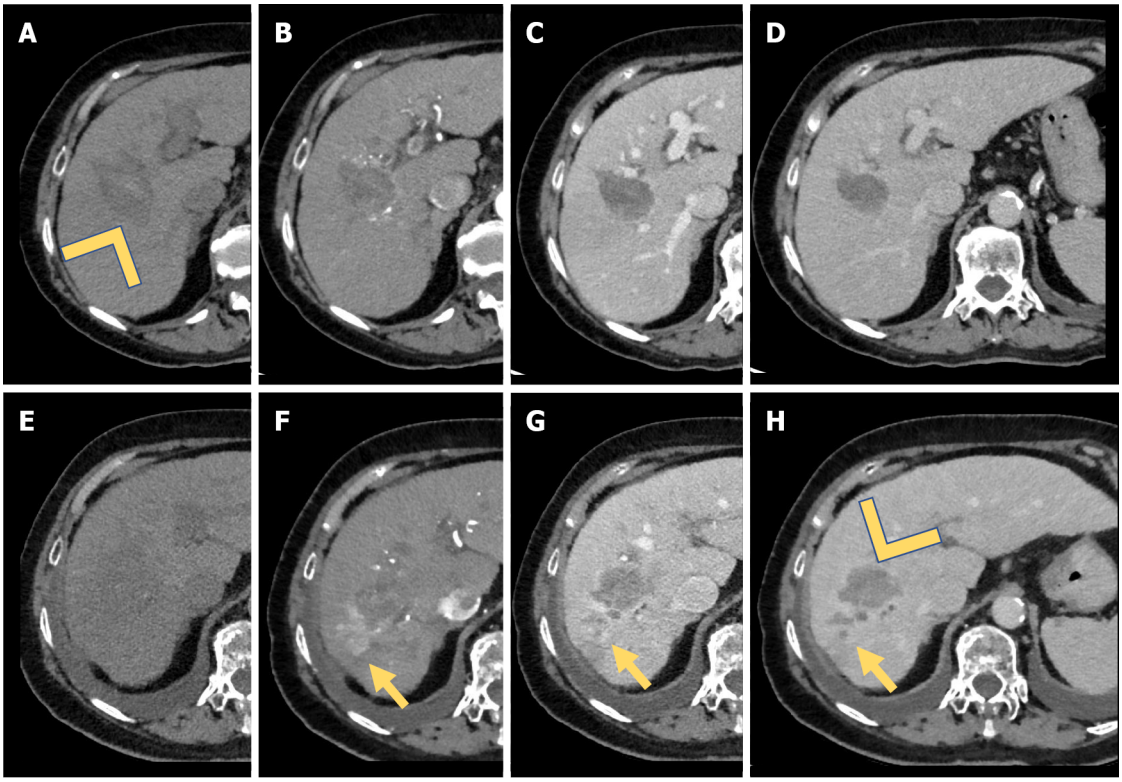

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Figure 1 Computed tomography study for assessment of treatment response (after microwave ablation). A: A 65-year-old male underwent microwave ablation of a hepatocellular carcinoma located in the V-VIII hepatic segment. Computed tomography scans were acquired after 2 wk of treatment. A large hypoattenuating area in the unenhanced (arrowhead) phase located in the V-VIII hepatic segment represented the treatment zone; B-D: During the dynamic study, no enhancement during the arterial phase (B) was seen, underlying the complete treatment response. Also, during the portal venous phase (C) and delayed phase (D) no wash-out was seen; E-H: After 1 year, the area of treatment was less hypoattenuating in the unenhanced phase (E), with a pseudonodular peripheral area of hypervascularization during the arterial phase (F, yellow arrow), with a wash-out during the portal venous and delayed phases (G and H, yellow arrow). On the other hand, the area of treatment did not show any arterial phase hyperenhancement or wash-out (H, arrowhead). The final diagnosis was hepatocellular carcinoma recurrence after microwave ablation (yellow arrows).

Combined therapies

Since RHCC frequently requires aggressive treatment to reach good therapeutic outcomes, the combined approaches have been evaluated by several studies for RHCC[16]. It has been proven that TACE alone is unable to cause complete tumor necrosis[41] and that RFA cannot detect satellite lesions [13]. Therefore, combined therapies may have a synergistic effect and be beneficial for patients with RHCC. TACE-RFA combined treatment can cause tumor necrosis up to 7 cm in diameter in one session [42].

The combination of TACE and RFA leads to theoretical advantages over either monotherapy. TACE can reduce the heat sink effect of the RFA, thereby increasing the ablation range. On the other hand, satellite lesions can be detected through TACE[41]. Furthermore, TACE with the intralesional accumulation of radio-opaque iodized oil used or drug-eluting beads increases the echogenicity and conspicuity of small HCC, otherwise hardly visible on ultrasound (US) guidance during RFA[43].

Song *et al*[44] showed that TACE-RFA had better DFS in comparison with TACE alone in patients with RHCC ≤ 5 cm. However, there were no significant differences between the two groups in OS and adverse events. Ascites is a frequent complication in the TACE-RFA group (Figure 3). Moreover, TACE-RFA provides comparable local efficacy and long-term survival results for patients with RHCC after hepatectomy, both for tumor size < 5 cm and > 5 cm. Furthermore, the TACE-RFA group has fewer complications[41,45] and lower hospitalization time in comparison with the LR group[45].

Zhang *et al*[46] demonstrated that DEB-TACE combined with RFA can increase the survival of patients with RHCC. Notably, OS rates were similar to primary HCC, while DFS rates were lower. A recent study[47] comparing MWA-TACE with TACE alone for small RHCC showed that the 5-year PFS of the combined therapy (37.5%) was higher than that of patients receiving TACE alone (18.7%), while the cumulative OS rates at 5 years were 61.1% for TACE-MWA and 50.3% for TACE alone, with no significant differences. Song *et al*[44] and Ji *et al*[47] demonstrated that combined therapies improve tumor control but not long-term survival outcomes.

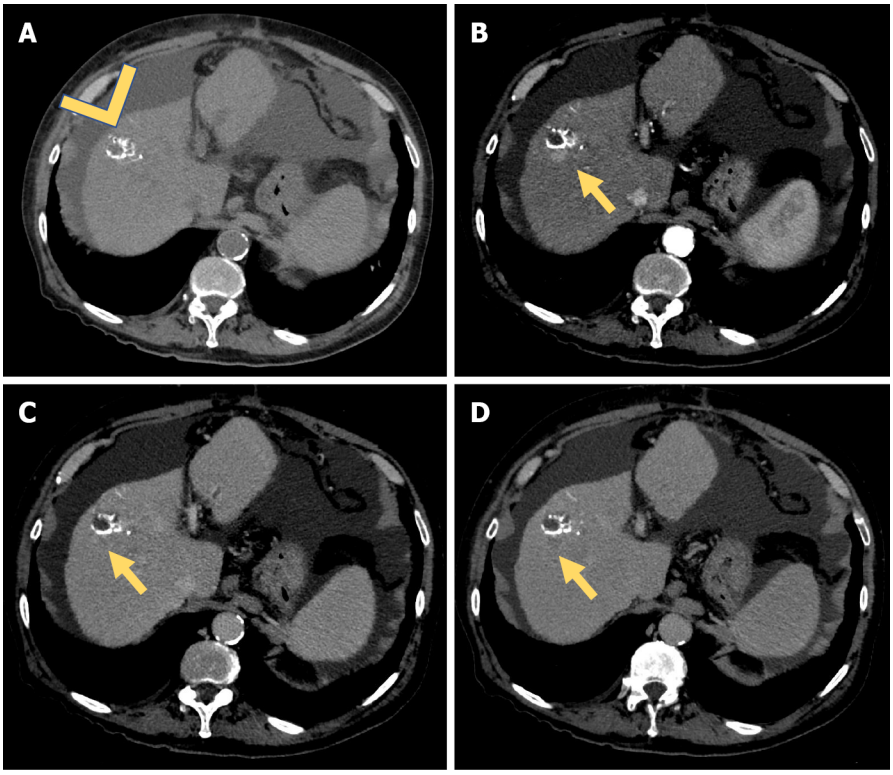

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Figure 2 Computed tomography study for assessment of treatment response (after transarterial chemoembolization). A: A 55-year-old male underwent conventional transarterial chemoembolization of a hepatocellular carcinoma lesion located in the VIII hepatic segment. Two years after treatment, a computed tomography scan showed areas of hyperattenuating components in the unenhanced phase (A), representing the ethiodized oil (arrowhead); B-D: During the arterial (B) phase, a pseudonodular area of hypervascularization during the arterial phase (B, yellow arrow) was seen, with a slight hypoattenuating appearance during the portal venous phase (C) and a clear washout during the delayed phase (D). This represents an example of recurrent hepatocellular carcinoma after transarterial chemoembolization.

MEDICAL THERAPY

Since 2007, sorafenib represented the standard medical treatment of advanced HCC[48] (Figure 4). Sorafenib was the first multityrosine-kinase inhibitor, blocking different receptors, including Raf, the vascular endothelial growth factor, and platelet-derived growth factor, expressed by signaling pathways in HCC. Considering its large approval worldwide, sorafenib was employed not only for patients in an advanced stage of the disease but also as a bridging therapy to downstage the disease and include patients in the transplantation list[49].

Currently, the clinical landscape for patients with advanced liver cancer has changed quickly. Different agents were approved for clinical use, including lavatinib, cabozantinib, regorafenib, and ramucirumab, all addressed to the aforementioned pathways[50]. Moreover, different signs of progress have been made in immunotherapy, in particular with the advent of immune check-point blockers. Nivolumab (anti-PD-1 antibody), pembrolizumab (anti-PD-1 antibody), tremelimumab (anti-CTLA-4 antibody), and atezolizumab (anti-PD-L1 antibody) were tested for advanced HCC[51].

In 2022, Reig *et al*[10] refreshed the BCLC strategy for prognosis prediction and treatment recommendations. It has been established that the first line treatment of advanced HCC should be based on a combined approach. Atezolizumab with bevacizumab (anti-vascular endothelial growth factor antibody) is currently the first-choice first-line treatment. Finn *et al*[52], in a global, open-label, phase 3 trial, demonstrated the best OS and PFS of the combined therapy in comparison with sorafenib alone. Conversely, the atezolizumab-bevacizumab treatment can be used in patients with compensated Child-Pugh A cirrhosis and risk of upper gastrointestinal bleeding.

The second-line treatment is not well established yet. If patients underwent sorafenib treatment, then it is possible to evaluate the benefit from regorafenib[53], cabozatinib[54], or ramucirumab[55]. If the second-line treatment cannot add a clinical benefit or is not feasible due to patient contraindications, then the third-line treatment with cabozatinib can be considered to increase OS[56]. Finally, if all previously mentioned cases are not manageable, patients should be enrolled in clinical trials. Clinical and laboratory data used to choose the preferred medical treatment are out of the scope of the present review.

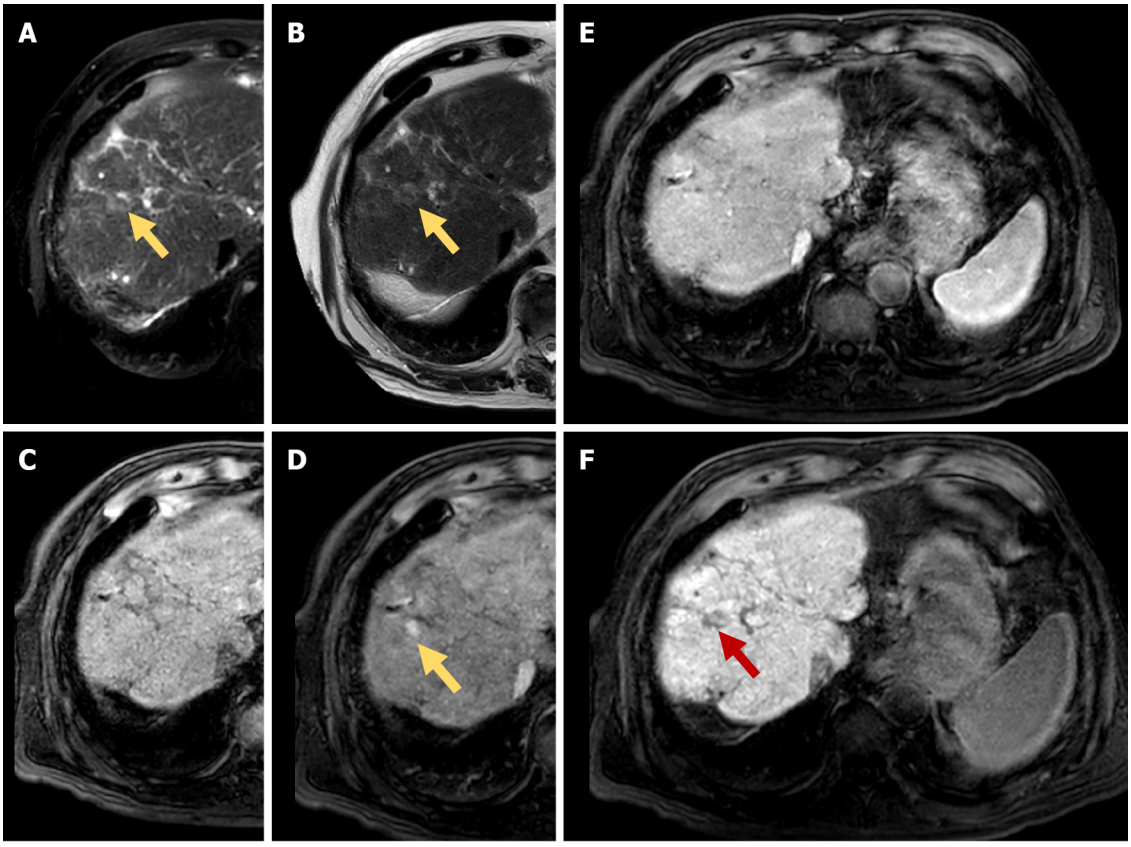

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Figure 3 Magnetic resonance imaging follow-up study with GD-EOB-DTPA for assessment of treatment response (after transarterial chemoembolization and radiofrequency ablation). A and B: A 70-year-old female underwent conventional transarterial chemoembolization-radiofrequency ablation of a hepatocellular carcinoma lesion located in the VIII hepatic segment. Eighteen months after treatment, confluent areas of hyperintense signal on T2 weighted imaging, with and without fat saturation, represented fibrosis. In this context a small slightly hyperintense nodular lesion was seen on T2 weighted imaging (T2 and T2 fs, yellow arrows); C-F: This lesion was isointense to the liver parenchyma in the unenhanced phase (C), with a non-peripheral wash-in appearance during the arterial phase (D), isointense during the portal venous phase (E), and hypointense during the hepatobiliary phase acquired after 20 min of Gd-EOB-DTPA administration (F). The final diagnosis was recurrent hepatocellular carcinoma after transarterial chemoembolization-radiofrequency ablation.

In this setting, patients who underwent LRTs should be followed up due to the risk of recurrence. In patients who underwent medical approaches it is important to monitor tumor response. All the above-mentioned medical strategies can determine apoptosis or necrosis of tumoral cells. One of the most important common findings to evaluate during follow-up is the change in tumor size. A significant increase in tumor volume or maximum axial diameter should be considered as a progression, according to the World Health Organization (WHO) criteria[56]. However, over time, different clinical studies were focused on the main issues related to the WHO classification. Consequently, RECIST 1.1 was introduced in clinical practice. However, RECIST 1.1 has some limitations, including the increase or decrease in size and necrosis, not being taken into account[57]. This last aspect is extremely important during medical treatments since the majority of drugs employed for HCC induce a reduction in tumor vascularization. For these reasons it is important to acquire images with complete protocols, to detect typical radiological findings of the primitive tumor, and to collect every significant change. First, increased dimensions of hypervascular areas or nodules should be considered as a main finding of tumor recurrence or progression[58,59]. To evaluate these, it is of utmost importance to acquire a correct arterial phase both on computed tomography (CT) and magnetic resonance imaging (MRI).

In 2014, Salvaggio *et al*[60] aimed to collect HCC enhancement changes after sorafenib treatment. The authors demonstrated that after medical treatment both arterial and portal venous enhancement was significantly reduced. In particular, the authors demonstrated that patients with partial response can manifest a greater decrease in arterial phase enhancement. However, they did not demonstrate the opposite. Patients with progressive disease did not show any statistically significant difference in arterial phase enhancement before and after treatment. To better understand the medical response, the international literature moved to the usefulness of MRI. Choi *et al*[61] reviewed the most common imaging findings of HCC during medical treatment by using MRI. The authors reported the importance of the hypervascular appearance during the arterial phase, as reported for CT. Moreover, MRI can help to detect early responders from non-responders by using diffusion-weighted imaging (DWI) and apparent diffusion coefficient maps, showing in the first group of patients an increase of DWI signal

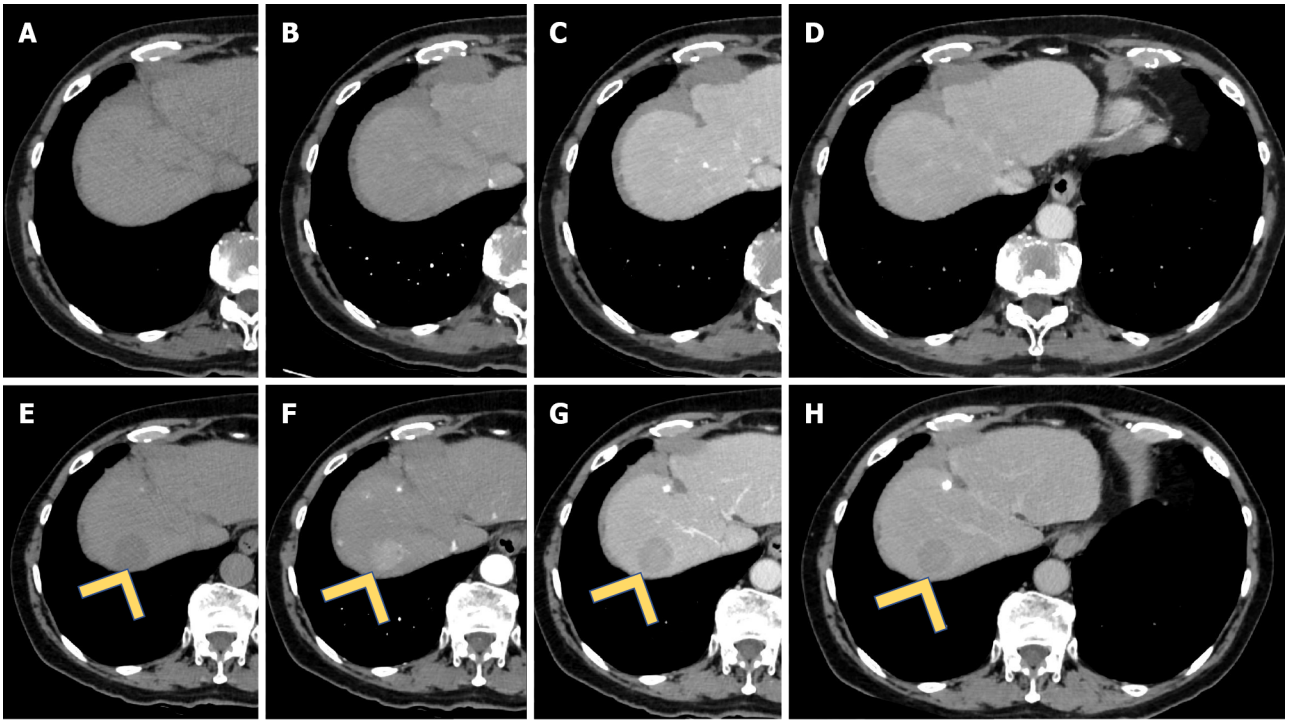

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Figure 4 Multiphasic computed tomography study for assessment of treatment response (after sorafenib). A-D: A 66-year-old female underwent conventional medical therapy (sorafenib) for an advanced hepatocellular carcinoma (HCC) lesion. Computed tomography images represented the complete response to the medical therapy, with no areas or nodular lesions suspected for HCC; E-H: During the follow-up, 2 years after completion of therapy, a nodular hypoattenuating lesion in the unenhanced phase (E) appeared in the VII hepatic segment. This lesion had similar features of primary HCC, with non-rim hyperenhancement during the arterial phase (F), wash-out during the portal venous phase (G) and delayed phase (H). This is an example of HCC recurrence after sorafenib.

with correspondence on apparent diffusion coefficient map due to necrosis and reduced tumor cellularity. Finally, MR can benefit from the usefulness of hepatobiliary contrast agents, as demonstrated in the SORAMIC trial[62]. However, by searching PubMed and EMBASE no important studies have been published yet about this promising added value, and future studies should be focused on these aspects.

The advent of all the above-mentioned strategies, alone or combined, introduced a new class of response[52]. While about 8% can show a hyperprogression, a new atypical response is included in the iRECIST criteria[63]. However, no predictive biomarkers can help clinicians to determine the risk of atypical response during immunotherapy, and only the radiological approach, both with CT and MRI, can help follow patients during the treatment. Even if in the past medical treatment was considered the last useful medical treatment in advanced HCC, different ongoing studies are testing a combination of only medical drugs and in combination with LRTs, such as TACE, as reported by Pinter *et al*[64].

Combined strategies may be useful in advanced RHCC. Peng *et al*[65] showed that sorafenib combined with TACE-RFA was superior to therapy with sorafenib alone concerning time to progression and OS in patients with RHCC with one intrahepatic tumor size ≤ 7 cm or ≤ 5 cm intrahepatic nodules, with each tumor ≤ 3 cm.

RADIOLOGICAL APPROACH TO RHCC

Radiology plays a central role in the assessment of patient response LRT for RHCC. The identification of viable tumor treatment guides for further management, and it potentially affects transplantation eligibility. In these instances, it is often helpful to engage in a multidisciplinary discussion to determine how to best manage each patient. The Liver Imaging Reporting and Data System (LI-RADS) was developed in 2011 to relay the likelihood of HCC on CT or MRI in a standardized manner, in patients at risk for HCC. In 2017, the LI-RADS treatment response algorithm (LI-RADS TRA) was introduced for the assessment of lesions that have been previously treated with LRT[66]. Unlike the prior response criteria RECIST and WHO that focus on disease progression on a systemic level, LI-RADS TRA is based on enhancement features to predict viability on a lesion level[67]. Although modified RECIST (mRECIST) has historically been used for the evaluation of HCC after locoregional therapy, differences from LI-RADS TRA include a lack of equivocal category and a lack of additional features for diagnosing tumor viability[68]. mRECIST uses the presence of arterial enhancing components alone to diagnose

viability while LI-RADS TRA includes additional imaging features such as washout during the portal venous or delayed phases and enhancement similar to pre-treatment to define viable tumors and encompass the equivocal category in addition to the binary evaluation[69].

RECOMMENDATIONS FOR HCC RECURRENCE DETECTION

Non-invasive imaging is superior to any other method for the surveillance of patients at risk of developing RHCC, either after OLT or other curative treatments. However, robust data lacks the optimal follow-up schedule of HCC-treated patients. Notably, international guidelines slightly differ in the recommended follow-up intervals, ranging from 3 mo to 6 mo, and duration of cross-sectional imaging after curative treatments. The National Comprehensive Cancer Network panel recommends ongoing total-body surveillance with multiphasic cross-sectional imaging (*i.e.* CT or MRI) every 3 mo to 6 mo for 2 years, then every 6 mo to 12 mo after curative therapies[70]. The 2018 Practice Guidance by the American Association for the Study of Liver Diseases suggests surveillance for HCC recurrence in posttransplant patients with abdominal and chest CT scan, though timing and duration as well as the impact of surveillance are not univocally defined[71]. After ablative therapies, the American Association for the Study of Liver Diseases recommends surveillance with contrast-enhanced CT or MRI every 3-6 mo[71].

The 2018 European Society for Medical Oncology Clinical Practice Guidelines were endorsed by the pan-Asian consensus conference, which included experts from several Asian societies. However, the Asian-adapted version slightly changed the follow-up timing after curative treatment, limiting the 3-mo interval by dynamic CT or MRI studies to the 1st year instead of 2[72,73]. Also, the European Association for the Study of the Liver recommends a follow-up after resection with curative intent with 3-4 mo intervals limited to the 1st year after treatment, with a return to regular surveillance thereafter[4].

Interestingly, Kim *et al*[74] found that HCC patients who undergo curative treatments with complete response and who present with increasing alpha-fetoprotein levels have a high probability of impending tumor recurrence even in the presence of a negative MRI. The follow-up schedule proposed within the European Society for Medical Oncology guidelines for patients treated with TACE or systemic therapies includes contrast-enhanced CT or MRI every 3 mo[74].

All the above-mentioned guidelines converge on the equivalent role of CT and MRI in clinical practice, given that the most important aspect for the diagnosis of HCC is the definition of criteria with the highest achievable accuracy, regardless of the imaging technique. Erkan *et al*[75] reviewed 3491 pathologically examined liver lesions, either studied by CT or MRI, comparing the diagnostic performance of different non-invasive diagnostic criteria of HCC. They found no statistically significant differences among criteria in diagnostic accuracy, with LI-RADS performing the best in terms of sensitivity and accuracy. Nevertheless, though CT and MRI have comparable performance in clinical practice, they present specific features to be considered.

CT

CT has the advantage of being the most practical and widely available tool to perform surveillance in HCC-treated patients. Its main limitations consist of ionizing radiation exposure and iodinated contrast agents-related nephrotoxicity. The detection and characterization of liver nodules with conventional contrast-enhanced CT is substantially limited to the size, morphology, and enhancement pattern of the lesions, which are sufficient elements to reach a confident diagnosis according to LI-RADS. RHCC imaging findings are analogous to the primary lesion. In particular, the typical hallmarks in the imaging diagnosis of RHCC are the combination of hyperenhancement in the arterial phase and washout on the portal venous or delayed phases[4]. Several studies and meta-analyses have compared the performance of CT with other imaging techniques. In a multicenter prospective trial including 544 nodules in 381 patients, the sensitivity and specificity for the diagnosis of 10-20 mm HCC nodules were 67.9% and 76.8%, respectively, while for the 20-30 mm HCC nodules, the sensitivity and specificity were higher (71.6% and 93.6%, respectively)[76]. In a meta-analysis, CT had an overall sensitivity of 72% with a subgroup analysis revealing a sensitivity of 31% *vs* 82% for sub-centimetric lesions compared to ≥ 1 cm ones[77]. Of note, this data did not consider the prevalence of HCC diagnosis in HCC-naïve patients compared to previously treated patients, for whom the pre-test probability of disease is expected to be increased. A multicenter prospective study that enrolled patients scheduled for liver imaging before surgery showed a sensitivity of 70%[78].

MRI

The accuracy of MRI in detecting HCC, especially small nodules, is superior to that of CT as shown by several studies and meta-analyses, one of which reported a sensitivity of 82% compared with 66% of CT and a comparable specificity[4,79]. However, MRI is yet to be definitively recommended over CT, given that the quality of the available evidence is considered low[79]. Moreover, a distinction between extracellular contrast agents (ECA) and hepatobiliary contrast agents (HBCA) should be considered. Analogous to those used in CT, ECA detects and characterizes lesions through the enhancement pattern.

Conversely, HBCA provides information on the hepatocellular function and bile excretion. Typical nodule hypointensity against a strongly enhanced background parenchyma in the hepatobiliary phase increases RHCC conspicuity and delineation, facilitating detection and consequently the diagnosis[80]. Despite this advantage, it must be pointed out that, if considered alone, hepatobiliary phase imaging is non-specific. Therefore, it always requires interpretation together with the dynamic study[81]. Martino *et al*[82] reported significantly higher diagnostic accuracy, sensitivity, and negative predictive value when dynamic and hepatobiliary phase MRI were combined compared to CT and dynamic phase MRI alone; a particular diagnostic benefit was obtained for lesions between 1 cm and 2 cm.

Nevertheless, although most HCC lesions are typically hypointense during the hepatobiliary phase, about 5%-12% HCC lesions can be hyperintense, owing to the overexpression of OATP[81]; conversely, some benign nodules may show no contrast uptake[83]. The knowledge of the pathological features of the originally treated nodules may predict the behavior of recurrent disease on hepatobiliary phase imaging, improving diagnostic confidence.

Different HBCA molecules have specific pharmacokinetic profiles. Gadoxetate disodium presents a 50% hepatic excretion, which contributes to an early liver parenchyma enhancement. Conversely, gadobenate-dimeglumine has a 3%-5% hepatic excretion that delays the hepatobiliary phase imaging onset. As a consequence, gadoxetate disodium does not provide a conventional delayed vascular phase but instead shows a transitional phase that lasts for several minutes, representing a transition from extracellular-dominant to intracellular-dominant enhancement[81]. Interestingly, Yim *et al*[84] recently observed that, in a retrospective cohort of patients who underwent both ECA and HBCA, RHCC was diagnosticated with higher accuracy using ECA.

DWI has been shown to improve the accuracy of RHCC detection, especially when combined with gadoxetic acid-enhanced imaging[85,86]. Finally, a recent meta-analysis confirmed that DWI may improve the ability to detect residual HCC or RHCC after TACE[87].

MRI likely has the highest accuracy compared to other imaging techniques in the detection of small recurrence after curative treatments[43]. However, results interpretation according to the standard LI-RADS may suffer from reduced sensitivity and specificity for disease recurrence detection. Wang *et al*[88] found that non-rim arterial phase hyperenhancement and three ancillary features (hepatobiliary phase hypointensity, mild-moderate T2 hyperintensity, and restriction of diffusion) were significantly related to RHCCs < 20 mm and concluded that the characterization of < 10 mm recurrence may show improved specificity compared with the LI-RADS 4 category combining at least two ancillary features. However, in patients treated with systemic therapies, according to the mRECIST criteria, new HCC lesions must measure at least 1 cm to define disease progression[58]. Despite the high sensitivity of MRI to detect recurrence after curative treatments, it has been shown that small viable RHCC may hide behind false-negative studies. This warrants regular short-term imaging surveillance[89].

However, in the absence of evidence to recommend a particular method or contrast agent over the other, practitioners are encouraged to base the choice on their judgment on an individual basis, considering the local availability of resources, personal experience, and imaging features of the previously-treated HCC[71].

Contrast-enhanced US

The use of contrast-enhanced US (CEUS) is encouraged as it has been demonstrated that its specificity can be even superior compared to CT/MRI[76]. Although CEUS is inferior to both CT and MRI in terms of objectivity and panoramic view, it provides advantages in cases of renal dysfunction and iodine allergy. The current indications for CEUS are multiple, the most important of which are equivocal or inconclusive findings on CT or MRI studies and assessment of treatment response after TACE or ablation[90]. Bansal *et al*[91] proposed an algorithm with alternating MRI and CEUS for secondary surveillance following potentially curative therapy of HCC. In their prospective studies, the authors found similar diagnostic performance of the two techniques; of note, CEUS was able to confirm or disprove equivocal findings on MRI. The comparable diagnostic performance of CEUS, CT, and MRI was previously reported[92].

It has been reported that RHCC may differ from the initial tumor at imaging, and this may help to distinguish recurrence form residual diseases, which may have a prognostic relevance. Wu *et al*[93] recently described different CEUS patterns of RHCC compared to initial tumors: Among the others, more homogeneous enhancement, poorly defined borders, and marked washout were found to be typical features of recurrent disease.

The application of artificial intelligence and radiomics to preoperative CEUS has recently gained large interest, and it has been demonstrated to potentially predict the prognosis in terms of HCC recurrence and overall survival[94-97]. CEUS, added to other conventional US-based techniques, has also shown the ability to improve the prediction of microvascular invasion, which is probably the most important factor associated with a worse prognosis[98]. Finally, CEUS can be useful as guidance for ablative therapies, especially to target recurrence of previously treated lesions[99,100].

Perfusion CT/MRI

Perfusion imaging does not have a definite role in clinical practice, and it is mainly performed for investigative purposes. Although several authors have independently demonstrated that perfusion CT-

derived parameters can discriminate between normal liver parenchyma, HCC, and hypervascular pseudolesions[101-103], they are yet to be included in clinical practice guidelines due to the absence of standardization among different centers[104]. However, perfusion imaging that provides quantitative parameters that could potentially be more reliable than qualitative/subjective parameters seems promising in the assessment of tumor response both to locoregional and systemic therapies[105-114].

Compared to CT, perfusion MRI has been investigated more regarding the possibility of predicting microvascular invasion of HCC before treatment. The microvascular invasion has been demonstrated to be correlated with poor outcomes of curative therapies due to higher rates of disease recurrence[115]. Perfusion MRI can be performed either with dynamic contrast-enhanced studies or with the intravoxel incoherent motion diffusion-weighted technique[116-119].

Nuclear medicine

The role of nuclear medicine in the diagnosis and staging of HCC is debated. If on the one hand there is insufficient evidence to recommend the use of fluorodeoxyglucose positron emission tomography preoperatively, it has been demonstrated that nuclear medicine studies are able to predict tumor aggressiveness and may aid in identifying those patients at risk for HCC recurrence after liver transplantation, resection, or ablation for better treatment allocation[120,121]. Fluorodeoxyglucose positron emission tomography, with or without CT, has also been shown to present low sensitivity but high specificity for diagnosing extrahepatic metastases or local residual/recurrent HCC after treatment [121].

CONCLUSION

On the one hand, the assessment of the response to LRTs has been widely described[121-123]. On the other hand, histologic modifications induced by molecular therapies may explain different imaging findings of recurrent disease. Differentiation between treatment-induced tumor necrosis and viable tumor with reduced arterial perfusion may be challenging. After treatment with systemic targeted therapy, the tumor may show areas of necrosis without any contrast enhancement that must be distinguished from areas of reduced but still unequivocal arterial uptake consistent with viable tumor[44]. Even RHCC under systemic treatments may present with atypical enhancing patterns, especially lacking arterial hyperenhancement, which makes radiological assessment more difficult. All these aspects should be considered, and multimodal imaging evaluation combined with multidisciplinary framework can improve image interpretation. Conventional non-invasive imaging techniques provide robust criteria for HCC residual/recurrence detection, with high accuracy, representing the current standard of practice. Advanced imaging tools, either hardware- or software-based, have a double potential role: to predict HCC treatment response or the risk of recurrence, to increase sensitivity, specificity, and thus operator confidence in early RHCC detection.

FOOTNOTES

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