pISSN 2287-2728
eISSN 2287-285X

CMH

https://doi.org/10.3350/cmh.2017.0006
Clinical and Molecular Hepatology 2017;23:95-101

Liver Imaging

Aggressive tumor recurrence after radiofrequency ablation for hepatocellular carcinoma

Tae Wook Kang*, Hyo Keun Lim*, and Dong Ik Cha

Department of Radiology and Center for Imaging Science, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Image-guided radiofrequency ablation (RFA) is an evolving and growing treatment option for patients with hepatocellular carcinoma (HCC) and hepatic metastasis. RFA offers significant advantages as it is less invasive than surgery and carries a low risk of major complications. However, serious complications, including aggressive tumor recurrence, may be observed during follow-up, and recently, mechanical or thermal damage during RFA has been proposed to be one of the causes of this kind of recurrence. Although the exact mechanism of this still remains unclear, physicians should be familiar with the imaging features of aggressive tumor recurrence after RFA for HCC and its risk factors. In addition, in order to prevent or minimize this newly recognized tumor recurrence, a modified RFA technique, combined RFA treatments with transarterial chemoembolization, and cryoablation can be used as alternative treatments. Ultimately, combining an understanding of this potential complication of RFA with an understanding of the possible risk factors for aggressive tumor recurrence and choosing alternative treatments are crucial to optimize clinical outcomes in each patient with HCC. **(Clin Mol Hepatol 2017;23:95-101)**

Keywords: Liver; Hepatocellular carcinoma; Radiofrequency ablation; Tumor recurrence

INTRODUCTION

Hepatocellular carcinoma (HCC) is a major health problem worldwide because it is the sixth most common cancer and the third most common cause of cancer-related death.[1] In addition, HCC is the leading cause of death among patients with liver cirrhosis.[2] For the treatment of HCC, a variety of modalities have been used, including local tumor ablation (e.g., radiofrequency ablation [RFA], cryoablation, microwave ablation, irreversible electroporation), transarterial chemoembolization (TACE), liver transplantation, and molecular-targeted therapy.[1] Among these, RFA is now accepted as a curative treatment for very early or early-stage HCC in several international guidelines for HCC treatment.[1,3,4] In particular, in patients with small HCC lesions (<2 cm) who are not potential candidates for liver transplantation, RFA may serve as an alternative to surgery for first-line therapy, according to the recent Barcelona Clinic Liver Cancer (BCLC) treatment strategy.[1] Furthermore, RFA has several advantages over surgical resection, such as increased preservation of surrounding hepatic tissues, a shorter hospital stay, decreased morbidity, and applicability for patients with advanced liver cirrhosis who are not candidates for surgery.[5,6] However, early or late complications related to mechanical or thermal damage during RFA may be observed during follow-up.[7] Among them, aggressive tumor recur-

Abbreviations:

AIR, aggressive intrasegmental recurrence; BCLC, Barcelona Clinic Liver Cancer; HCC, hepatocellular carcinoma; RFA, radiofrequency ablation; TACE, transarterial chemoembolization

* Tae Wook Kang and Hyo Keun Lim contributed equally to this work.

Corresponding author : Tae Wook Kang
Department of Radiology and Center for Imaging Science, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 06351, Korea
Tel: +82.2-3410-0518, Fax: +82.2-3410-0049
E-mail: kaienes.kang@samsung.com; angelrad7@gmail.com

rence after RFA has recently come into focus because it can lead to less favorable overall survival in patients who undergo RFA for HCC.[8] Thus, physicians should be aware of this newly recognized tumor recurrence after RFA for HCC.

The aims of this review are to summarize the definition, mechanism, and imaging findings of aggressive tumor recurrence after RFA for HCC, to summarize the known risk factors, and to discuss the clinical implications of this complication and the preventive measures for tumor recurrence in patients who undergo local tumor ablation.

DEFINITION OF AGGRESSIVE TUMOR RECURRENCE

There have been various terminologies used in previous studies and case reports representing the phenomenon of aggressive tumor recurrence after RFA for HCC, such as "rapid intra-hepatic dissemination",[9] "aggressive recurrence",[10,11] "scattered and rapid intrahepatic recurrence",[12] "early diffuse recurrence",[13] "diffuse intrahepatic recurrence",[14] "rapid aggressive tumor progression",[15] and "aggressive intrasegmental recurrence".[8] Among these terminologies, we restricted our search to publications that included a definition of tumor recurrences. Shiozawa et al.[15] reported that "rapid aggressive tumor recurrence" was defined as the presence of a tumor with the following characteristics: identified within or adjacent to the ablated area, rapidly increased in size to more than twice the size of the ablated area during the follow-up period, and not detected on previous imaging studies. Lee et al.[13] defined "early and diffuse recurrence" as the occurrence of three or more new recurrent tumors identified within 1 year of initial RFA. Recently, Kang et al.[8] defined "aggressive intrasegmental recurrence (AIR)" as the simultaneous development of multiple nodular (>3) or infiltrative HCC recurrence in the treated segment of the liver. In addition, AIR was restricted to the initial manifestation of tumor recurrence in patients who were previously considered to have disease-free status at least 6 months after initial RFA to avoid confusion with tumor progression from residual tumor and unidentified microscopic metastasis or vascular invasion before treatment.

MECHANISM OF AGGRESSIVE TUMOR RECURRENCE

Although the exact mechanism of this kind of tumor recurrence remains unclear, intravascular tumor spread may be one of the causes of this serious complication. Abnormal communication between the hepatic artery and portal vein within HCC, such as an iatrogenic arterioportal fistula[16] or intratumoral shunt,[17] may develop during RFA, and this may enable cancer cell spread into the peripheral liver due to RFA-related mechanical injury (Fig. 1). Another hypothesis is that rapid heating of a tumor may lead to a sudden increase in internal pressure of ablated tissue and cause the scattering of malignant cells around the ablation zone.[14,18] In addition, although the results were based on an animal model studies, Ahmed et al.[19] recently reported that RFA of normal liver tissue can stimulate distant tumor growth mediated by the hepatocyte growth factor/c-Met pathway and vascular endothelial growth factor activation. Furthermore, RFA does not allow for systemic removal of the corresponding hepatic segment fed by tumor-bearing portal tributaries, and thus, micro-satellite nodules around the index tumor may not be effectively treated with RFA.[5]

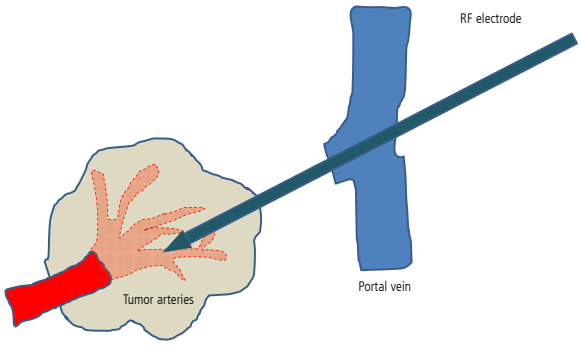

Figure 1. A representative diagram of iatrogenic arterio-portal fistula. The radiofrequency (RF) needle can create a communication pathway along its track between two vascular districts (arterious and venous-portal areas) during treatment.

IMAGING FINDINGS OF AGGRESSIVE TUMOR RECURRENCE

Based on the results of previous studies,[8,11-16] the imaging findings of aggressive tumor recurrence after RFA for HCC can be classified either as multiple nodular tumors or as a diffusely infiltrative mass with tumor thrombus formation. In general, multiple tumor nodules were all relatively uniform in size and developed simultaneously in the same segment of the liver peripheral to the ablation zone or both hepatic lobes (Fig. 2 and Fig. 3).[13] Diffusely infiltrative tumor recurrences also developed in the peripheral part of the treated segment around the ablation zone with or without

https://doi.org/10.3350/cmh.2017.0006

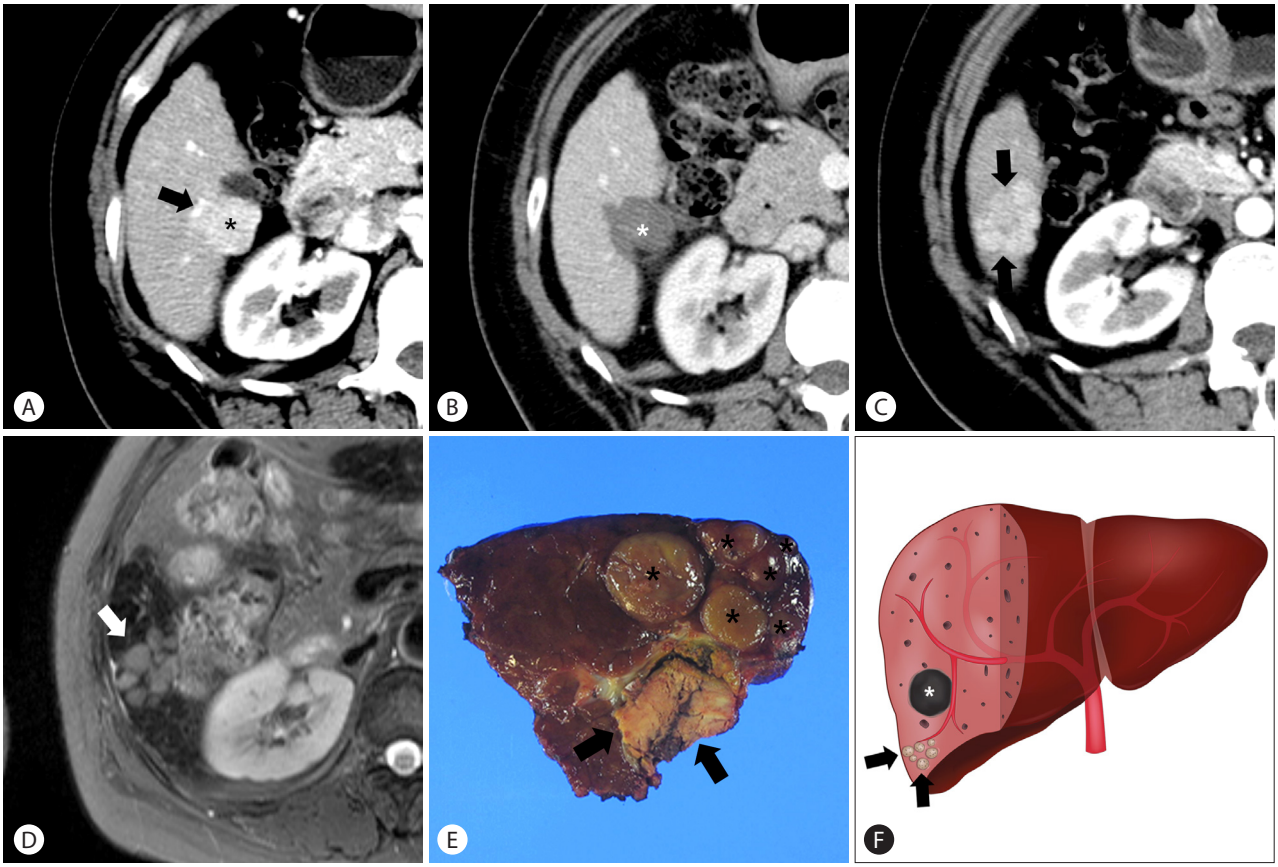

Figure 2. Multiple nodular form of aggressive tumor recurrence of hepatocellular carcinoma (HCC) after radiofrequency ablation. (A) Contrast-enhanced axial computed tomography (CT) scan obtained during hepatic arterial phase shows HCC (asterisk) in segment VI before RFA. Note the index tumor contacting the segmental portal vein (arrow). (B) CT scan obtained during portal venous phase 4 months after RFA ablation shows that the ablation zone (asterisk) is free from local tumor progression. (C) CT scan obtained during hepatic arterial phase 7 months after RFA shows multiple small arterial enhancing nodules (arrows), with delayed washout at equilibrium phase (not shown). These developed simultaneously in the peripheral area of the treated segment, fed by the previous peritumoral portal vein. (D) Superparamagnetic iron oxide–enhanced multishot T2-weighted magnetic resonance image shows hyperintense lesions corresponding to recurrent multiple nodular HCC (arrow). (E) Photograph of gross specimen after segmentectomy displays multiple nodular HCC lesions (asterisks) in the peripheral portion of segment VI at a distance from the previous ablation zone (arrows). The patient died from rapid progression of HCC accompanied by multiorgan metastases 56 months after initial RFA. (F) Illustration demonstrates multiple nodular-type aggressive intrasegmental recurrence (AIR) (arrows) after RFA for HCC. Asterisk = previous ablation zone (Reprint from Radiology 2015; 276:274–285 with permission). RFA, radiofrequency ablation.

tumor thrombus formation in the adjacent portal vein (Fig. 4).[8]

INCIDENCE AND RISK FACTORS OF AGGRESSIVE TUMOR RECURRENCE AFTER RFA FOR HCC

Although the reported incidence of aggressive tumor recurrence after RFA for HCC is very low, ranging from 0.7–8.0%, its frequency increased up to 15% in the subgroup of patients with periportal HCC.[8,12,15] To date, several known risk factors of aggressive tumor recurrence after RFA for HCC have been identified. These include: larger tumor size, ill-defined tumor margin,[13] higher serum protein induced by vitamin K absence-II level,[15] rapid incremental increase in RF electrical power,[12,18] periportal tumor location, young age of patients,[8] and enhanced expression levels of hypoxia-inducible factor-1 and epithelial cell adhesion molecule in residual HCC after insufficient RFA.[20] These factors could be associated with this serious complication during the RFA procedure for HCC. Most risk factors are tumor-related factors regardless of whether or not the tumor has an aggressive behavior. However, among these risk factors, it is worth noting tumor location and energy deposition protocol because they are technical aspects of RFA procedures. In patients with periportal tumors, factors that promote tumor spread from the ablation zone into the adjacent

CMH
Clin Mol Hepatol
Volume 23 Number 1 March 2017

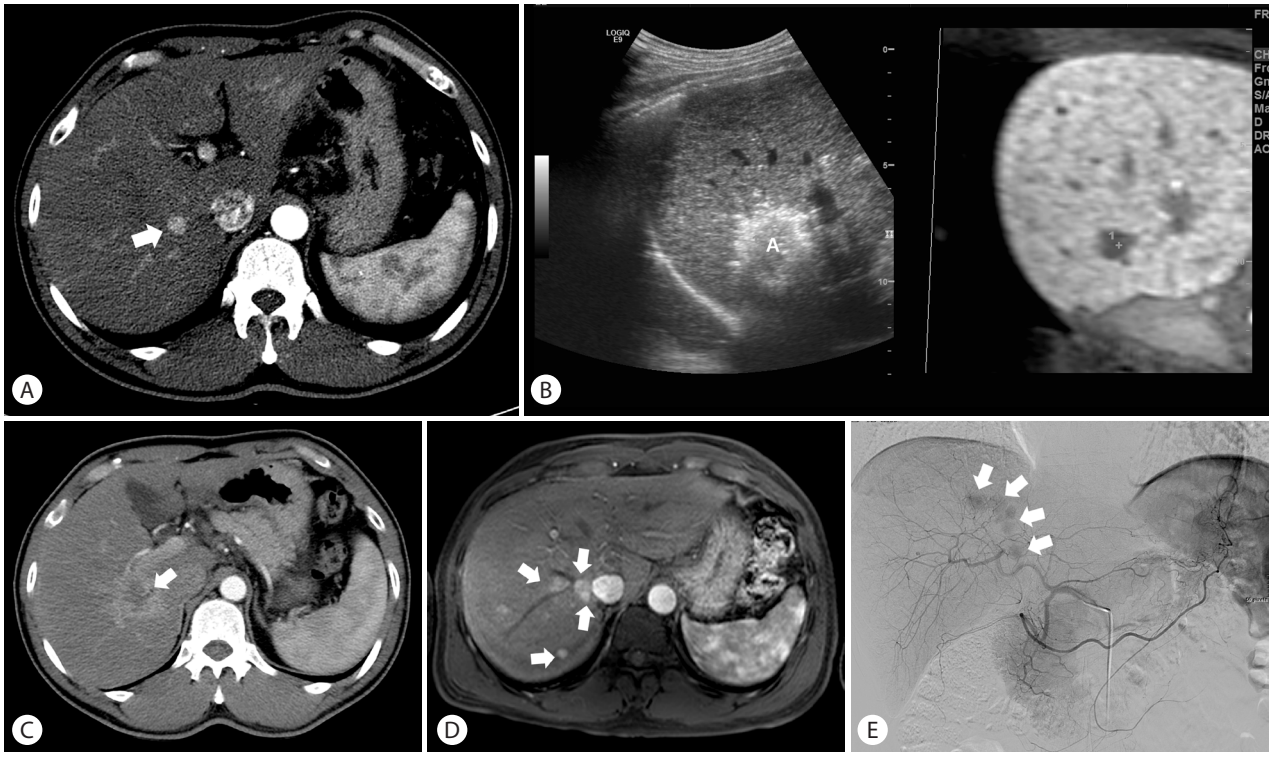

Figure 3. Second case representing the multiple nodular form of aggressive tumor recurrence of hepatocellular carcinoma (HCC) after radiofrequency ablation. (A) Contrast-enhanced axial computed tomography (CT) scan obtained during hepatic arterial phase shows a 1.1 cm HCC (arrow) lesion in segment VII/VIII before RFA. (B) Fusion-guided RFA was performed. The ablation zone (A, right) is completely covered with the index tumor and ablative margin (marker, left). (C) Immediately after RFA, the CT scan shows a small air bubble (arrow) within the small portal vein adjacent to the ablation zone. (D) CT scan obtained during hepatic arterial phase 25 months after RFA shows multiple small arterial enhancing nodules (arrows), with delayed washout at equilibrium phase (not shown). These developed simultaneously in the peripheral area of the treated segment, fed by the previous peritumoral portal vein. (E) During transarterial chemoembolization (TACE) for HCC recurrence, multiple tumor nodules (arrows) are seen; nodules are all relatively uniform in size and developed simultaneously in the same segment of the liver peripheral to the ablation zone. RFA, radiofrequency ablation.

portal vein via abnormal arterioportal communications in and around tumors, representing transportal tumor spread during RFA, may be present.[8]

CLINICAL SIGNIFICANCE OF AGGRESSIVE TUMOR RECURRENCE AFTER RFA FOR HCC

Although several studies have investigated the risk factors and imaging findings of aggressive tumor recurrence after RFA for HCC,[9-12, 14-16] there has been only one study that directly evaluated the therapeutic outcomes of RFA for HCC according to the occurrence of aggressive tumor recurrence during follow-up. Kang et al.[8] reported that the occurrence of AIR during follow-up had a significant unfavorable effect on overall survival. This is because patients with AIR had a higher BCLC staging compared to those with usual local tumor progression or intrahepatic distant recurrence after RFA, which led to the use of palliative treatments, including radiation treatment or sorafenib therapy, in patients with AIR.

PREVENTION OF AGGRESSIVE TUMOR RECURRENCE AFTER RFA FOR HCC

In clinical practice, there are no available guidelines related to avoiding or preventing aggressive tumor recurrence following RFA for HCC. Until conditions for safe and effective RFA are better understood, we recommend that careful consideration be given to treatment for aggressive HCC, such as consideration of high tumor marker levels, ill-defined margins, or larger tumor size, which is associated with an increased chance of microvascular invasion and micro-satellite nodules around the index tumor, and perioportal tumors. In view of the relatively high frequency of AIR of HCC

https://doi.org/10.3350/cmh.2017.0006

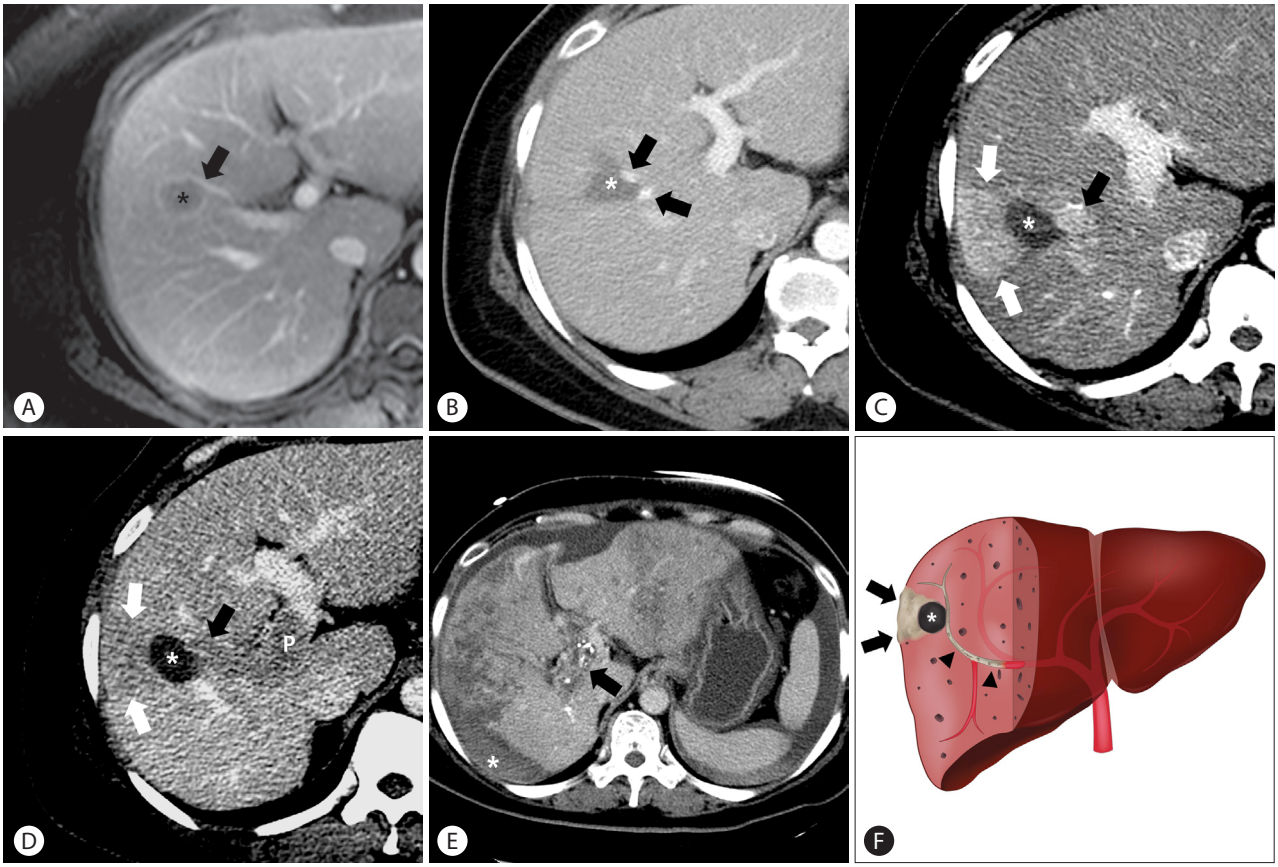

Figure 4. Diffusely infiltrative form of aggressive intrasegmental recurrence of hepatocellular carcinoma with tumor thrombus formation (HCC) after radiofrequency ablation. (A) Gadoxetic acid–enhanced magnetic resonance image obtained during portal venous phase before RFA shows HCC (asterisk) in the bottom portion of segment VIII. HCC was diagnosed by percutaneous liver biopsy before treatment because arterial hypervascularization was equivocal. The index tumor was in broad contact with a small peritumoral portal vein (arrow). (B) Contrast-enhanced axial computed tomography (CT) scan obtained during portal venous phase 7 months after RFA shows neither local tumor progression around involution of the ablation zone (asterisk) nor intrahepatic distant recurrence. Adjacent portal veins appear patent, with no evidence of tumor thrombus (arrows). (C) CT scan obtained during hepatic arterial phase 24 months after RFA shows an ill-defined enhancing lesion with a diffusely infiltrative pattern (white arrows) in the peripheral portion of the ablation zone (asterisk). Note the enhancing tumor thrombi expanding the lumen of the peritumoral portal vein (black arrow). This was an initial tumor recurrence after RFA. (D) CT scan obtained during equilibrium phase 24 months after RFA shows delayed washout in both lesions (arrows). Tumor thrombi extend into the right main portal vein (P). The patient underwent transarterial chemoembolization (TACE) and subsequent external radiation therapy. However, only a partial response was achieved after the initial treatment session. (E) CT scan obtained during equilibrium phase 29 months after RFA reveals extensive tumor progression in both hepatic lobes. Note the hemoperitoneum (asterisk) resulting from the ruptured tumor. Partial iodized oil uptake is seen in tumor thrombi of the right portal vein (arrow). The patient died of HCC 30 months after initial RFA. (F) Illustration demonstrates diffusely infiltrative type of AIR (arrows) with tumor thrombus formation (arrowheads) in the adjacent portal vein after RFA for HCC. Asterisk = previous ablation zone (Reprint from Radiology 2015; 276:274–285 with permission). RFA, radiofrequency ablation.

observed in patients with periportal HCCs and the previously reported clinical significance of AIR, we should know how to prevent or minimize this newly recognized tumor recurrence. Recently modified ablation techniques, in accordance with studies recommending use of sonazoid,[21] no-touch multi-polar ablation technique,[22,23] longer ablation times at lower power,[18] combined RFA treatments with TACE,[24] or cryoablation, to prevent aggressive tumor recurrence after RFA for HCC have been used to prevent this serious complication, especially in patients with periportal tumors. However, the effectiveness of these techniques should be validated with further prospective studies.

CONCLUSION

To minimize or prevent this newly recognized tumor recurrence,

which is a serious complication of percutaneous RFA for HCC, it is important for physicians to have knowledge of the mechanisms, risk factors, and methods of prevention. In addition, physicians should be familiar with the imaging features of various types of aggressive tumor recurrence after RFA for HCC. With understanding of this serious complication, hepatic RFA can be performed with greater safety, better patient outcomes, and a reduced risk of treatment failures in patients with HCC.

Funding support

This work was supported by Nano-Convergence Foundation (www.nanotech2020.org) funded by the Ministry of Science, ICT and Future Planning (MSIP, Korea) and the Ministry of Trade, Industry and Energy (MOTIE, Korea) [Flexible nanosensor integrated RF ablation system for in-vivo tissue pressure measurement/ R201603110].

Conflicts of Interest

The authors have no conflicts to disclose.

REFERENCES

1. Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma. Lancet 2012;379:1245-1255.
2. Alazawi W, Cunningham M, Dearden J, Foster GR. Systematic review: outcome of compensated cirrhosis due to chronic hepatitis C infection. Aliment Pharmacol Ther 2010;32:344-355.
3. European Association For The Study Of The Liver; European Organisation For Research And Treatment Of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2012;56:908-943.
4. Lee JM, Park JW, Choi BI. 2014 KLCSG-NCC Korea Practice Guidelines for the management of hepatocellular carcinoma: HCC diagnostic algorithm. Dig Dis 2014;32:764-777.
5. Kang TW, Kim JM, Rhim H, Lee MW, Kim YS, Lim HK, et al. Small hepatocellular carcinoma: radiofrequency ablation versus nonanatomic resection--propensity score analyses of long-term outcomes. Radiology 2015;275:908-919.
6. Pereira PL. Actual role of radiofrequency ablation of liver metastases. Eur Radiol 2007;17:2062-2070.
7. Akahane M, Koga H, Kato N, Yamada H, Uozumi K, Tateishi R, et al. Complications of percutaneous radiofrequency ablation for hepatocellular carcinoma: imaging spectrum and management. Radiographics 2005;25(Suppl 1):S57-S68.
8. Kang TW, Lim HK, Lee MW, Kim YS, Rhim H, Lee WJ, et al. Aggressive intrasegmental recurrence of hepatocellular carcinoma after radiofrequency ablation: risk factors and clinical significance. Radiology 2015;276:274-285.
9. Pua U. Rapid intra-hepatic dissemination of hepatocellular carcinoma with pulmonary metastases following combined loco-regional therapy. Korean J Radiol 2013;14:640-642.
10. Portolani N, Tiberio GA, Ronconi M, Coniglio A, Ghidoni S, Gaverini G, et al. Aggressive recurrence after radiofrequency ablation of liver neoplasms. Hepatogastroenterology 2003;50:2179-2184.
11. Takada Y, Kurata M, Ohkohchi N. Rapid and aggressive recurrence accompanied by portal tumor thrombus after radiofrequency ablation for hepatocellular carcinoma. Int J Clin Oncol 2003;8:332-335.
12. Kotoh K, Enjoji M, Arimura E, Morizono S, Kohjima M, Sakai H, et al. Scattered and rapid intrahepatic recurrences after radio frequency ablation for hepatocellular carcinoma. World J Gastroenterol 2005;11:6828-6832.
13. Lee HY, Rhim H, Lee MW, Kim YS, Choi D, Park MJ, et al. Early diffuse recurrence of hepatocellular carcinoma after percutaneous radiofrequency ablation: analysis of risk factors. Eur Radiol 2013;23:190-197.
14. Mori Y, Tamai H, Shingaki N, Moribata K, Shiraki T, Deguchi H, et al. Diffuse intrahepatic recurrence after percutaneous radiofrequency ablation for solitary and small hepatocellular carcinoma. Hepatol Int 2009;3:509-515.
15. Shiozawa K, Watanabe M, Takahashi M, Wakui N, Iida K, Sumino Y. Analysis of patients with rapid aggressive tumor progression of hepatocellular carcinoma after percutaneous radiofrequency ablation. Hepatogastroenterology 2009;56:1689-1695.
16. Nicoli N, Casaril A, Abu Hilal M, Mangiante G, Marchiori L, Ciola M, et al. A case of rapid intrahepatic dissemination of hepatocellular carcinoma after radiofrequency thermal ablation. Am J Surg 2004;188:165-167.
17. Choi BI, Lee KH, Han JK, Lee JM. Hepatic arterioportal shunts: dynamic CT and MR features. Korean J Radiol 2002;3:1-15.
18. Kotoh K, Nakamuta M, Morizono S, Kohjima M, Arimura E, Fukushima M, et al. A multi-step, incremental expansion method for radio frequency ablation: optimization of the procedure to prevent increases in intra-tumor pressure and to reduce the ablation time. Liver Int 2005;25:542-547.
19. Ahmed M, Kumar G, Moussa M, Wang Y, Rozenblum N, Galun E, et al. Hepatic radiofrequency ablation-induced stimulation of distant tumor growth is suppressed by c-Met inhibition. Radiology 2016;279:103-117.
20. Yamada S, Utsunomiya T, Morine Y, Imura S, Ikemoto T, Arakawa Y, et al. Expressions of hypoxia-inducible factor-1 and epithelial cell adhesion molecule are linked with aggressive local recurrence of hepatocellular carcinoma after radiofrequency ablation therapy. Ann Surg Oncol 2014;21(Suppl 3):S436-S442.

21. Min JH, Kim YS, Rhim H, Lee MW, Kang TW, Song KD, et al. Effect of parenchymal uptake of perfluorobutane microbubbles (Sonazoid(®)) on radiofrequency ablation of the liver: in vivo experimental study. Liver Int 2016;36:1187-1195.
22. Hocquelet A, Aubé C, Rode A, Cartier V, Sutter O, Manichon AF, et al. Comparison of no-touch multi-bipolar vs. monopolar radiofrequency ablation for small HCC. J Hepatol 2017;66:67-74.
23. Kawamura Y, Ikeda K, Fujiyama S, Hosaka T, Kobayashi M, Saitoh S, et al. Potential of a no-touch pincer ablation procedure that uses a multipolar radiofrequency ablation system to prevent intrasubsegmental recurrence of small and single hepatocellular carcinomas. Hepatol Res 2016 Nov 15. [Epub ahead of print]
24. Song KD, Lee MW, Rhim H, Kim YS, Kang TW, Shin SW, et al. Aggressive intrasegmental recurrence of hepatocellular carcinoma after combined rransarterial chemoembolization and radiofrequency ablation. AJR Am J Roentgenol 2016;207:1122-1127.