Editorial

eISSN 2005-8330
https://doi.org/10.3348/kjr.2022.0555
Korean J Radiol 2023;24(1):10-14

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Korean Journal of Radiology
KJR

2022 Korean Liver Cancer Association-National Cancer Center Korea Practice Guidelines for Local Ablation Therapy of Hepatocellular Carcinoma: What's New?

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Take-home points

- Tumor location and biology have been introduced as prognostic factors affecting treatment outcomes after local ablation therapy.
- No-touch radiofrequency ablation (RFA) has been introduced as an alternative to conventional tumor-puncturing RFA.
- Contrast-enhanced ultrasound, fusion imaging of real-time ultrasound, and pre-acquired CT/MRI modalities have been added to the recommendations and are emphasized as valuable guiding tools for local ablation therapy.
- Percutaneous ethanol injection has been removed from the recommendations.

Recently, the 2022 Korean Liver Cancer Association (KLCA)-National Cancer Center (NCC) Korea practice guidelines for hepatocellular carcinoma (HCC) management were published [1]. Regarding local ablation therapy, only minor modifications have been introduced since the previous version (v2018) [2]. In v2022, tumor location and biology were added as prognostic factors affecting treatment outcomes after local ablation therapy. No-touch radiofrequency ablation (RFA) has also been introduced and compared with conventional tumor-puncturing RFA. Contrast-enhanced ultrasound (CEUS), fusion imaging of real-time US, and pre-acquired computed tomography (CT)/ magnetic resonance imaging (MRI) modalities are also emphasized as valuable guiding tools for local ablation therapy and have been added to the recommendations. Percutaneous ethanol injection (PEI) has been removed from the recommendations because the therapeutic efficacy of PEI compared with that of RFA was established on the basis of old data, and it has since been replaced by RFA. In this editorial, updates on local ablation therapy in the new KLCA-NCC guidelines for HCC management are summarized, and a perspective is provided on unaddressed issues.

Indications of Local Ablation Therapy

Local ablation therapies for HCCs are generally indicated for patients with a single HCC ≤ 5 cm or up to three nodules ≤ 3 cm. Although local ablation therapies have been attempted for larger HCCs, treatment outcomes are closely associated with tumor size. The larger the tumor size, the higher the local tumor progression (LTP) rate. Therefore, combined transcatheter arterial chemoembolization (TACE) and ablation therapy are recommended for HCCs 3–5 cm in diameter. Many studies have reported that, compared

Received: August 6, 2022 **Accepted:** September 14, 2022
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with RFA or microwave ablation (MWA) alone, combined treatment with TACE and RFA or MWA increases local tumor control and survival rate for patients with HCCs measuring 3–5 cm that are not amenable to surgical resection [3,4].

Tools to Overcome the Technical Difficulties of US-Guided Local Ablation Therapy

Percutaneous thermal ablation can cause collateral thermal injury to the surrounding organs. Traditionally, artificial ascites or pleural effusion has been used to overcome this risk. Use of artificial ascites also helps enhance sonographic windows, especially in hepatic dome lesions.

Another technical challenge of RFA is that HCCs < 2 cm are not always sufficiently conspicuous on conventional US [5]. Sometimes mistargeting is encountered and a pseudolesion is ablated [6]. However, CEUS and fusion imaging with real-time US and pre-acquired CT/MRI scans improve the detection and technical success rates of local ablation therapy for HCCs < 2 cm [7,8]. In particular, the HCC detection rate is higher when CEUS is performed with fusion imaging than when it is used alone. Although fusion imaging helps localize small HCCs, the incidence of mistargeting after fusion imaging-guided RFA is 1.3%, likely because of registration errors between image sets [9]. Therefore, caution should be exercised when ablating subcapsular HCCs ≤ 1.5 cm, especially in patients with hepatitis B-related liver disease [9].

RFA

The initial complete tumor necrosis rate after RFA has been reported to exceed 95% on the basis of post-RFA CT/MRI. If RFA is repeated for residual unablated tumors, complete tumor necrosis can be achieved in almost all cases. However, the 3-year LTP rate after RFA ranges from 0.9% to 21.4% [10,11]. The 5-year overall survival rates were 83.7%–85.1% in recent RFA studies of Korean patients with HCC within the Milan criteria [12,13]. The independent factors associated with overall survival after RFA include initial complete tumor necrosis, Child–Pugh score, number and size of tumors, and preoperative serum alpha-fetoprotein level.

Patients with a single HCC < 2 cm and Child–Pugh class A liver function can achieve the best treatment outcomes after RFA. If the tumor location is ideal for RFA, its efficacy is comparable with that of hepatectomy. Hence, RFA is considered the primary treatment for single HCC < 2 cm [11,14]. According to randomized controlled trials (RCTs) and meta-analyses [15,16], compared with hepatic resection, RFA has an equivalent survival rate, higher LTP rate, and lower complication rate in patients with a single nodular HCC ≤ 3 cm in diameter.

Tumor location affects treatment outcomes after RFA for HCC. The best results can be expected when the tumor is separated from the hepatic capsule, intrahepatic blood vessels, and central bile duct [17]. Subphrenic HCCs are challenging to treat with US-guided RFA and thus have a high risk of LTP and peritoneal seeding after treatment [12,18]. Laparoscopic RFA can help overcome the technical difficulties of US-guided RFA for subphrenic HCCs if the tumor is accessible under laparoscopic guidance [19,20]. When the tumor is in contact with the portal or hepatic vein ≥ 3 mm in diameter, RFA may be ineffective because of the heat-sink effect and result in complications due to blood vessel or bile duct damage [12,21].

In addition to tumor location, tumor biology is associated with treatment outcomes after RFA. MRI findings such as peritumoral arterial enhancement or peritumoral hypointensity in the hepatobiliary phase, serum tumor marker levels, and tumor size are related to microvascular invasion (MVI) in HCC. In general, HCCs with a high risk of MVI show poor prognosis after RFA [22]. However, to our knowledge, no RCT or meta-analysis investigating the effect of MVI on treatment outcomes is available in the literature; therefore, more evidence is needed to reach a solid conclusion.

No-touch RFA refers to an RFA performed after the placement of multiple electrodes outside the tumor rather than within the tumor. It has gained attention because of its theoretical advantages over conventional tumor-puncturing RFA, including the creation of a sufficient ablative margin [23]. In addition, the risk of tumor spread around the tumor is low because the electrodes are not in direct contact with the tumor. Moreover, tumor feeding and draining vessels are destroyed in the earlier period of RFA, preventing tumor spread via the blood vessels. In two recent RCTs and a prospective multicenter clinical trial, compared with conventional tumor-puncturing RFA, no-touch RFA provided a lower LTP rate [24-26]. However, further investigation is warranted to evaluate whether no-touch RFA enhances survival outcomes after treating patients with small HCCs.

PEI

Limited attention has been paid to PEI since the 2018v guidelines. Generally, compared with PEI, RFA has a lower LTP rate and a higher survival rate. However, the survival rate was not significantly different among subgroups of HCCs < 2 cm [27]. Therefore, PEI may be considered for treating HCCs < 2 cm if RFA is not feasible. However, previous RCTs comparing PEI and RFA were conducted more than a decade ago, when RFA technology was not as mature as PEI technology. Currently, advanced RFA techniques are utilized with multiple or perfusion electrodes. In addition, centripetal ablation using no-touch RFA has been performed at many institutions. Given that local tumor control for HCCs < 2 cm is excellent with RFA, treatment outcomes between RFA and PEI may not be similar if an RCT is performed. This assumption is supported by PEI being largely replaced by RFA, even in HCCs < 2 cm.

The diffusion of injected ethanol may be blocked by the fibrous septum or tumor capsule. Consequently, obtaining a sufficient ablative margin using PEI is challenging and decreases its therapeutic effect. Conversely, the size of the ablation zone is more predictable with RFA than PEI. Therefore, a sufficient ablative margin can easily be obtained using RFA.

MWA

MWA has advantages over RFA because effective ablation can be expected, even for tissues with low electrical conductivity, and higher and faster heating over 100°C is possible. Therefore, theoretically, MWA is less affected by the heat-sink effect caused by blood vessels near the tumor, and the ablation zone is larger. Therefore, MWA is frequently used for HCCs ≥ 2 cm. However, no significant differences were observed in treatment outcomes, including overall survival, disease-free survival, and complication rates, between MWA and RFA for HCCs < 3 cm [28]. Despite the better physical properties of MWA, its therapeutic efficacy seems similar to that of RFA for HCCs < 3 cm. Meanwhile, as no-touch RFA provides excellent local tumor control, a comparative study between no-touch RFA and MWA is warranted for HCCs > 2 cm.

Cryoablation

Cryoablation has several advantages over thermal ablation. An ice ball created by cryoablation shows a clear margin under various guidance modalities: US, non-enhanced CT, or MRI. Therefore, monitoring of the ablation zone during the procedure is relatively easy. Moreover, cryoablation causes less procedure-related pain than does thermal ablation. Cryoablation is advantageous because it results in a lower complication rate than does RFA when treating HCCs near the bile duct or intrahepatic vessels [29,30].

However, the size of the ablation zone with a single cryoprobe is relatively small and usually requires multiple cryoprobes. The procedure time is longer with cryoablation than with other thermal ablation therapies. In patients with one or two HCCs ≤ 4 cm, a multicenter RCT showed no significant difference in the 1-, 3-, and 5-year overall survival, disease-free survival, and major complication rates between RFA and cryoablation [31]. Cryoablation is expected to be comparable with RFA in terms of survival, recurrence, and complication rates.

Key words
HCC; KLCA-NCC; Guideline; Recommendation; Ablation

Availability of Data and Material
Data sharing does not apply to this article as no datasets were generated or analyzed during the current study.

Conflicts of Interest
Min Woo Lee and Jeong Min Lee who is on the editorial board of the *Korean Journal of Radiology* was not involved in the editorial evaluation or decision to publish this article. All remaining authors have declared no conflicts of interest.

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Funding Statement
This work was supported by the Korea Medical Device Development Fund grant funded by the Korea government

(the Ministry of Science and ICT, the Ministry of Trade, Industry and Energy, the Ministry of Health & Welfare, the Ministry of Food and Drug Safety) (Project Number: RS-2020-KD000303, 1711138983).

REFERENCES

1. Korean Liver Cancer Association (KLCA), National Cancer Center (NCC) Korea. 2022 KLCA-NCC Korea practice guidelines for the management of hepatocellular carcinoma. *Korean J Radiol* 2022;23:1126-1240
2. Korean Liver Cancer Association (KLCA), National Cancer Center (NCC). 2018 Korean Liver Cancer Association-National Cancer Center Korea practice guidelines for the management of hepatocellular carcinoma. *Korean J Radiol* 2019;20:1042-1113
3. Peng ZW, Zhang YJ, Chen MS, Xu L, Liang HH, Lin XJ, et al. Radiofrequency ablation with or without transcatheter arterial chemoembolization in the treatment of hepatocellular carcinoma: a prospective randomized trial. *J Clin Oncol* 2012;31:426-432
4. Zaitoun MMA, Elsayed SB, Zaitoun NA, Soliman RK, Elmokadem AH, Farag AA, et al. Combined therapy with conventional trans-arterial chemoembolization (cTACE) and microwave ablation (MWA) for hepatocellular carcinoma >3-<5 cm. *Int J Hyperthermia* 2021;38:248-256
5. Lee MW, Rhim H, Cha DI, Kim YJ, Lim HK. Planning US for percutaneous radiofrequency ablation of small hepatocellular carcinomas (1-3 cm): value of fusion imaging with conventional US and CT/MR images. *J Vasc Interv Radiol* 2013;24:958-965
6. Lee MW, Lim HK, Kim YJ, Choi D, Kim YS, Lee WJ, et al. Percutaneous sonographically guided radio frequency ablation of hepatocellular carcinoma: causes of mistargeting and factors affecting the feasibility of a second ablation session. *J Ultrasound Med* 2011;30:607-615
7. Ahn SJ, Lee JM, Lee DH, Lee SM, Yoon JH, Kim YJ, et al. Real-time US-CT/MR fusion imaging for percutaneous radiofrequency ablation of hepatocellular carcinoma. *J Hepatol* 2017;66:347-354
8. Calandri M, Mauri G, Yevich S, Gazzera C, Basile D, Gatti M, et al. Fusion imaging and virtual navigation to guide percutaneous thermal ablation of hepatocellular carcinoma: a review of the literature. *Cardiovasc Intervent Radiol* 2019;42:639-647
9. Lim S, Lee MW, Rhim H, Cha DI, Kang TW, Min JH, et al. Mistargeting after fusion imaging-guided percutaneous radiofrequency ablation of hepatocellular carcinomas. *J Vasc Interv Radiol* 2014;25:307-314
10. Kim YS, Lim HK, Rhim H, Lee MW, Choi D, Lee WJ, et al. Ten-year outcomes of percutaneous radiofrequency ablation as first-line therapy of early hepatocellular carcinoma: analysis of prognostic factors. *J Hepatol* 2013;58:89-97
11. Livraghi T, Meloni F, Di Stasi M, Rolle E, Solbiati L, Tinelli C, et al. Sustained complete response and complications rates after radiofrequency ablation of very early hepatocellular carcinoma in cirrhosis: is resection still the treatment of choice? *Hepatology* 2008;47:82-89
12. Lee MW, Kang D, Lim HK, Cho J, Sinn DH, Kang TW, et al. Updated 10-year outcomes of percutaneous radiofrequency ablation as first-line therapy for single hepatocellular carcinoma < 3 cm: emphasis on association of local tumor progression and overall survival. *Eur Radiol* 2020;30:2391-2400
13. Lee DH, Lee JM, Lee JY, Kim SH, Kim JH, Yoon JH, et al. Non-hypervascular hepatobiliary phase hypointense nodules on gadoxetic acid-enhanced MRI: risk of HCC recurrence after radiofrequency ablation. *J Hepatol* 2015;62:1122-1130
14. Reig M, Forner A, Rimola J, Ferrer-Fàbrega J, Burrel M, Garcia-Criado Á, et al. BCLC strategy for prognosis prediction and treatment recommendation: the 2022 update. *J Hepatol* 2022;76:681-693
15. Ng KKC, Chok KSH, Chan ACY, Cheung TT, Wong TCL, Fung JYY, et al. Randomized clinical trial of hepatic resection versus radiofrequency ablation for early-stage hepatocellular carcinoma. *Br J Surg* 2017;104:1775-1784
16. Wang Q, Tang M, Zhang S. Comparison of radiofrequency ablation and surgical resection for hepatocellular carcinoma conforming to the Milan criteria: a meta-analysis. *ANZ J Surg* 2021;91:E432-E438
17. Lee DH, Kim JW, Lee JM, Kim JM, Lee MW, Rhim H, et al. Laparoscopic liver resection versus percutaneous radiofrequency ablation for small single nodular hepatocellular carcinoma: comparison of treatment outcomes. *Liver Cancer* 2021;10:25-37
18. Song KD, Lim HK, Rhim H, Lee MW, Kang TW, Paik YH, et al. Hepatic resection vs percutaneous radiofrequency ablation of hepatocellular carcinoma abutting right diaphragm. *World J Gastrointest Oncol* 2019;11:227-237
19. Kwak MH, Lee MW, Ko SE, Rhim H, Kang TW, Song KD, et al. Laparoscopic radiofrequency ablation versus percutaneous radiofrequency ablation for subphrenic hepatocellular carcinoma. *Ultrasonography* 2022;41:543-552
20. Ko SE, Lee MW, Ahn S, Rhim H, Kang TW, Song KD, et al. Laparoscopic hepatic resection versus laparoscopic radiofrequency ablation for subcapsular hepatocellular carcinomas smaller than 3 cm: analysis of treatment outcomes using propensity score matching. *Korean J Radiol* 2022;23:615-624
21. Lee S, Kang TW, Cha DI, Song KD, Lee MW, Rhim H, et al. Radiofrequency ablation vs. surgery for perivascular hepatocellular carcinoma: propensity score analyses of long-term outcomes. *J Hepatol* 2018;69:70-78
22. Lee S, Kang TW, Song KD, Lee MW, Rhim H, Lim HK, et al. Effect of microvascular invasion risk on early recurrence of hepatocellular carcinoma after surgery and radiofrequency ablation. *Ann Surg* 2021;273:564-571

23. Kim TH, Lee JM, Lee DH, Joo I, Park SJ, Yoon JH. Can "no-touch" radiofrequency ablation for hepatocellular carcinoma improve local tumor control? Systematic review and meta-analysis. *Eur Radiol* 2022 Jul 30. [Epub]. http://doi.org/10.1007/s00330-022-08991-1
24. Park SJ, Cho EJ, Lee JH, Yu SJ, Kim YJ, Yoon JH, et al. Switching monopolar no-touch radiofrequency ablation using octopus electrodes for small hepatocellular carcinoma: a randomized clinical trial. *Liver Cancer* 2021;10:72-81
25. Suh YS, Choi JW, Yoon JH, Lee DH, Kim YJ, Lee JH, et al. No-touch vs. conventional radiofrequency ablation using twin internally cooled wet electrodes for small hepatocellular carcinomas: a randomized prospective comparative study. *Korean J Radiol* 2021;22:1974-1984
26. Lee DH, Lee MW, Kim PN, Lee YJ, Park HS, Lee JM. Outcome of no-touch radiofrequency ablation for small hepatocellular carcinoma: a multicenter clinical trial. *Radiology* 2021;301:229-236
27. Yang B, Zan RY, Wang SY, Li XL, Wei ML, Guo WH, et al. Radiofrequency ablation versus percutaneous ethanol injection for hepatocellular carcinoma: a meta-analysis of randomized controlled trials. *World J Surg Oncol* 2015;13:96
28. Gupta P, Maralakunte M, Kumar-M P, Chandel K, Chaluvashetty SB, Bhujade H, et al. Overall survival and local recurrence following RFA, MWA, and cryoablation of very early and early HCC: a systematic review and Bayesian network meta-analysis. *Eur Radiol* 2021;31:5400-5408
29. Kim R, Kang TW, Cha DI, Song KD, Lee MW, Rhim H, et al. Percutaneous cryoablation for perivascular hepatocellular carcinoma: therapeutic efficacy and vascular complications. *Eur Radiol* 2019;29:654-662
30. Ko SE, Lee MW, Rhim H, Kang TW, Song KD, Cha DI, et al. Comparison of procedure-related complications between percutaneous cryoablation and radiofrequency ablation for treating periductal hepatocellular carcinoma. *Int J Hyperthermia* 2020;37:1354-1361
31. Wang C, Wang H, Yang W, Hu K, Xie H, Hu KQ, et al. Multicenter randomized controlled trial of percutaneous cryoablation versus radiofrequency ablation in hepatocellular carcinoma. *Hepatology* 2015;61:1579-1590