Chapter 5:

Percutaneous Ablation

● Introduction

In Japan, various treatment modalities have been developed and reported as locoregional therapy for HCC since the 1970s, at which time HCC was diagnosed based on palpation, AFP levels, liver scintigraphy, and abdominal angiography because CT, MRI, and US had not yet been introduced to the clinical setting. In this context, the clinical application of angiographic techniques was tried, and TAE, the treatment modality first reported by Yamada et al. in 1979[1], became the first locoregional therapy to have proven utility for HCC.

In the years that followed, diagnostic accuracy for the smallest HCCs improved from 5 cm to 2 cm due to advancement and incorporation of US devices, and this prompted the development of US-driven diagnostic and treatment modalities. In 1983, inspired by percutaneous transhepatic portography for esophageal varices, Sugiura et al. developed a treatment involving the injection of pure ethanol into tumors[2]. This treatment, known as PEI, is probably the starting point of US-guided percutaneous treatments. Its relative simplicity and the affordable price of needles and ethanol quickly led to widespread use worldwide. However, ethanol does not spread consistently throughout HCC tumors due to the presence of septa, and this can result in problems including residual tumor and local recurrence.

To overcome the drawbacks associated with PEI, a new treatment modality was developed that involved thermal coagulation of tumors by introducing electrical energy via electrodes. Through the percutaneous application of microwaves, which were frequently used in surgery in those days, Seki et al. developed microwave coagulation therapy (MCT) in 1994[3]. However, despite consistently achieving coagulative necrosis, the drawbacks of MCT include the small area of necrosis it produces and many complications such as bile duct injury.

In 1995, Rossi et al. performed RFA for small HCC and reported good treatment outcomes[4]. Following the introduction of RFA to Japan in 1999, many hospitals had started to apply it because of its advantages over MCT, such as a large necrotized area per ablation and fewer complications. RFA has been covered by the National Health Insurance system since April 2004 and is currently the standard percutaneous ablation treatment for HCC in Japan.

Technological advances in medical devices and contrast agents have greatly improved the therapeutic effect of RFA. The major contrast agents Levovist® and Sonazoid® were approved for use in contrast-enhanced US in 1999 and 2007, respectively, and help to improve the recognition of lesions in US-guided RFA. The Real-time Virtual Sonography System® developed in 2003 by the Hitachi Medical Corporation (currently Hitachi, Ltd.) was the precursor imaging technology for fusion imaging. Until then, imaging modalities such as US and CT/MRI could not be used together interactively. Fusion imaging now offers imaging interaction in the clinical setting and can support percutaneous ablation therapy. In addition, advances in microcatheters and guidewires has led to the development of transcatheter interventional techniques. Superselective TACE can achieve selective

ischemic necrosis of the tumor tissues. Therefore, combination RFA and TACE can provide synergistic efficacy and fewer complications. The current Guidelines includes the new evidence that combination therapy with TACE and percutaneous ablation can improve prognosis in patients with large HCC.

Percutaneous ablation therapy has evolved with the many advances made in medical devices and imaging. New knowledge in ablation therapy is expected with more such developments in the future.

■ References

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CQ31 Which patients are eligible for percutaneous ablation?

Recommendation

Strong recommendation: Percutaneous ablation is indicated for patients with Child–Pugh class A or B liver function, up to 3 tumors, and tumor diameter ≤ 3 cm.

■ Background

In principle, the treatment algorithm recommends hepatectomy, percutaneous ablation, and TACE in this order for patients who have indications for all three treatment modalities. The ranking of hepatectomy, percutaneous ablation, and TACE as first-, second-, and third-line treatment reflects the difference in predicted prognosis after treatment. However, prognostic difference is assumed to change depending on liver function and tumor conditions. Here, we evaluated indications for percutaneous ablation in comparison with indications for other treatments.

■ Scientific Statement

This CQ is a continuation of CQ32 in the third edition. A literature search conducted with the search query used in the third edition and a publication date between January 1, 2012 and June 30, 2016 extracted 636 articles. This was narrowed down to 85 articles in the first screening, from which 27

were extracted based on the following inclusion criteria: RCT or non-RCT studies that compared percutaneous ablation with other treatment options such as resection, TACE, and best supportive care (BSC). Further evaluation of the 27 articles and the 12 articles from the third edition eventually extracted 12 articles with high-quality evidence and a large number of patients[1–12].

Table 1 shows 4 articles that report RCTs of RFA and surgical resection[1–4]. Although tumor conditions vary among the studies, no significant difference in survival rate was observed in 3 of the 4 RCTs, but in the study by Huang et al., survival rate was significantly better with surgical resection than with RFA[2].

The most recent literature search extracted 4 new meta-analyses of studies that compared RFA and surgical resection and were published after 2012[5,10-12]. The meta-analysis conducted by Qi et al., representative of the 4 meta-analyses, reviewed 3 RCTs and reported a significantly better survival rate with surgical resection than with RFA (hazard ratio, 1.41; 95% CI, 1.06-1.89; p = 0.02)[5]. However, in the analysis, the fact that tumors were not subgrouped based on size (< 3 cm and 3-5 cm) could have affected the study results.

In a non-RCT study, Zhang et al. compared patients with solitary HCC ≤ 3 cm who underwent percutaneous microwave coagulation therapy (PMCT, n = 68) or hepatectomy (n = 122) and found that a significantly better recurrence-free survival rate with hepatectomy (p = 0.006)[6]. Also, in a cohort study of Japanese patients with up to 3 HCC ≤ 3 cm and Child-Pugh A/B liver function, Hasegawa et al. reported a significantly better survival rate in the hepatectomy group (n = 5,361) than in the RFA group (n = 5,548)[7].

Table 1. Comparison of survival rate between RFA and hepatectomy for HCC

Author	Year of publication	Study design	Case number (RFA/hepatectomy)	Conditions	Survival (%) (RFA/hepatectomy)	p value
Chen[1]	2006	RCT	90/90	Solitary HCC ≤ 5 cm	67.9 vs. 64.0 (4 years)	NS
Huang[2]	2010	RCT	115/115	Within the Milan criteria	54.78 vs. 75.65	0.001
Feng[3]	2012	RCT	84/84	Up to 2 HCCs ≤ 4 cm	74.8 vs. 67.2	NS
Fang[4]	2014	RCT	60/60	Up to 3 HCCs ≤ 3 cm	82.5 vs. 77.5	NS

Murakami et al. compared patients with solitary HCC ≤ 5 cm or up to 3 HCCs ≤ 3 cm each who underwent RFA (n = 105) or TACE (n = 133) and found a significantly lower local recurrence rate in the RFA group (p = 0.013)[8]. Also, Kim et al. showed significantly better recurrence-free survival

rates in patients with solitary HCC ≤ 2 cm after RFA (n = 165) than after TACE (n = 122; p = 0.034), although the overall survival rate was not significantly different (p = 0.079)[9].

■ Explanation

In the third edition of the Guidelines, Child-Pugh A/B in patients with up to 3 HCCs ≤ 3 cm was an indication for percutaneous ablation.

For many years, PEI played the central role in percutaneous ablation and was frequently indicated for patients with up to 3 HCCs ≤ 3 cm. When performed for HCC > 3 cm, PEI was associated with a high local recurrence rate. In the thermal coagulation therapy RFA, it is theoretically possible to expand the area of ablation by increasing the number of the therapy sessions, but RFA is associated with complications when the number and area of ablation is increased. Also, because the area of ablation is about 3 cm with most RFA electrodes, the Revision Committee has decided to continue to use "up to 3 HCCs ≤ 3 cm" as the indication for percutaneous ablation including RFA.

The aim of treatment with hepatectomy and RFA is basically the same—achieving local control. In percutaneous ablation, as the tumor diameter increases, it becomes increasingly difficult to ensure sufficient ablative margins. As such, the indications for RFA should be decided after careful consideration of the tumor conditions, patient background, and surgical skills. Then, according to the 4 RCTs (with different patient characteristics), the CQ asking which between surgical resection or percutaneous ablation is better for the first-line therapy remains a controvertial one. In the meta-analysis of 4 studies published after 2012 that compared RFA and hepatectomy, while treatment response was significantly better after hepatectomy in 3 studies, no significant difference was observed in the remaining study. Furthermore, several other studies have reported that treatment outcomes were good (5-year survival rate, 60-74%) only in Child-Pugh A patients with solitary HCC ≤ 2 cm[6,7]. However, even among patients with relatively good hepatic functional reserve and early-stage HCC, it is unclear whether percutaneous ablation should replace hepatectomy as first-line therapy.

The most recent literature search did not extract any studies published after Murakami's study[8] that was cited in the third edition and that presented high-quality evidence about differences in survival rate between RFA monotherapy and TACE monotherapy for HCC within the Milan criteria. Therefore, as in the third edition, RFA was determined to be more appropriate than TACE for up to 3 unresectable HCCs ≤ 3 cm. The Revision Committee has graded the recommendation strong due to the lack of strongly opposing comments.

In Japan, a multicenter collaborative study called SURF-RCT* is currently underway to address the need for evidence that can serves as a basis for selecting treatment modalities for primary HCC. SURF-RCT, which was initiated in April 2009, enrolled patients with up to 3 primary HCCs ≤ 3 cm

and good liver function (Child-Pugh score ≤ 7) and is currently collecting data on treatment outcomes of hepatectomy and RFA. Previous studies were all conducted overseas and thus do not reflect actual clinical practice in Japan. The results from SURF-RCT will be the first evidence obtained in Japan.

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*SURF-RCT, Surgery vs. RFA for Hepatocellular Carcinoma: A Randomized Controlled Trial (official name, Efficacy of Surgery vs. Radiofrequency Ablation on Primary Hepatocellular Carcinoma: A Multicenter Randomized Control Trial).

CQ32 How should suitable ablation therapybe chosen?

Recommendations

Strong recommendation: RFA is recommended as percutaneous ablation.

Weak recommendation: RFA and PEI with artificial ascites are options for patients who are at higher risk of gastrointestinal perforation.

■ Background

The history of percutaneous ablation began with PEI in the 1980s. After the introduction of other types of locoregional therapy such as percutaneous acetic acid injection (PAI) and PMCT, percutaneous ablation currently involves RFA. Here, we investigated the most appropriate way to select percutaneous ablation for individual patients. Technological advances now offer us a wide range of medical devices and supplies to use in percutaneous ablation, such as the bipolar RFA device (CELON Power System®), electrodes with adjustable tip length (VIVA RF System® for next-generation MCT), cryoablation systems, and irreversible electroporation devices.

■ Scientific Statement

This CQ is a continuation of CQ33 in the third edition. A literature search conducted with the search query used in the third edition and a publication date between January 1, 2012 and June 30, 2016 extracted 636 articles. This was narrowed down to 10 in the first screening. Five articles reporting statistical analysis were extracted in the second screening. A total of 19 articles, including the 14 articles from the third edition, are cited for CQ32[1–19].

・Comparison of RFA and PEI

Two meta-analyses were added to the current edition[1,2]. Shen et al. reported better survival and local recurrence rates with RFA than with PEI[1]. Yang et al.[2], in a review of 3 European studies, 4 Asian studies, and 1 African study, reported significantly better survival and local recurrence rates after RFA only in the Asian study.

・Comparison of RFA and MCT

A meta-analysis conducted by Facciorusso et al. revealed no significant difference in the complete ablation rate between RFA and MCT (OR, 1.12; 95% CI, 0.67-1.88; p = 0.67) or in the local recurrence rate (OR, 1.01; 95% CI, 0.53-1.87; p = 0.98)[3]. However, the local recurrence rate was

significantly better after MCT than after RFA in patients with relatively large nodules (hazard ratio, 0.46; 95% CI, 0.24-0.89; p = 0.02). Also, the 3-year survival rate did not differ significantly (OR, 0.95; 95% CI, 0.58-1.57; p = 0.85) but tended to be higher after RFA. The number of major complications were slightly, but not significantly, higher after MCT (OR, 1.63; 95% CI, 0.88-3.03; p = 0.12).

・Comparison of RFA and cryoablation

A meta-analysis by Huang et al.[4] and an RCT by Wang et al.[5] showed no significant difference in the overall survival rate between RFA and cryoablation. Huang et al. showed a significant decrease in the local recurrence rate after RFA[4], whereas Wang et al. reported a significant increase after RFA[5].

・Complications

A meta-analysis by Bertot et al. revealed overall mortality after percutaneous ablation was 0.16% (95% CI: 0.10-0.24), and mortality by treatment modality was 0.16% (0.10-0.24) for RFA, 0.15% (0.08-0.23) for MCT, and 0.23% (0.0-0.58) for PEI[6]. The incidence of severe complications after percutaneous ablation was 3.29% (range, 2.43-4.28%), and the rate by treatment modality was 4.1% (3.3-5.1) for RFA, 4.6% (0.7-11.8) for MCT, and 2.7% (0.28-7.4) for PEI. The incidence of complications did not differ significantly between RFA and PEI in a meta-analysis by Germani et al. (OR, 1.21; 95% CI, 0.89-1.63; p = 0.22)[7], but it tended to increase after RFA in a meta-analysis by Shen et al. (hazard ratio, 2.04; 95% CI, 0.81-5.15; p = 0.059)[1].

■ Explanation

In PEI, the fibrous capsule and septa inside HCC prevent ethanol from dispersing throughout the HCC and therefore the ability of PEI to achieve radical cure diminishes as the size of tumor increases. In contrast, one of the advantages of MCT and RFA is to induce necrosis in lesions as well as in surrounding tissues where satellite nodules are present. The literature search extracted many articles suggesting the superiority of RFA to PEI in terms of survival and local recurrence rates[5–10]. Also, subgroup analysis showed that treatment outcomes tend to differ more in patients with HCC ≥ 2 cm[1,7]. Another meta-analysis reported a comparable response to RFA and MCT, but the analysis included only one RCT that was published back in 2002[3]. Therefore, it is too early to conclude that MCT is superior to RFA due to the lack of sufficient evidence. It is also important to accumulate more evidence about cryoablation and IRE, which are relatively new treatment modalities and have not been approved for the treatment of HCC in Japan. Because the most recent literature search did not extract any studies that compared treatment outcomes between different RFA devices, further study is needed to address this issue in the future. Based on these findings, the Revision Committee has decided that there is enough evidence to recommend RFA strongly as the most appropriate means of percutaneous ablation.

As for complications, no significant difference was observed between the different modalities of

percutaneous ablations (RFA, MCT, and PEI) in the studies conducted by Germani et al.[7] and Shen et al.[1]. However, complications often occur in the vicinity of the porta hepatis and in areas of the liver adjacent to other organs[9]. In particular, gastrointestinal perforation occurs more often after RFA than after PEI[6], and patients with postoperative adhesions are at high risk of gastrointestinal perforation[9]. Nevertheless, RFA or PEI with artificial ascites improves treatment outcome in such cases, according to many retrospective studies conducted in Japan[8,10,11]. Therefore, PEI with artificial ascites is recommended for areas at high risk of gastrointestinal perforation, but the recommendation is graded weak because of the lack of high-quality evidence.

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CQ33 Can the combination of percutaneous ablation and TACE improve the survival of HCC patients?

Recommendation

Weak recommendation: It is expected that combination therapy with percutaneous ablation and TACE can improve survival in patients with relatively large tumors.

■ Background

It is possible to diminish the cooling effect of blood and thereby expand the area of ablation by performing TACE prior to percutaneous ablation. Here, we investigated the possibility of improving prognosis by combining percutaneous ablation with TACE.

■ Scientific Statement

This CQ is a continuation of CQ34 in the third edition. A literature search conducted with the search

query used in the third edition and a publication date between January 1, 2012 and June 30, 2016 extracted 636 articles. This was narrowed down to 17 in the first screening, from which 11 studies reporting statistical analysis were extracted in the second screening. A total of 16 articles, which include 5 from the third edition, are cited for CQ33[1–16].

・Area of ablation

Kitamoto et al. showed a significantly larger area of ablation after combination therapy with TACE + RFA (maximum and minimum diameter 39.9 and 32.3 mm) than after RFA monotherapy (34.6 and 26.0 mm, respectively; $p < 0.05$)[1]. Morimoto et al. also reported that the area of ablation was significantly larger after combination therapy with TACE + RFA (mean maximum and minimum diameter 50 and 41 mm) than after RFA monotherapy (58 and 50 mm, respectively; $p = 0.012$)[2].

・Survival rate

Table 2 shows studies published after 2012 that compared the outcomes of combination therapy with TACE + RFA and RFA monotherapy[3–6]. Despite diverse patient characteristics, combination therapy with TACE + RFA showed a significantly higher survival rate in 3 of the 4 studies and no significant difference in the remaining study. Seven meta-analyses also showed significantly a better survival rate after combination therapy with TACE + RFA[7–13].

■ Explanation

In previous studies, the timing of TACE varied widely from on the same day as ablation to within 2 months of ablation, but TACE performed within 1 month of ablation has been adopted most frequently in Japanese studies.

There is a general agreement in previous studies that the area of ablation increases when TACE is performed prior to RFA. Therefore, TACE is expected to decrease the number of treatments and the local recurrence rate through expansion of the ablation area. For example, the study by Morimoto et al. found significantly fewer therapy sessions were needed and the local recurrence rate was lower after combination therapy with TACE + RFA than after RFA monotherapy (TACE + RFA vs. RFA: 1.1vs.1.4 times, $p < 0.01$; 6% vs. 39%, $p = 0.012$; respectively)[2.]

Table 2. Comparison of combination therapy with TACE + RFA and RFA monotherapy in patients with HCC

Author (Publication year)	Study design	Number of patients (TACE+RFA / RFA)	Tumor condition	3-year survival rate (%)	5-year survival rate (%)	P value
Kim (2012)[3]	NRCT	82/213	Tumor diameter 2-3 cm	72 vs. 73	63 vs. 53	0.545
Peng (2012)[4]	RCT	69/70	・Recurrence after TACE ・Tumor diameter ≤ 5 cm	69 vs. 47	46 vs. 36	0.037

Peng (2013)[5]	RCT	94/95	Tumor diameter < 7 cm	66.6 vs. 59	61.8 vs. 45 (4-year)	0.002
Song (2016)[6]	NRCT	87/43	Within the Milan criteria	77 vs. 30	66 vs. 18	0.041

NRCT, non-RCT

In the third edition, the recommendation made under CQ34 “Does a combination of TACE and percutaneous ablation therapy improve prognosis?” was that “there is inadequate evidence demonstrating that pretreatment with TACE will improve RFA outcomes”. However, the most recent literature search revealed an increasing number of studies suggesting that combination therapy with TACE + RFA improves survival rate. For example, a meta-analysis by Jiang et al. (of 8 RCTs and 11 retrospective cohort studies) showed that ORs for 1-, 3-, and 5-year survival were 2.14 (95% CI, 1.57-2.91; $p < 0.001$), 1.98 (95% CI, 1.28-3.07; $p = 0.001$), and 2.70 (95% CI, 1.42-5.14; $p < 0.001$), respectively, indicating the superiority of combination therapy with TACE + RFA[11]. In addition, subgroup analysis revealed a greater contribution to survival in patients with larger tumors. Therefore, combination therapy with percutaneous ablation and TACE is expected to improve prognosis in patients with relatively large tumors, as stated in the Recommendation section. However, the recommendation was graded weak because of the small number of patients (< 100) even though the references include 2 RCTs.

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CQ34 Is contrast-enhanced US or fusion imaging useful for image-guided percutaneous ablation?

Recommendation

Weak recommendation: Contrast-enhanced US and/or fusion imaging are useful for image-guided percutaneous ablation in patients with HCCs that are difficult to visualize on B-mode US.

■ Background

It is crucial to accurately define liver-tumor boundaries before setting ablative margins in RFA. Therefore, achieving successful treatment requires clear visualization of the entire HCC in US-guided percutaneous ablation. However, it may be difficult to visualize liver nodules on B-mode US when there is (1) a poorly defined liver-tumor boundary due to poor encapsulation, (2) a small liver lesion hidden behind large regenerative nodules, and (3) a locally recurrent tumor isoechoic to the area necrotized in past ablative treatment. To visualize and treat tumors that are poorly defined on B mode, contrast-enhanced US guidance and fusion imaging guidance have been developed for percutaneous ablation. Here, we investigated the utility of these imaging guidance techniques.

■ Scientific Statement

This CQ is a continuation of CQ35 in the third edition. A literature search conducted with the search query used in the third edition and a publication date between January 1, 2012 and June 30, 2016 extracted 636 articles. This was narrowed down to 152 articles in the first screening, from which 3 articles that compared the outcomes of treatment with US or fusion imaging guidance were extracted in the second screening. Twelve articles are cited for CQ34 here[1-12]: the 3 articles extracted in the current search, 2 hand-searched articles about contrast-enhanced US and fusion imaging guidance, and the 7 articles cited in the third edition.

・US guidance

Minami et al. performed RFA under the guidance of Sonazoid®-enhanced US in 108 patients with liver nodules that were poorly visualized on B-mode US and reported a mean number of therapy sessions of 1.1 ± 0.3[1].

Masuzaki et al. also performed RFA under the guidance of Sonazoid®-enhanced US in 291 patients and found significantly fewer therapy sessions were needed compared with well-matched controls (n = 2,261; 1.33 vs. 1.49; p = 0.0019)[2].

・Fusion imaging guidance

Minami et al. have shown that HCCs poorly defined on B-mode US are treated more effectively in RFA guided by the Real-time Virtual Sonography System® than in RFA guided by B-mode US (mean therapy sessions, 1.1 vs. 1.3 times; p = 0.021)[3].

Lee et al. reported that the positive predictive value of fusion imaging (90.5%) was significantly higher than that of B-mode US (78.8%; p = 0.0003)[4].

・Combination of contrast-enhanced US and fusion imaging

Min et al. successfully treated 92.0% of poorly defined HCCs on B-mode US by combining contrast-enhanced US and fusion imaging[5].

Minami et al. observed no significant difference in the 3-year local recurrence rate after RFA guided by contrast-enhanced US, fusion imaging, or their combination (4.9%, 7.2%, and 5.9%,

respectively)[6].

■ Explanation

The US contrast agent perfluorobutane microbubbles (Sonazoid®) (1) enables continuous observation and stable visualization of lesions throughout different phases, (ii) improves recognition of lesions by targeting defects in the post-vascular phase, and (3) enables localization and qualitative diagnosis of HCCs ill-defined on B-mode US in defect reperfusion imaging. These features of Sonazoid have contributed to the simplification of RFA, which was previously quite cumbersome when performed under the guidance of contrast-enhanced US with galactose + palmitic acid (Levovist®). However, it may be still difficult to visualize lesions located deep in the liver or in the liver with advanced cirrhosis.

Fusion imaging technology displays multiplanar reconstruction images in real time similar to B-mode images, by synchronizing the coordinate system of pre-existing volume data from CT or MRI and the coordinate system of volume data generated by using a US probe mounted an electromagnetic tracking sensor. One of the merits of fusion imaging is the ability to display reference images in contrast-enhanced US even under difficult conditions. Furthermore, technological advances in imaging devices (the addition of a position tracking sensor and Active Tracker® for automatic fusion between US and CT images) have contributed to the improved accuracy in image adjustment and the reduced labor-intensiveness. However, it should be kept in mind that even fusion imaging does not always produce images that completely match the real image of the liver, because of displacement by respiratory excursion and liver contortions.

In the study by Minami et al., the local recurrence rate after RFA guided by two imaging modalities was comparable with that for other treatments despite the much more challenging cases of HCCs, which were poorly defined on B-mode US and poorly identified on contrast-enhanced US or fusion imaging[6]. Contrast-enhanced US and fusion imaging should not be viewed as competing imaging systems. What is important in the treatment of HCC is to achieve local control by using them in combination or selecting one that is appropriate to the tumor conditions or patient characteristics.

As in the third edition, in the current Guidelines the Revision Committee recommends contrast-enhanced US and fusion imaging as useful guiding systems. However, the recommendation is graded weak because all the references are retrospective studies.

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CQ35 What imaging modalities are useful for assessing treatment response to percutaneous ablation?

Recommendation

Strong recommendation: Dynamic CT or dynamic MRI is recommended for assessing treatment response to percutaneous ablation.

■ Background

The Response Evaluation Criteria in Solid Tumors (RECIST)[1] is commonly used for the assessment of response in solid tumors. However, accurate assessment of response based on the RECIST is difficult in percutaneous ablation for HCC, due to the presence of residual tumor even after curative treatment. Therefore, to evaluate treatment outcomes in HCC, RECIST was modified in the United States and Europe to incorporate the effect of tumor necrosis into the evaluation (the modified version is designated mRECIST)[2,3]. In Japan, the Response Evaluation Criteria in Cancer of the Liver (2015 version)[4] was published as RECICL[5]. Here, we investigated diagnostic imaging modalities that are useful in assessing the treatment outcome of percutaneous ablation.

■ Scientific Statement

This CQ is a continuation of CQ36 in the third edition. A literature search conducted with the search query used in the third edition and a publication date between January 1, 2012 and June 30, 2016 extracted 636 articles. This was narrowed down to 141 in the first screening, from which 2 articles comparing response to percutaneous ablation were extracted in the second screening. A total of 9 articles, including the 7 articles from the third edition, are cited for CQ35.

・Simple MRI

Koda et al. reported that ablative margins were visualized as high-intensity rims on T1WI MRI in 86% of nodules after RFA[6]. Also, analysis of the ablative margins showed a good correlation between simple MRI and dynamic CT (κ coefficient = 0.716).

・Gd-EOB-DTPA-enhanced MRI (EOB-MRI)

Granata et al. compared the diagnostic accuracy of EOB-MRI and dynamic CT against pathology-proven post-RFA residual tumors (n = 42)[7]. They found that at 1 month after RFA, EOB-MRI had a sensitivity of 92%, specificity of 97%, positive predictive value of 92%, and negative predictive value of 97%, showing the superiority of EOB-MRI over dynamic CT ($p < 0.05$).

・Contrast-enhanced US

According to Kudo et al., defect reperfusion imaging detected HCC in small nodules that contrast-enhanced CT could not[8].

Zhou et al. investigated chronological changes in post-RFA tumor margins on B-mode images and reported the detection rate of tumor margins was 65.2% at 1 day after RFA, 54.3% at 3 days, 43.5% at 4 days, and 39.1% at 5 days[9].

■ Explanation

Dynamic CT/MRI is recommended as the standard imaging modality for assessing treatment response to percutaneous ablation because objectivity is required when assessing imaging findings such as ablation margins and because it is necessary to examine many nodules. The strength of recommendation continues to be “strong” because there has been no major change in the evidence available. Dynamic CT has been used as the standard in many studies, and dynamic CT appears to be the standard imaging modality based on its widespread distribution in Japan. Although Granata et al. reported the superiority of EOB-MRI over dynamic CT for detecting residual tumors, the study included a small number of patients[7]. Therefore, further study is needed to accumulate more evidence.

Angiographic findings are absolutely necessary for the assessment of treatment response to percutaneous ablation. However, contrast-enhanced CT/MRI should be contraindicated in patients with kidney failure and allergic disorder such as iodine allergy and asthma. Nephrogenic systemic fibrosis (NSF), a severe late-onset complication of Gd-based contrast agents used in MRI, is of particular importance in patients with kidney failure because renal dysfunction is a risk factor for NSF. In principle, an eGFR of < 30 mL/min/1.73 m^2 is a contraindication for medical examinations using contrast agents. Simple MRI and contrast-enhanced US may be viable alternatives. Simple MRI clearly visualizes many tumors and ablation margins owing to its high contrast resolution. Contrast-enhanced US has a low risk of complications associated with contrast agents and has excellent spatial, contrast, and time resolution. Accordingly, CT and MRI often detect small lesions that are indistinguishable on contrast-enhanced US due to the partial volume effect. Furthermore, as reported by Zhou et al., ablation margins become unclear over time on B-mode US[9]. Approximately, one-third of tumor margins were ill-defined on the day after RFA, showing the limitation of B-mode US, even if combined with contrast-enhanced US, in the assessment of ablation margins.

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CQ36 What factors predict treatment response to percutaneous ablation?

Recommendation

No recommendation: The factors predicting treatment response are tumor size, tumor marker levels, and sufficient ablative margin.

■ Background

After percutaneous ablation, short-term treatment outcomes depend on local recurrence in the area surrounding the ablation site. Here, we reviewed predictors of local recurrence.

■ Scientific Statement

This CQ was newly established in the current Guidelines (fourth edition). A literature search of articles published in the last 10 years extracted 612 articles, which was narrowed down to 103 in the first screening. Forty articles reporting statistical analysis to identify the predictors of clinical response were extracted in the second screening. From these 40 articles, 10 with a relatively large number of patients were extracted[1-10], and 8 articles are cited here as evidence[1-8].

Murakami et al. reported their experience of RFA for 109 HCCs and showed that HCC ≤ 2 cm was associated with the lowest local resection rate ($p < 0.01$)[1]. Kim et al. performed multivariate analysis of 62 HCCs ≤ 4 cm after RFA and revealed that HCC > 3 cm and insufficient ablation margins were factors significantly correlated with local recurrence[2]. Significant correlation was also observed between high AFP levels and intrahepatic recurrence ($p < 0.05$).

Nouso et al. examined 621 HCCs after RFA and found that significant factors associated with local recurrence were HCC > 3 cm (risk ratio, 2.80; 95% CI, 1.77-4.45; $p < 0.0001$), tumor number >

tumor size (risk ratio, 1.74; 95% CI, 1.23-2.47; p = 0.002), and > 100 ng/mL AFP (risk ratio, 1.62; 95% CI, 1.09-2.41; p = 0.014)[3]. In a study of RFA in 201 HCCs, Suh et al. reported that RFA was significantly correlated with local recurrence when the product of AFP × PIVKA values was > 1600 (p = 0.008)[4]. Tamura et al. performed RFA in 138 patients with HCC and reported an association between ≥ 15% AFP-L3 and recurrence-free survival (p = 0.006)[5]. Zytoon et al. performed multivariate analysis of 48 HCCs after RFA and found that local recurrence was associated with HCC ≥ 2.3 cm, insufficient ablation margins, and multiple tumors (p < 0.05)[6].

Chuma et al. analyzed recurrence rates after performing RFA or hepatectomy for 103 HCCs associated with hepatitis B and reported that recurrence was suppressed when pre-treatment serum HBV-DNA levels were low due to antiviral therapy[7]. Multivariate analysis also revealed that independent risk factors for recurrence were high serum HBV-DNA levels (hazard ratio, 2.67; 95% CI, 1.31-5.47; p = 0.007) and absence of antiviral therapy (hazard ratio, 2.57; 95% CI, 1.34-4.94; p = 0.005). Also, in a study of RFA or hepatectomy in 55 patients with HCC associated with hepatitis B, Hosaka et al. found that elevated hepatitis B core-related antigen (HBcrAg) level is an independent risk factor for recurrence (hazard ratio, 8.96; 95% CI, 1.94-41.4)[8].

■ Explanation

A cross-sectional review of articles extracted in the second screening revealed that, as factors related to treatment response, tumor diameter, insufficient ablation margins, and high tumor marker levels are frequently associated with local recurrence (30/40, 75%). AFP was the most common tumor marker, but PIVKA-II and AFP-L3 fraction were also used in some studies. Also, viral load and HBcrAg levels were correlated with liver cancer associated with hepatitis B[7,8].

As for other factors, Hosokawa et al. showed that the 1-, 2- and 3-year recurrence rates of HCC in patients with poorly controlled diabetes were 50.6%, 83.5%, and 93.8%, respectively, indicating that poorly regulated blood glucose level is associated with first recurrence after curative therapy (OR, 1.97; 95% CI, 1.33-2.91; p = 0.0007)[9]. Chen et al. found that overall survival after RFA was better when patients with diabetes were treated with anti-diabetic drugs compared with patients without anti-diabetic drugs[10]. However, further study is needed to accumulate sufficient evidence on the association between diabetes with poor glycemic control and response to RFA.

Similarly, the current edition does not include the following because of insufficient evidence: histological differentiation/macroscopic classification, primary tumor location, serum albumin level, serum vascular endothelial growth factor (VEGF) level, aspartate aminotransferase-to-platelet ratio index, neutrophil-to-lymphocyte ratio, or platelet-to-lymphocyte ratio. As for studies that investigated suppression of recurrence by interferon therapy and administration of vitamin K analogues and branched-chain amino acid analogues, the Revision Committee has concluded that these regimens do not predict clinical response and therefore did not include them in the current

Guidelines.

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