Percutaneous Radiofrequency Ablation for Liver Tumors: Technical Tips

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Abstract

Percutaneous radiofrequency ablation (RFA) has been accepted as a minimally invasive therapeutic treatment for liver malignancies. Although RFA is usually applied for the treatment of small liver tumors (<3 cm), several technical developments have expanded the use of RFA. RFA is now used for the treatment of large liver tumors, and the number of complications associated with this treatment has decreased. These refinements may ultimately lead to better long-term prognosis. Here, we review recent refinements of liver RFA and provide technical tips.

Key words: Radiofrequency ablation, Transarterial chemoembolization, Ablation zone Complications

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Introduction

Percutaneous radiofrequency ablation (RFA) has been accepted as a minimally invasive therapeutic treatment for liver malignancies. An initial complete response of curative RFA in patients with localized hepatocellular carcinoma (HCC) is associated with improved survival, and an ablative margin at least ≥5 mm is important to prevent local tumor progression [1]. Therefore, complete ablation with adequate safety margin is necessary. However, previous studies have clearly shown that liver tumor size significantly affects the therapeutic response [2, 3]. Tumor location is another important factor affecting therapeutic response. Liver tumors are sometimes located in so-called "difficult locations", for instance close to the diaphragm, large vessels, gallbladder, or gastrointestinal (GI) tracts (i.e. stomach and bowel) [4]. The ablative margin for tumors in "difficult locations" may be insufficient, resulting in incomplete ablation and possibly in subsequent severe complications.

Several methods with RFA for tumors lying near critical organs or vessels have recently been reported that achieve complete ablation and reduce complications [5-7]. Hence, this review article provides technical tips on how to enhance therapeutic effects and avoid complications due to RFA for liver tumors.

How to enhance therapeutic effects

Transarterial chemoembolization (TACE) combined with RFA

TACE is a standard treatment for unresectable HCC [8]. When TACE is combined with RFA, the following synergistic effects are anticipated in addition to direct antitumor effects of RFA [9]. Several studies examining TACE combined with RFA have been performed and discussed below.

First, a decrease in the blood flow in the liver causes expansion of the ablation zone size (heat-sink effect) [5], 10, 11]. Additionally, several techniques such as TACE, portal venous embolization, balloon occlusion of the hepatic artery, and balloon occlusion of the hepatic vein have been combined with RFA to increase ablation zone size [11-16]. RFA following TACE is the most popular combination therapy among these options [5]. In Japan, TACE using emulsion of epirubicin and iodized oil is generally performed before

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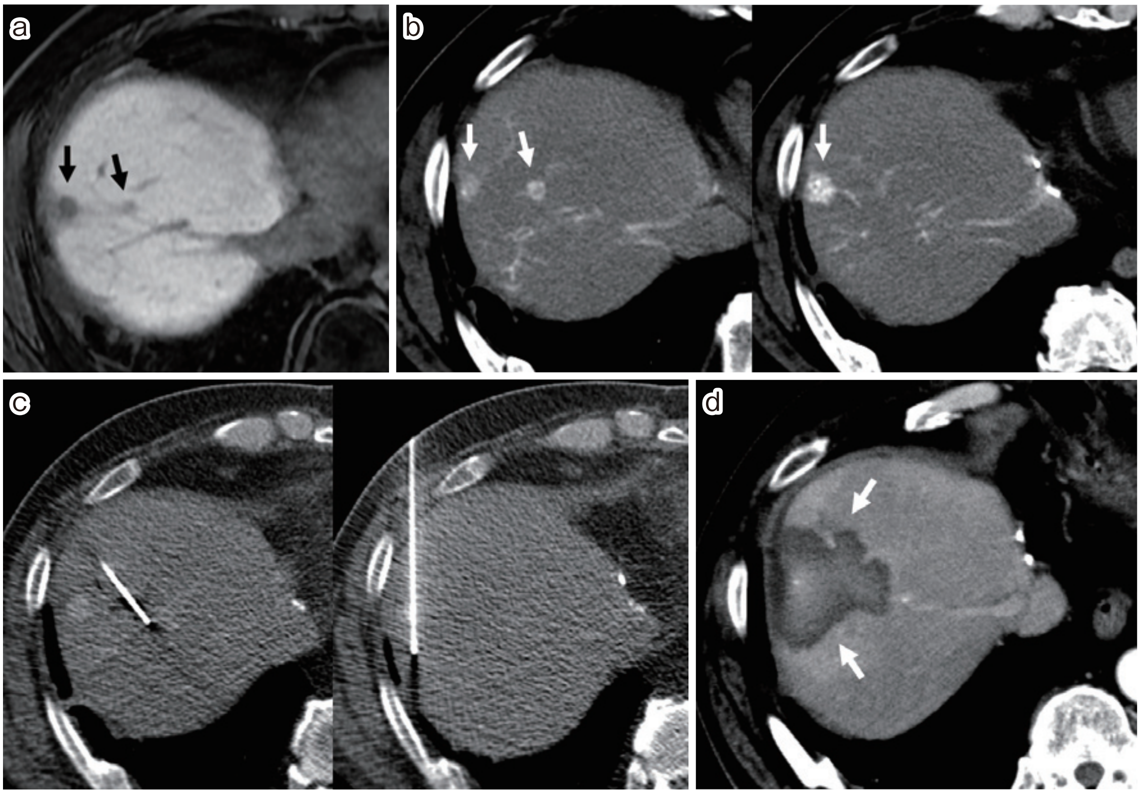

Figure 1. Case: Liver metastases from colorectal cancer after extended left hepatectomy.
a, b) Magnetic resonance imaging (MRI) (hepatobiliary phase image) (a) and computed tomography during hepatic angiography (CTHA) (b) showing two liver metastases (arrows) in the right lobe. c) RFA under CT-fluoroscopic guidance was performed immediately after TACE using degradable starch microspheres mixed with mitomycin C. d) Contrast-enhanced CT showing adequate ablative margin (arrows) two days after RFA.

RFA [11, 14, 15, 17]. The ablation zone size can be expanded significantly when RFA is continued up to four weeks after TACE treatment [11]. Morimoto et al. compared local tumor progression in HCC tumors 3.1-5.0 cm in patients treated with RFA alone and with RFA combined with TACE. The three-year local tumor progression rate was significantly lower with combination therapy than with RFA alone, 6% vs. 39%, respectively (P = 0.012) [17]. Moreover, a randomized trial comparing RFA alone or in combination with TACE in HCC patients with tumors smaller than 7 cm showed that RFA combined with TACE was superior to RFA alone in improving overall survival and recurrence-free survival (hazard ratio [HR], 0.525; 95% confidence interval [CI], 0.335 to 0.822; P = 0.002; HR, 0.575; 95% CI, 0.374 to 0.897; P = 0.009, respectively) [18]. Yamakado et al. performed a multicenter prospective study with colorectal cancer liver metastases (CRCLM) patients and showed that combination therapy of RFA with TACE using degradable starch microspheres mixed with mitomycin C (MMC) had a strong anticancer effect due to the synergetic effect of both therapeutic modalities (**Figure 1**) [19].

Second, TACE combined with a radiopaque agent, such as iodized oil, enhanced visibility of the index tumor on computed tomography (CT) [9]. Ultrasound (US) and CT fluoroscopy are widely used as imaging modalities for targeting the tumor during percutaneous liver RFA [20]. Visualization of intrahepatic vessels, no radiation exposure, and the angle of electrode insertion are potential advantages of US-guided RFA. However, Rhim et al. reported that approximately 45% of small HCCs referred for possible percutaneous RFA were not conspicuous with US, which is the most common guidance tool for liver RFA [21]. Dynamic contrast-enhanced US overcomes that weakness and facilitates RFA electrode placement in hypervascular HCC, which is poorly depicted with B-mode US [22]. Additionally, CT/magnetic resonance-US (CT/MR-US) fusion imaging, which enables the synchronous display of real-time US images and cross-sectional multiplanar reconstruction CT or MR images, has been useful for RFA treatment guidance [23]. On the other hand, CT fluoroscopy-guided RFA has some specific advantages compared to US-guided RFA. CT fluoroscopy images are objective and not affected by air or bone; therefore, CT fluoroscopy enables precise targeting of liver tumors with US-invisible location [20]. Takaki et al. performed CT-guided RFA followed by intra-arterial iodized-oil injection and found that all 150 US-invisible HCCs became visible on CT fluoroscopy after iodized oil injection [24]. Recently, we conducted a prospective trial of the combination treatment of a miriplatin-iodized oil suspension injection and RFA in HCC (UMIN000011285). The miriplatin-

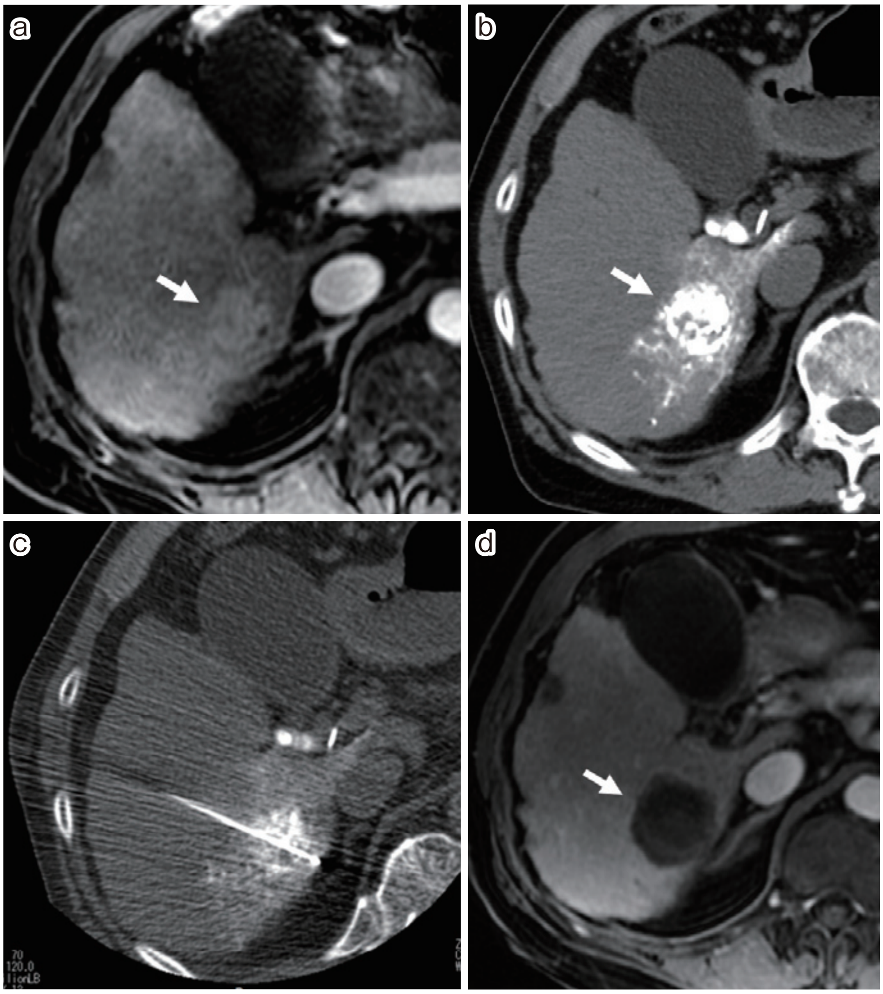

Figure 2. Case: Recurrent hepatocellular carcinoma (HCC)
a) MRI (arterial phase image) showing an HCC measuring 3 cm (arrow) in the posterior segment. b, c) RFA under CT-fluoroscopic guidance was performed immediately after miriplatin-iodized oil suspension injection (arrow). d) MRI (portal phase image) showing adequate ablative margin (arrow) one month after RFA.

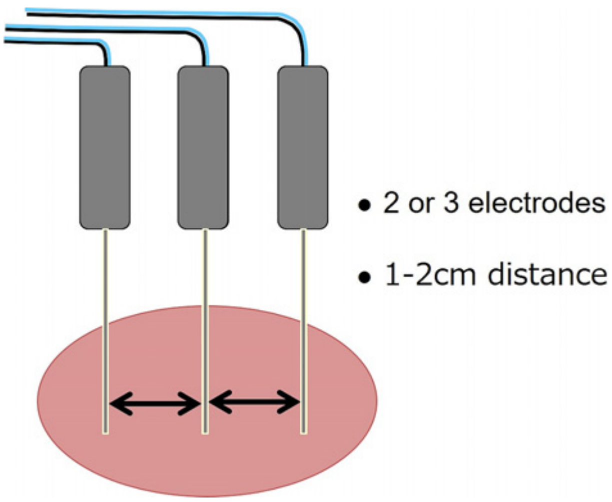

Figure 3. The schema of multiple electrode switching system

mediated anticancer effect was enhanced as well as the tumor visibility on CT due to iodized oil was improved (**Figure 2**).

Multiple electrode switching system

Recently, a multiple electrode switching system has been introduced [25-28] that enables the simultaneous use of up to three RF electrodes and sequentially switches the power between the RF electrodes (**Figure 3**). The power of each RF electrode is switched automatically from one electrode to the next when the impedance reaches 30 Ω above the baseline level or when an interval of 30 seconds is reached, resulting in a large confluent ablation zone created through thermal synergy[25]. Two prospective studies of RFA for HCCs smaller than 5 cm using the multiple electrode switching system showed similar results compared to RFA alone. The 1- and 3-year local tumor progression rates were 4% and 12%, respectively, in one study [27] and 6% and 11%, respectively, in the other[28], suggesting that RFA with multiple electrode switching system enhances the therapeutic effect.

Multibipolar radiofrequency ablation

Multibipolar RFA consists of several linear electrodes (up to six) inserted inside the tumor but also around the tumor in a sequential bipolar mode (**Figure 4**). Multibipolar RFA, using a no-touch concept, ensures efficient tumor ablation with very low rate of local recurrence in HCC < 5 cm. Three- and five-year local tumor progression rates were 96% and 94%, respectively [29]. Additionally, another recent study indicated multibipolar RFA for large HCC > 5 cm with an acceptable safety profile [30]. However, multibipolar RFA may be technically more complex than the commonly used monopolar RFA, because it requires linear insertion of more than one electrode.

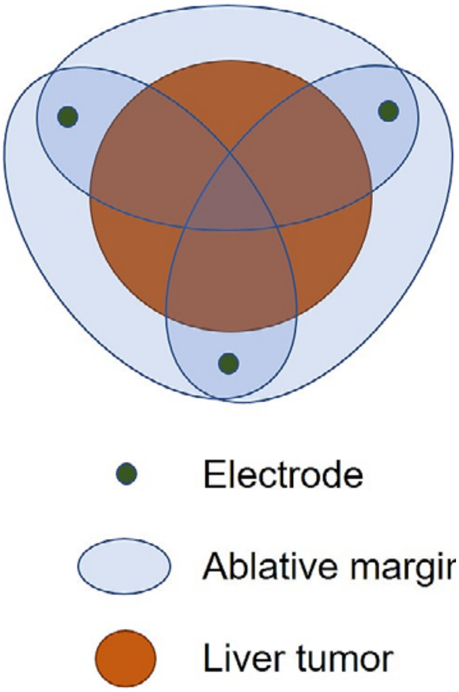

Figure 4. The schema of multibipolar radiofrequency ablation

Systemic chemotherapy

Another strategy to enhance the therapeutic effect of RFA is in combination with a multi-kinase inhibitor [31, 32]. The multi-kinase inhibitor sorafenib is the standard treatment for advanced HCC, and the utility of RFA combined with sorafenib has been reported [8]. Fukuda et al. showed that combination treatment resulted in a significantly larger ablative zone [31]. However, sorafenib alone was not effective in the adjuvant setting. A randomized trial for HCC showed that sorafenib administration following resection or ablation did not result in better survival benefit [33]. Unfortunately, studies are scant on other multi-kinase inhibitor combination strategies, therefore, data are not sufficient to allow for a conclusion on their effectiveness.

Regarding immune therapies, several recent preclinical and clinical studies have suggested that thermal ablation induces therapeutically effective systemic antitumor immune responses when appropriate immunomodulators are combined [34].

How to avoid complications

Mortality and major and minor complication rates of liver RFA have been reported at 0-1.4%, 0.9-10.0%, and 0.8-32.5%, respectively [20, 35-41]. Takaki et al. reported that major complications, such as hemorrhage, liver abscess, and injury to other structures occurred in 2.8% of patients who underwent liver RFA under CT fluoroscopic guidance [20]. Various preparation techniques to avoid such complications have been reported.

Patient selection

Appropriate patient selection for liver RFA is key to avoid

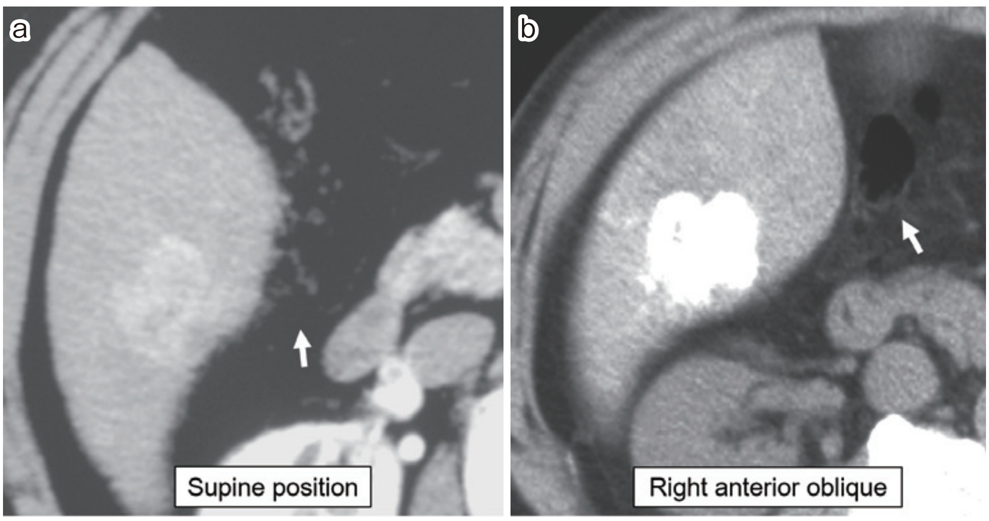

Figure 5. Case: HCC adjacent to the nearby colon (courtesy of Dr. Haruyuki Takaki)
a) HCC is located adjacent to the nearby colon (arrow) in supine position. b) The position of colon (arrow) changed to right anterior oblique.

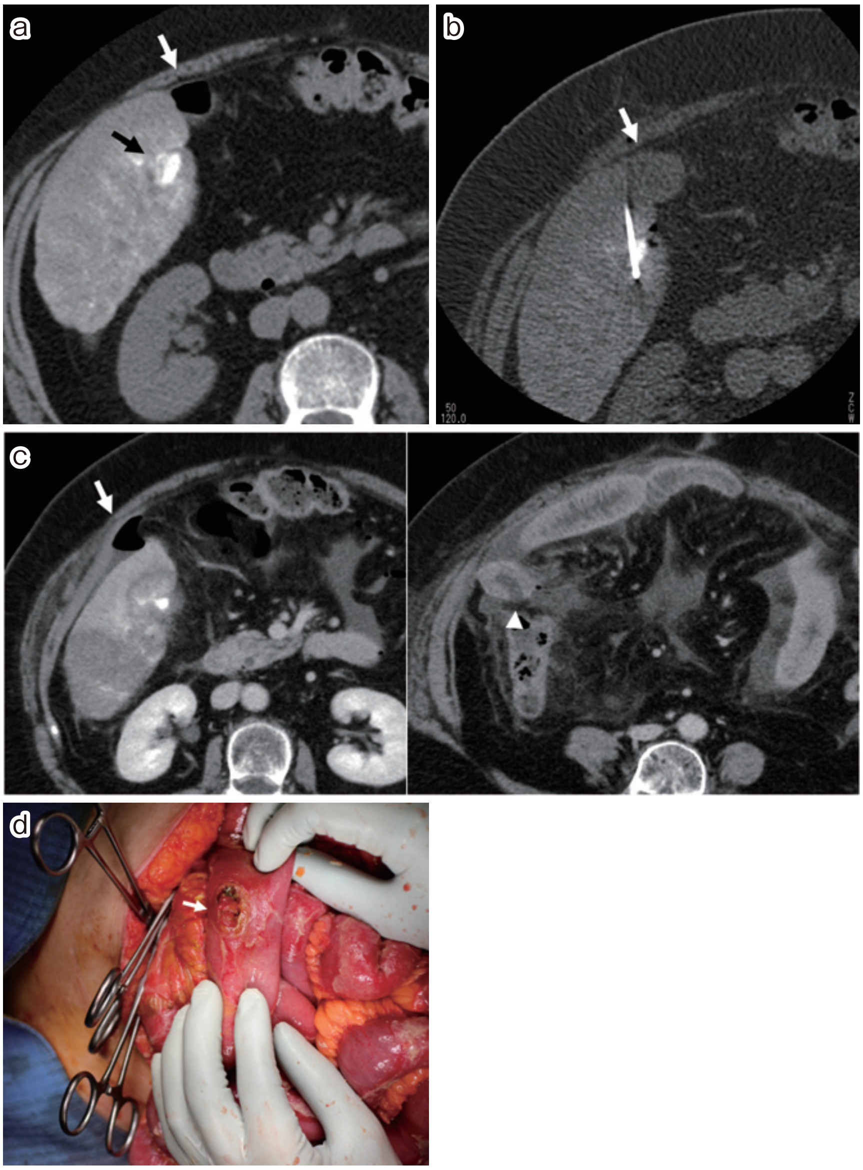

Figure 6. Case: Recurrent HCC

a) Plain CT after TACE showing an HCC with iodized-oil accumulation (black arrow) and the adjacent bowel loop (white arrow). b) RFA under CT-fluoroscopic guidance was performed (arrow: the adjacent bowel loop). c) Contrast-enhanced CT showing free air (arrow) around the liver and necrosis of the bowel wall (arrow head) two days after RFA. d) This patient underwent emergency surgery and intestinal perforation was observed (arrow).

complications. The following exclusion criteria should be applied: Eastern Cooperative Oncology Group performance status 3 or more, Child-Pugh class C, platelet count $<50\times 10^3/\mu L$, international normalized ratio >1.5, uncontrollable ascites, and bilioenteric anastomosis [5].

Preparations to avoid complications

1. Change in body position

If the liver tumor is located adjacent to a nearby structure that may interfere with RFA or potentially be harmed by the procedure (e.g. GI tract), changing body position may help to avoid injury (**Figure 5**). This method is non-invasive and simple to implement.

2. GI decompression

GI tract decompression is a basic preparation technique when the liver tumor is located adjacent to the stomach. Gastric decompression with a nasogastric tube is useful to avoid gastric injury. Although infrequent, intestinal perforation can cause mortality. Liver RFA of a subcapsular mass within 1 cm of the adjacent bowel loops should be carefully performed and followed up closely (**Figure 6**)[40]. In addition, gallbladder needle decompression may be useful to avoid perforation of the gallbladder when the liver tumor is located nearby [42].

3. Transcatheter cooling of the biliary tract

In tumors located nearby the liver hilum or gallbladder, injury of the bile duct is a possible complication. Transcatheter cooling of the intrahepatic bile duct via endoscopic nasobiliary drainage tube has been reported [43]. In this report, injection (1 ml/sec) and subsequent drainage (5 ml/sec)

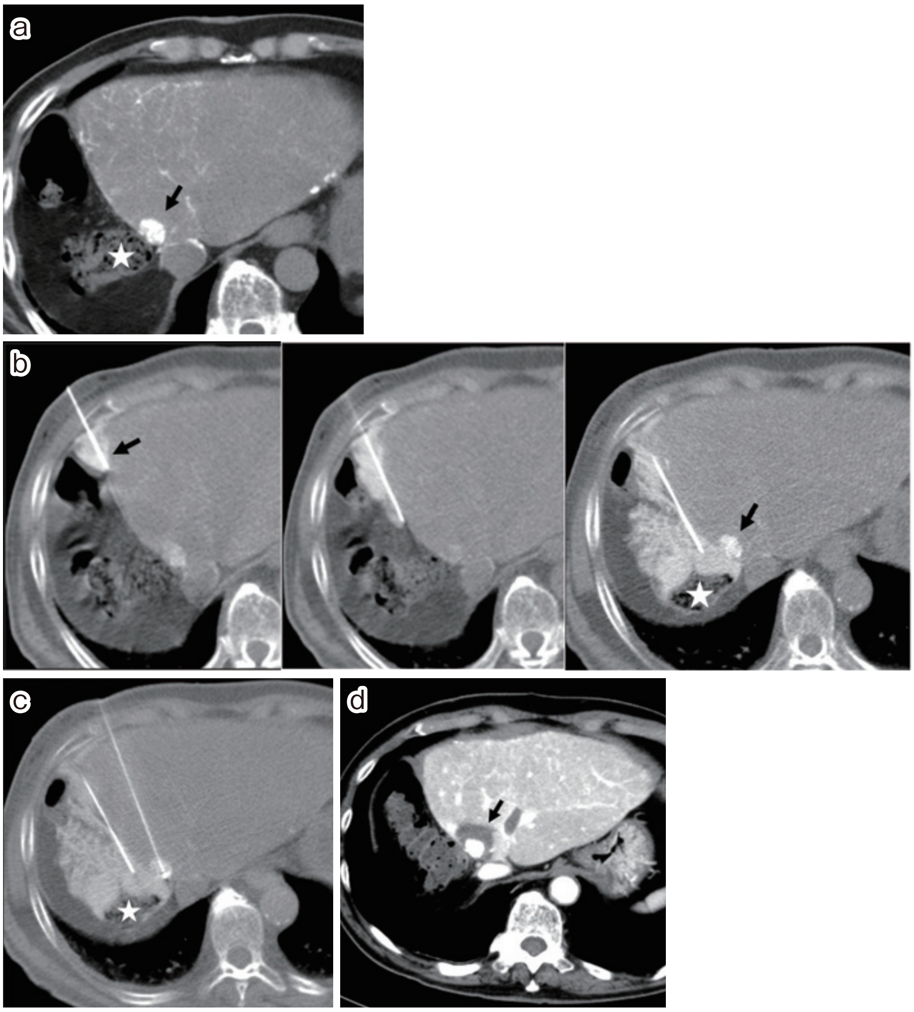

Figure 7. Case: Recurrent HCC after extended right hepatectomy (courtesy of Dr. Haruyuki Takaki)
a) Plain CT after iodized oil injection showing an HCC with iodized-oil accumulation (arrow) adjacent to the colon (star). b) Hydrodissection was performed to separate the target tumor (arrow) from the colon (star). c) RFA under CT-fluoroscopic guidance was performed immediately after hydrodissection (star: colon). d) Contrast-enhanced CT showed clear ablative margin surrounding the tumor (arrow).

of cooled saline were applied repeatedly during the procedure.

4. Hydrodissection

Hydrodissection is a well-established thermo-protective technique, in which fluid is injected to separate the tumor from nearby structures [9, 44].

Mixing of the injected fluid with an iodinated contrast agent improves visibility of the injected fluid and demarcation of nearby structures (**Figure 7**). Campbell et al. suggested that a 1:50 ratio of iohexol (300 mg/mL) in saline or 5% dextrose in water are optimal solutions for increased visibility on CT without introducing streaking artifacts [45]. However, the injected fluid occasionally leaks from the ideal position and in these situations, use of hyaluronic acid gel may be helpful because of its high viscosity [46]. Recently, hydrodissection of the retrohepatic space in tumors close to inferior vena cava (IVC) and the ostia of the hepatic veins (HV) was reported [47]. A safe distance between the tumor and major veins using hydrodissection could theoretically minimize the heat-sink effect generated by the IVC/HV. Hence, this technique could reduce not only the risk of non-target injury, but also of the heat-sink effect.

5. Balloon catheter interposition

When the previously described methods cannot be implemented, placement of a balloon catheter between the target tumor and nearby structures appears to be a practical, safe, and effective technique to separate the tumor from nearby structures [48].

6. Transarterial embolization

Transarterial embolization before RFA reduces the incidence of hemorrhagic complications by reducing the arterial blood flow [9]. Hemorrhage is one of the most serious complications after liver RFA, with a frequency between 1.5-8.1% [20, 49]. Takaki et al. have shown that arterial embolization was a significant independent factor for reducing the risk of major hemorrhage during RFA for liver tumors ($p < 0.01$; odds ratio, 4.3; 95% CI, 1.5-12.7) [20]. However, a recent case report revealed formation of a pseudoaneurysm of the hepatic artery near the ablated area, due to a late complication of infection three years post-TACE and RFA for HCC [50]. Therefore, the risk of hemorrhagic complications should be considered, even several years after RFA, especially when the ablated area is located near the hepatic artery.

Conclusions

The above techniques can be applied alone or in combination. Development of novel techniques and the advancement of technology can further reduce the number and severity of complications associated with RFA treatment and potentially improve local control of liver tumors, which ultimately will result in longer survival rates for patients who receive this treatment.

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