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Efficacy and Safety of Computed Tomography-guided Radiofrequency Ablation For Hepatocellular Carcinoma: A Retrospective Study

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Keywords:

Computed tomography-guided radiofrequency ablation; Hepatocellular carcinoma; Artificial pneumothorax

1. Abstract

1.1. Aims: We investigated the results of CT-guided radiofrequency ablation (CT-guided RFA) for HCC, with or without artificial pneumothorax for lesions of sub-phrenic and caudate lobe location or inconspicuous lesions by ultrasonography. The usefulness and safety were discussed.

1.2. Methods: I.Patient background, II.Treatment details: position, route of puncture (with or without artificial pneumothorax), operative time, anesthesia method (two-lung ventilation /one-lung ventilation). III. Prognosis: success rate and recurrence rate (local, intrahepatic, and distant metastatic recurrence), postoperative complication rate, in-hospital mortality rate, survival rate were retrospectively evaluated.

1.3. Results: I. Patient background: mean age 69.4 years, gender (male 90/female 23), hepatitis virus (B16/C84/BC12/Alcoholic 1/ NBNC0), Child-Pugh (A98 /B15): II. Clinical considerarions: position (69 supine/38 prone/6 prone): puncture route (trans-hepatic 60/ trans-hepatic + trans-thoracic53): operative time (3.3hr), mean number of cauterizations: 3.5/node, mean total radiation dose: 40.5mSV, mean hospital stay: 9.9 days. III. Prognosis: Success rate was 99.1%, recurrence rate was 60.2%, and local recurrence rate was 29.2%. There were 9 cases in postoperative complications, but no case in hospital death. Survival rate (1-year 89.9%, 3-years 68.0%, 5-years44.5%, 10 -years 26.5%) was comparable to other HCC treatments.

1.4. Conclusion: CT guided-RFA with or without artificial pneumothorax is safe and effective treatment, especially for the tumor considered difficult to ablate by US guidance. However, local tumor recurrence was not satisfactory suppressed and some supplemental treatment for the residual tumor is necessary to improve local cure.

2. Introduction

According to current practice guidelines in the management of hepatocellular carcinoma (HCC), radiofrequency ablation (RFA) is recommended for the small tumors less than 2 or 3 cm in diameter and 3 or less in number as the standard treatment, especially in patients who are not suitable for resection. With the advantages of less invasiveness and encouraging efficacy, RFA become a central role in the curative treatment for the selected patients in recent years. Image guidance technique plays an essential role to achieve successful RFA. Ultrasonography is the most widely applied modality as an ideal targeting guidance considering its convenience, low cost and real-time visualization. However, US has the blind areas, and limitation to detect inconspicuous tumors. It is reported that as many as 20-25% of HCC less than 3cm in size were not visible with smaller tumors, subphrenic location and presence of liver cirrhosis which were significantly affecting factors of US detection [1,2]. Further, under US guidance the repositioning of needle electrode during the ablation process is interfered by the development of gas bubbles even though many tumors require overlapping ablation. Therefore, in a considerable number of the patients US-guided ablations may not be feasible [3]. In these situations, CT guidance is advocated in expert

institutions for the placement of needle electrode and monitoring of ablated area. Contrast enhanced CT enables spatial anatomical relationship of the tumor and surrounding structure, and immediate evaluation of ablated area. Particularly it is useful for tumors located in the subphrenic lesion. Multi-planar reformation (MPR) images obtained by CT enables safe approach of puncture in the caudal-cranial oblique to avoid pneumothorax [4]. The use of artificial pneumothorax is also safe and effective technique in the transthoracic puncture without lung injury for the subphrenic tumors [5]. However, the evaluation of CT guided RFA has been scarcely reported. The purpose of this study was to retrospectively evaluate the efficacy and safety of CT-guided RFA including standard transhepatic approach.

3. Materials and Methods

3.1. Materials (Patients): A total of 113 consecutive patients with HCC (156 nodules) who underwent CT guided RFA between April 2001 and June 2021 were included in the study (Table 1). Patients were included based on the following inclusion criteria: (1) Contrast enhanced CT (CECT) was performed within 1 month before ablation, (2) tumor diameter less than 3 cm and less than 3 nodules without extrahepatic metastasis, (3) well preserved liver function, i.e., Child–Pugh Class A/B, (4) nodules can be identified on CT, but difficult to identify on ultrasonography, or difficult in securing a percutaneous puncture rout under ultrasonography guidance, (5) refusal to undergo hepatectomy or liver transplantation, (6) Performance status score ≤ 2. The exclusion criteria were as follows: (1) bleeding tendency : severe coagulation disorder (platelet count < 5× 103 /μL or prothrombin activity <50%) and uncontrollable ascites, (2) biliary tract reconstruction or duodenal papillotomy, (3) macroscopic tumor thrombus, (4) high possibility of vascular, biliary tract and gastrointestinal damage by ablation, (5) severe dysfunction of the heart, brain, kidney, or other organs and difficulty in general anesthesia, (6) active infection (except viral hepatitis); and (7) refusal to undergo ablation. This retrospective study was performed at a single institution with the approval of the Review and Ethics Committee of the Tobata Kyoritsu Hospital and in accordance with the Helsinki Declaration. Written informed consent was obtained from all participants before treatment.

Table 1: Characteristics of Hepatocellular carcinoma Patients

Variable	Total (n=113)
Gender (Male/Female)	90 / 23
Age (years)	69.4
Etiology (HBV / HCV / Alcoholic / NBNC)	16 / 84 / 12 / 10
Albumin (g/dl)	3.8 ± 0.3
AST (IU/L)	39.1 ± 3.4
ALT (IU/L)	36.7 ± 3.4
Total bilirubin (mg/dl)	0.8 ± 0.7
PT (%)	82.3 ± 18.7
Platelet count (x 1000/μl)	12.6 ± 7.7
Cirrhosis (Present/Absent)	18 / 95
Child-Pugh (A / B / C)	98 /15 / 0
UICC (I / II / III)	83 /30 / 0
Total number of nodules	156
Single / Double / Triple nodules	74 / 35 / 4
Mean tumor size (cm)	19.2 ± 0.7
Tumor size (≤ 2 cm / <2 and ≤ 3 cm)	90 / 66
Serum AFP (ng/ml)	10.2 ± 0.4
PIVKA-II (mAU/ml)	34.2 ± 9.3
Hospital stay (days)	9.4 ± 4.4
Follow up (months)	59.6 ± 34.7

Value are presented as number (%) or mean±standard deviation.

HBV: hepatitis virus B, HCV: anti-hepatitis C antibody

AST: aspartate transaminase, ALT: alanine aminotransferase, PT: prothrombin time

UICC: Union for International Cancer Control and classification of TNM

AFP: alpha-fetoprotein, PIVKA-II: protein induced by Vitamin K absence or antagonist-II

3.2. Methods

3.2.1. Characteristics of HCC patients: Baseline evaluation included gender, age, presence or absence of cirrhosis, HBsAg, anti-HCV, albumin, aspartate transaminase (AST), alanine aminotransferase (ALT), total bilirubin, PT (prothrombin time), platelet count, Child-Pugh class, alpha-fetoprotein (AFP), protein induced by Vitamin K absence or antagonist-II (PIVKA-II), size and number of HCC, length of hospital stay, complication, and aspects of recurrence of all patients. Determination of cirrhosis was done by integrating radiologic findings suggestive of cirrhosis such as diffuse liver nodularity, change of echotexture, atrophy or hypertrophy of parenchyma and signs of portal hypertension. The size of the HCC was measured with the maximum diameter of mass from the abdominal CT conducted before treatment procedure.

3.2.2. Clinical Considerations (Operating procedure): Regarding the treatment, patient position, route of puncture with or without artificial pneumothorax, number of ablation tumors (times), operative time (hr), anesthesia method (general: two-lung ventilation/one-lung ventilation), total radiation exposure (mSV) were considered.

3.2.3. CT-guided RFA technique: The procedure of RFA was performed in the interventional CT-suit. The general anesthetized patients were fixed on the CT table. Since the intraoperative position of the patient depended on the location of the tumor, the supine position was chosen if the tumor was in the left lobe or anterior region, the left lateral position if the tumor was in the posterior region, and the prone position if the tumor was in the S1 or dorsal region of the liver (Figure 1). In cases of trans-thoracic approach, artificial pneumothorax was performed using an artificial pneumothorax prior [6] from the right side of the eighth to tenth intercostal space in order to successfully elevate the lung base. Thereafter, a dual-phase contrast enhanced planning CT was obtained. To compensate respiratory motion temporally disconnection of tracheal tube was performed during planning CT, needle electrode puncture and final evaluation CT. RFA instruments were used as: CC-I (Radionics, Burlington, MA, USA) with clustered cooled-tip needle (17 gauge, Cool-tip TM electrode length of 2–3 cm). For percutaneous intervention, local anesthesia from skin to hepatic capsule was conducted along to expected electrode insertion route and electrode was inserted into the center of targeting HCC under real time CT guidance. RFA was performed with consecutive activation mode and a 17-G dual clustered cooled-tip electrode was introduced to index tumor. RF current was conducted through from generator with settings to deliver maximal power in the automatic impedance control mode. RFA was applied for 8–12 minutes continuously. Multiple sequential needle electrode placements were planned on the multiplanar and three-dimensional reconstructed images for multiple overlapping ablation to cover the entire tumor volume with safety margin. Generally, tumors larger than a diameter of 2.0 cm required multiple overlapping ablations 7. After completion of RFA procedure, to verify the complete ablation of the tumor, contrast CT was performed. When the incomplete ablation was detected additional RFA was done. Dynamic CT was conducted on 4 or 5 days after intervention, and when low attenuation shown in the images of arterial and portal phases contained enough to cover the index HCC and there was no contrast enhancement near the region of thermal therapy, patient discharge was planned without additional sessions of RFA. But if tumoral enhancement was detected, additional sessions were performed for residual tumor.

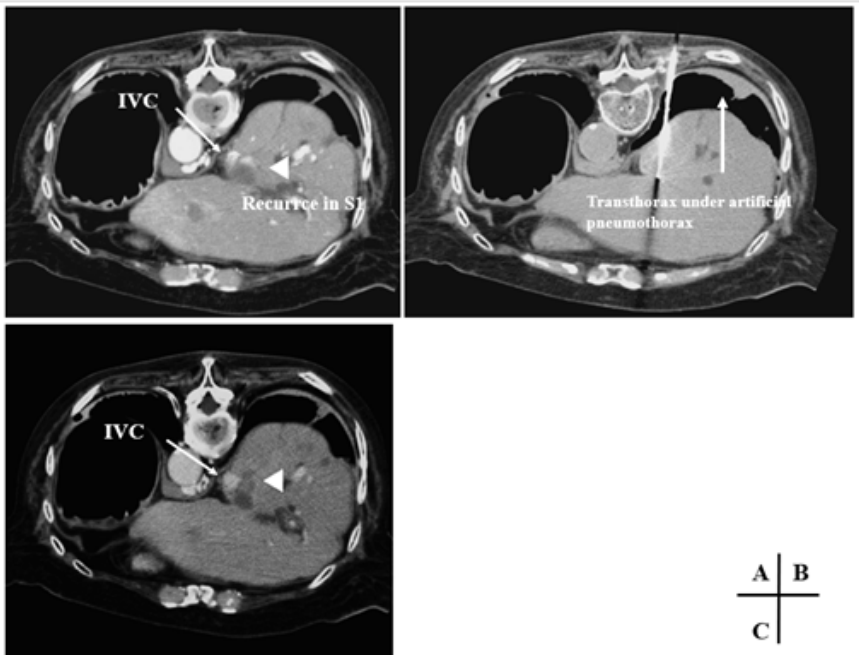

Figure 1: (a) The anesthetized patients fixed with the prone position. The local recurrence tumor was identified at the paracaval portion of the caudate lobe adjacent to the vena cava. Artificial pneumothorax had been inducted to secure a puncture route of the needle electrode. (b) The needle electrode was introduced to the tumor through the thoracic cavity without injury of lung tissues. (c) contrast-enhanced CT immediate after ablation procedure shows Low density area induced by RFA.

3.2.4. Prognosis: Assessment of treatment efficacy: The primary endpoint of this study was local control of RFA which was defined as success rate (SR) and local recurrence rate (LR)), and complications. SR was the completeness of RFA confirmed with dynamic CT performed 4 or 5 days after procedure. LR was defined as the recurrence at the peripheral region of the ablated area in follow up CT scans after complete ablation. Intrahepatic distant recurrence was defined as the recurrence at a region not adjacent to the ablated area or in the different segments. Complications were recorded and classified based on the Clavien-Dindo (C-D) Classification. Major complications were defined as events requiring major treatment of C-D Class III or higher and potentially leading to death or permanent adverse sequelae. The secondary endpoints included overall survival rate (OS) and disease- free survival rate (DFS). The concluding time of OS was based on the date of death in cases of death and on the date of the most recent follow-up visit in cases of survival. The concluding time of DFS was based on the date of the confirmation of the recurrence by imaging test in cases of recurrence and on the date of the last imaging test in cases of non-recurrence.

3.2.5. Follow up: All of the patients underwent abdominal US, CECT or CE MRI and laboratory tests, mainly including tests for measuring serum AFP level and serum PIVKA-II level, liver function, blood biochemistry, and blood coagulation every 1 month during the first 3 months and every 3 months thereafter.

4. Statistical Analysis

Data were analyzed using SPSS for Microsoft Windows (version 11.0.1; SPSS Inc. Chicago, IL, USA). The baseline and clinical characteristics were summarized as mean ± standard deviation (continuous variable with normal distribution), median ± range (continuous variable with non-normal distribution), or frequency (categorical variables). Chi square test or Fisher's exact test was used to compare the baseline and clinical characteristics of categorical variables, and ANOVA test or Mann–Whitney U test was used to compare the differences of continuous variables. $P < 0.05$ was defined as statistically significant.

5. Results

5.1. Characteristics of hepatocellular carcinoma patients: (Table 1 and 2). The male to female ratio of total HCC cases was 3.9:1, with there being more male patients than female patients. Mean age was 69.4 ± 3.4, cirrhosis was found in 18 patients (15.9%). In the etiology of liver, hepatitis C infection was the most common infection (74.3%), respectively. In Child-Pugh class, 88 of the HCC patients (77.9%) was diagnosed as class A and 25 (22.2%) as class B. In UICC class, 83 of the HCC patients (73.5%) was diagnosed as class A and 30 (26,5%) as class B. The mean diameter of the HCC was 22.2 ± 2.7 mm, respectively. The mean serum AFP level was 10.2 ± 3.4 ng/ml, PIVAKA-II level was 34.2 ± 9.3 g/ml, total bilirubin was at 0.7 ± 1.6 mg/dl, serum albumin was 3.8 ± 0.5 g/dl. The mean lengths of hospital-stay were 11.4 ± 4.4 days.

5.2. Clinical considerations: (Table 2) The lesions were localized in S1:3, S2:7, S3:34, S4:26, S5:23, S6:25, S7:18, and S8:16. The route of puncture was trans-hepatic in 60 cases (53.1%), trans-thoracic in 43 cases (38.1%), and trans-thoracic with artificial pneumothorax under general or one- lung ventilation in 10 cases (8.8%). The patient positions were supine in 69 cases, lateral recumbent in 38 cases, and prone in 6 cases. The average operating time was 3.3 hours, and the average number of electrode repositioning per a nodule in multiple overlapping ablation was 3.5 times. The average radiation dose of the whole procedure was 40.5 mSV.

Table 2: Operating Procedure

Variable	Total (n=113)
Location of the nodular lesion	156
Segment I	3 (1.9%)
Segment II	7 (4.5%)
Segment III	34 (21.8%)
Segment IV	26 (16.7%)
Segment V	23 (14.7%)
Segment VI	25 (16.0%)
Segment VII	18 (11.5%)
Segment VIII	16 (10.3%)
Approach	
Trans-hepatic	60 (53.1%)
Trans-thoracic	43 (38.1%)

Trans-thoracic + API	10 (8.8%)
Position	
Supine	69 (61.1%)
Lateral	38 (33.6%)
Prone	6 (5.3%)
Operation time (hours)	3.3 ± 0.6
Number of ablation tumors (times)	3.5 ± 0.8
Total radiation exposure (mSV)	40.5 ± 5.3

Value are presented as number (%) or mean±standard deviation.

API: artificial pneumothorax injection

*Number of ablation tumors: the average number of electrode placement (repositioning) per a nodule in multiple overlapping ablation

5.3. Prognosis

5.3.1. Success rate (SR) and Recurrence rate (LR): (Table 3) In SR, one of 113 patients (0.9%) showed incomplete necrosis, however one week later, CT-guided RFA was performed again to achieve complete necrosis. Sixty-eight of 113 patients (60.2%) treated with CT-guided RFA developed recurrence. LR was found in 33 patients (29.2%), intrahepatic distant recurrence was 32 patients (28.3%), and distant metastases was 3 patients (2.7%). Of the local recurrence, 14 of 33 recurrence cases (42.2%) developed recurrence within 1 year, 15cases (45.5%) with 1 to 3 years, and 4 cases (12.1%) with 3 to 5 years.

5.3.2. Complications: (Table 4) The percentage of incidence of complications was 7.9%, there were 6 patients (5.3%) with minor complications of C-D class I or II, including 2 with minor self-limiting pneumothorax, 2 with pneumonia, 1 with minimum liver abscess and 1 with cholecystitis. Three patients (2.6%) suffered from a major complication of C-D class III, 1 with bile duct injury, 1 with liver abscess and 1 with skin burn due to short circuit of radiofrequency current which was required skin implantation. There was no procedure -related mortality in study.

Table 3: Success Rate and Local Recurrence Rate of HCC after CT-guided RFA

Variable	Total (n=113)
Success Rate (%)	112 (99.1%)
Recurrence, n (%)	68 (60.2%)
Local recurrence	33 (29.2%)
≤ 2cm *	9 (10%)
< 2cm and ≤ 3 cm #	24 (36%)
-1 < 1-3 / 3-5 / 5-yr $	14 / 15 / 4 / 0
Intrahepatic distant recurrence	32 (28.3%)
Distant metastases	3 (2.7%)

HCC: hepatocellular carcinoma

≤ 2cm *:total number of nodules 2cm or smaller was 90.

< 2cm and ≤ 3 cm #: total number of nodules between 2cm and 3cm was 66.

-1 < 1-3 / 3-5 / 5-yr $: time to recurrence after CT-guided RFA

Table 4: Mobidity and Mortality after CT-guided RFA

Clavien - Dindo Class and Variables	Number of Cases
C-D Class I	2
Minor pneumothorax	2
C-D Class II	4
Cholecystitis	1
Minimal liver abscess	1
Pneumonia	2
C-D Class III	2
Bile duct injury	1
Liver abscess	1
C-D Class IV	1
Skin burn	1
C-D Class IV and V	0

C-D : Clavien-Dingo classfication

5.3.3. Overall survival (OS) rates and Disease-free survival (DFS) rates: (Figure 2 and 3) The 1-, 3-, 5-, and 10-year OS rates were 89.9%, 68.0%, 44.5%, and 26.5%, respectively, and the mean OS was 50.7 ± 2.1 months (Figure 2). The 1-, 3-, 5-, and 10-year DFS rates were 68.1%, 37.7%, 25.2%, and 10.2%, respectively (Figure 3). The mean DFS was 12.6 ± 1.3 months.

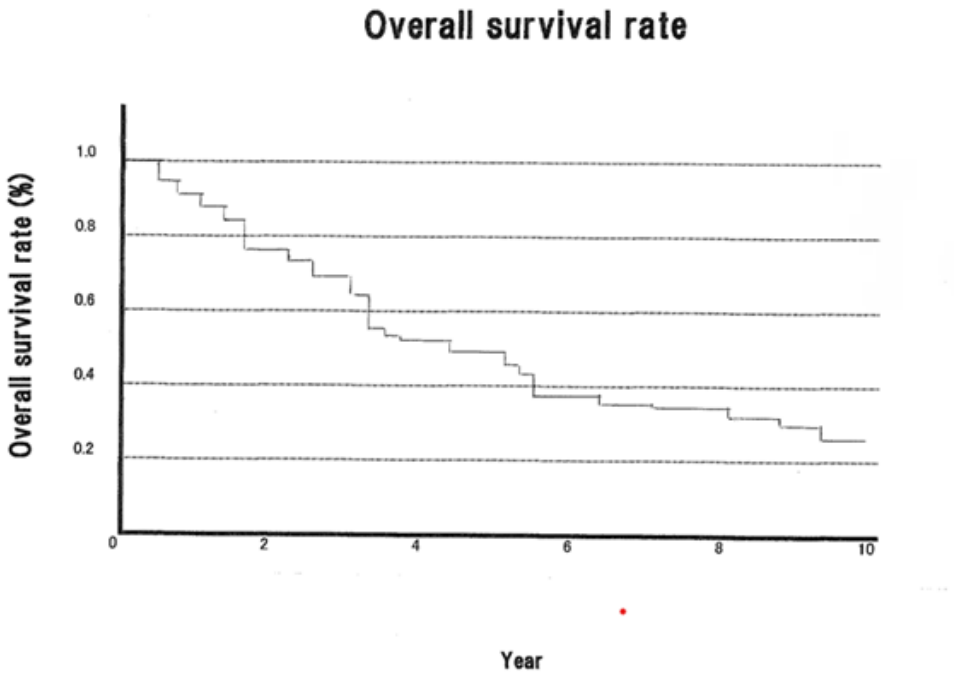

Figure 2: The 1-, 3-, 5-, 10-year overall survival rates were 89.9%, 68.0%, 44.5% and 26.5%.

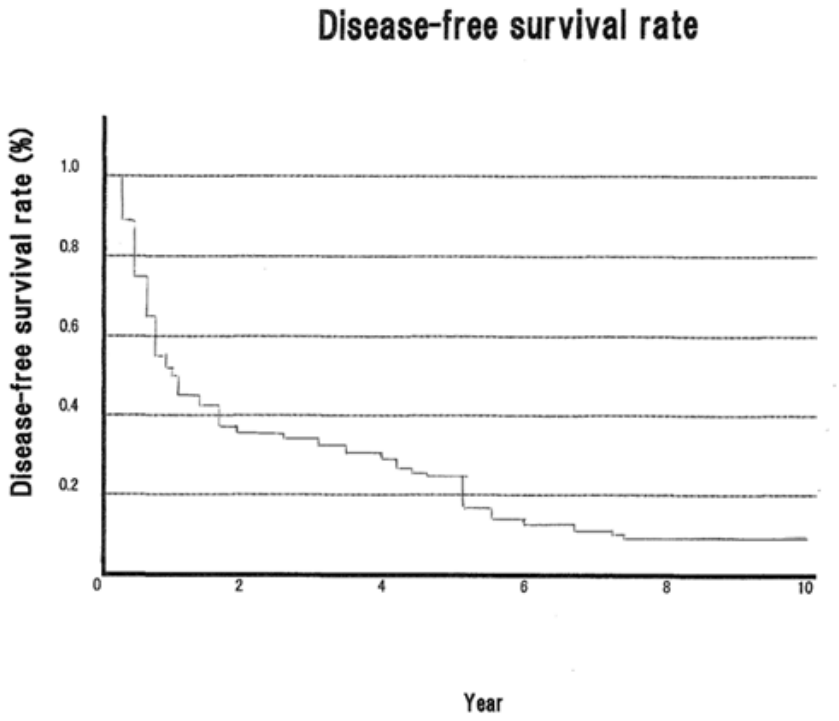

Figure 3: The 1-, 3-, 5-, 10-year disease-free rates were 68.1%, 37.7 %, 25.2% and 10.2%.

6. Discussion

CT-guided RFA has two advantages over other treatment modalities. First, as reported in Fujiwara et al. [5], an artificial pneumothorax could be introduced to shift the position of the lungs, allowing the safe and free needle electrode puncture without lung injury in transthoracic approach. Our method was performed under general anesthesia with respiratory and circulatory control by an anesthesiologist, and was useful for deep case puncture as well as just below the diaphragm by stopping breathing. Further, under ventilator control with one-lung ventilation combined with artificial pneumothorax, the lungs could be collapsed more, making puncture easier. We did ablation with artificial pneumothorax under one-lung ventilation in 10 patients. The prolonged breath-holding enabled puncture without missing the center of the tumor, thus avoiding large blood vessels and bile ducts. The reason why there were few cases of lung injury and bile duct injury in our own study was that an artificial pneumothorax was created in advance and the lungs were completely collapsed by one-lung ventilation, as described above.

Another is that immediately after ablation, it is difficult to confirm the extent of ablation by ultrasonography, whereas under CT, the extent of ablation can be confirmed by instantaneous re-imaging, and if insufficient, additional punctures can be made. This advantage contributes a lot to the improvement of technical success of RFA. In addition, contrast-enhanced CT before the end of treatment could confirm the extent and condition of tumor ablation, as well as vascular damage and intra-abdominal bleeding.

Several authors demonstrated that the technical success rate of US-guided RFA was 83 – 95 % [6-9]. However, in cases of HCC of subphrenic and caudal lobe location, it is technically difficult to place the needle electrode precisely with US guidance. Hirooka et al. [10] reported that 12 out of 113 patients with HCC located in the caudal lobe was abandoned to be treated by RFA because the procedure thought to be very high risk. In our institution CT-guided RFA is adopted without hesitate, when US-guided RFA is not feasible. Yuan C, et al. [9]. compared the technical success rate among US-guided, CT-guided and MRI-guided RFA. As the results, the technical success rates were 82.8 % in US, 92.0 % in CT and 77.4 % in MRI. Technical success rate of our CT-guided RFA was as high as 99% with satisfying considering that many of tumors located at subphrenic area or caudate lobe, and were undetectable or obscure in ultrasonography.

Generally, in spite of the high success rate of RFA procedure, the local tumor recurrence developed frequently, and it is a major issue of RFA. Previous studies have shown that rate of local tumor recurrence ranged from as low as 4.8% to as high as 38.6%, and the most of studies reported to be around 20% [7,8,11,12]. In our study, the local recurrence rate was fairly high of 29.2 %. The local recurrence was not suppressed satisfactorily by our manner. Concerning pathological examination after RFA, several studies used the histopathological analysis of the explanted liver after liver transplantation. As their results, histological complete tumor necrosis was observed in only 47-75% of cases, with apparent discrepancies between histological and radiological tumor response to RFA [13-18]. It was reported imaging correlation to histological complete necrosis showed 100% of specificity and 36 - 50 of sensitivities [14,15]. The therapeutic

effect of RFA relies on thermal injury using electric current. The effect is partially limited by the heat-sink effect induced by electric shunt or perfusion mediated tissue cooling [19]. As a result, ablation zones can vary widely and unpredictably and those leads incomplete ablation of tumor. Further, Brillet et al. demonstrated that ablation zone, even which was produced the complete intra-tumoral necrosis, was associated with a high rate of histological small satellite nodules and microvascular invasion [16,17].

These findings suggested the necessity of supplemental ablation against residual tumors.

RFA following trans-arterial chemoembolization (TACE), may be one of the effective treatments. TACE could embolize tumor's feeding vessels and peripheral vessels, causing reduction of the heat sink effect during ablation, and expanding ablation area [20]. Further, the retention of lipiodol in the tumor is a good target marker during the CT-guided needle electrode placement, and the ablated margin is clearly defined by lipiodol after RFA. The superiority of RFA with TACE to sole RFA in improving recurrence free rate and overall survival was reported [21,22]. In addition, the prognosis as a secondary endpoints is that the cumulative OS rate was 44.5% at 5 years and 26.5% at 10 years, and the cumulative DFS rate was 25.5% at 5 years and 10.2% at 10 years, which was comparable to other reported cases [23]. Finally, caution is warranted. (1) A limited number of patients were recruited in this study, and the sample size may have led to bias. (2) CT guided RFA under with or without artificial pneumothorax induction was a single-center study, and the results may not be generalizable. (3) It was a retrospective study and thus has all the relevant disadvantages.

7. Conclusion

CT guided-RFA with or without artificial pneumothorax is safe and effective treatment, especially for the tumor considered difficult to ablate by US guidance. However, local tumor recurrence was not satisfactory suppressed and some supplemental treatment for the residual tumor is necessary to improve local cure.

8. Declarations of Conflict of Interest

8.1. Ethics Approval and Consent to Participate: The Review and Ethics Committee of the Tobata Kyoritsu Hospital approved the study. All patients enrolled for the validation of this study gave a written informed consent.

8.2. Consent for Publication: Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written informed consent is available for review by the Editor-in-Chief of this journal.

8.3. Availability of Data and Material: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

8.4. Competing Interests: The authors declare that they have no competing interests.

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8.7. Author contribution: Y Wada, H Satoh, D Muroya and S Taniwaki performed the operations and Y Wada and Y Nagao managed the postoperative intensive care. K Okuda supervised the study and drafted the manuscript. All authors conceived the study and participated in its design and coordination. All authors declare that the paper is being submitted for consideration for publication in the journal that the content has not been published or submitted for publication elsewhere. All authors read and approved the final manuscript.

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