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Original Article

Radiofrequency Ablation for Hepatocellular Carcinoma in Elderly

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SUMMARY

Background: Surgical resection is traditionally suggested for treating early stage of hepatocellular carcinoma (HCC). However, resection is frequently unsuitable for elderly patients because of comorbidities. Radiofrequency ablation (RFA) has been shown to be as effective to treat small HCCs. This study aimed to investigate the effectiveness and outcomes of RFA for HCC in elderly.
Methods: A total of 134 patients with 266 RFA sessions from 2008 to 2017 were retrospectively reviewed. Patients were divided into younger adult group (N = 56) and elderly group (N = 78) with a cut-off of 65 years of age. The elderly group was further divided into younger and older elderly by 75 years of age. Statistical analyses were performed, and a Kaplan-Meier method was applied for analyzing overall and recurrence-free survival.
Results: Primary technique effectiveness was observed in 90.1% in younger adult group and 91.5% in elderly group. After a median follow-up of 32.0 months in younger adult and 38.6 months in elderly group, one-, three-, and five-year survival rates in younger adult group were 90.6%, 68.4%, and 56.1%, and in elderly group, 94.6%, 80.0%, and 61.7%, respectively. The recurrence-free survivals were similar between both groups. Older elderly group had inferior recurrence-free survival than younger elderly but the survival rates of all-cause or liver-related mortalities were similar in these two groups.
Conclusion: RFA is a well-tolerated local ablative therapy across different ages. RFA for HCC in elderly has comparable rates of complete tumor ablation, recurrence-free survival, overall survival with that of younger adults.

1. Introduction

Hepatocellular carcinoma (HCC) is one of the leading causes of cancer related mortality worldwide. Surgical resection and local ablation are recommended treatment modalities for early stage HCC.[1] Radiofrequency ablation (RFA) induces coagulation necrosis at target tumors by converting electrical current to thermal energy.[2] RFA has been shown to be an effective and was one of the suggested therapies for early stage of HCC.[3] RFA has comparable outcomes to surgical resection especially for early to very early stage HCC.[4,5] Recently, RFA also expands its application to intermediate stage through advance of ablation techniques or combination with other treatment modalities.[6]

HCC is more common in elderly and is rare in younger population less than ages 40.[7] The suggested risks factors for the development of HCC include viral hepatitis, chronic hepatitis, liver cirrhosis, and advanced age.[7] Currently, most HCC treatment guidelines incorporate liver reserve and tumor associated factors as selection criteria for eligible treatment of HCC.[1,8] For resectable T1 or T2 HCC in patients with Child-Pugh class A cirrhosis, surgical resection is still favored over RFA.[1] However, surgical resection may be easily limited in elderly HCC patients because of comorbidities such as heart or lung compromises. Only 20–30% HCC patients were suitable for surgical resection because of limiting factors such as reduced hepatic functional reserve.[9] For those HCC patients not suitable or unwilling for resection, RFA is the most common local ablative therapy for HCC.[5] In the current study, we aimed to explore the effectiveness and factors regarding RFA for HCC in elderly patients.

2. Materials and methods

2.1. Patients

Patients diagnosed with HCC and received RFA for HCC from 2008 to 2017 were retrospectively enrolled in this study. The diagnosis of HCC was made with either pathology assessment of tumor specimens or typical imaging findings of arterial enhancement with venous or delayed washout in dynamic contrast enhanced computed tomography (CT) or magnetic resonance (MR) imaging.[3] Hepatic metastasis or other primary liver cancer such as cholangiocarcinoma was excluded. The study protocol was approved by the Institutional Review Board of MacKay Memorial Hospital.

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2.2. Monopolar RFA

The monopolar RFA was performed with single or multiple internally cooled 17-gauge monopolar radiofrequency electrodes with an electrically active tip (Medtronic). The electrodes were placed percutaneously under real-time sonographic guidance to the target HCCs by experienced operators. Intravenous sedation was performed for patients with continuous monitoring of vital signs, electrocardiogram, and oxygen saturation during RFA. The RFA was performed as with energy delivered via electrodes with a 480-kHz power generator (ValleyLab, Medtronic) with a maximum power of 200 Watts. The energy was automatically regulated with a feedback algorithm based on impedance of tissue surrounding electrodes. Besides, the tips of electrodes were internally cooled with a continuous circulation of chilled distilled water maintained by a pump (ValleyLab, Medtronic). During withdrawal of electrodes, tract ablation was performed to minimized tumor seeding. Primary technical effectiveness of RFA was defined as complete necrosis (non-enhancement areas in portal phase imaging on CT or MR during follow-up after RFA) of the HCCs intended to be treated. Alpha-fetoprotein and liver biochemistries were checked as well. If primary technical effectiveness had been achieved, the patients were then regularly followed; otherwise, patient may receive a repeat ablation or other treatment for HCC.

2.3. Statistical analysis

For continuous variables, independent sample t-test was performed to evaluate differences among groups. Chi-square test was performed to analyze discrete variables. The survival probabilities and recurrence-free survival probabilities were analyzed using a Kaplan-Meier method. The log-rank test was performed to assess the difference of survival or recurrence-free survival curves. All statistical analyses described were performed using R statistics package.[10] Statistical significance was defined at a two-tailed probability value of less than 0.05 in all analyses.

3. Results

3.1. Patient characteristics

This study enrolled 134 patients with a total of 266 RFA treatment sessions. 56 patients (42 men and 14 women) were younger than 65 years old and 78 patients (38 men and 40 women) were older than 65. The majority of patients belonged to Child-Pugh classification A and had early stage of HCC. The distribution of Child-Pugh classification and tumor stage was similar between younger adult and elderly patients. About half of the patients in younger group and 38.8% elderly group (N = 30) had received other treatment prior to receiving RFA. More patients in younger group had endoscopic presence of esophageal or gastric varices than the patients in elderly (53% vs. 31%, p = 0.039). Hepatitis B virus (HBV) infection is much more prevalent in younger adults, presenting in nearly two third of patients. On the contrary, hepatitis C virus (HCV) is more prevalent in elder group (57.7%, N = 45). The follow-up periods were similar in both groups of patients (median, 32.0 vs. 38.6 months). The demographic features described above were summarized in Table 1.

3.2. RFA treatment and effectiveness of treatment in younger adult and elderly

Among enrolled 266 RFA treatment sessions, 101 treatment sessions were defined in younger adult group and the other 165 treatment sessions were included in elderly group. Laboratory studies prior to RFA showed that serum level of albumin (median, 3.7 vs. 3.78 g/dL), ALT (median, 34 vs. 30 IU/L), AST (median, 47 vs. 39 IU/L), and platelet (115 vs. 121 $\times 10^9$/L) were similar in younger adult or elderly group (Table 2). Younger adult group had a higher percentage of presence of ascites at the time of RFA treatment (11.9% vs. 3.6%, p = 0.019) and a slightly but statistically significant longer prothrombin time. The sizes of HCC were similar between both groups, but the younger adult group had more HCCs to treat. The ablation time required to complete RFA treatment session was similar (Table 2). Primary technique effectiveness was achieved in 90.1% (N = 91) of younger adult group while a comparable 91.5% (N = 151) treatment in elderly group achieved technique effectiveness.

3.3. Comparison of RFA treatment in younger and older elderly

We further investigated RFA treatment in elderly patients. The 165 RFA treatments were further divided into 2 groups according to younger elderly, defined as age older than 65 years old but younger than 75, and older elderly, defined as age older than 75. 94 treatment sessions were defined in younger elderly group and the other 71 treatment sessions were included in older elderly group. Regarding tumor characteristics, the tumor size (median 2.0 vs. 2.1 cm), tumor numbers, and required ablation time to complete RFA (median 24 vs. 24 minutes) were similar in younger versus older elderly group (Table 3). Primary technique effectiveness was achieved in 90.4% (N = 85) treatment of younger elderly group and 93.0% (N = 66) of older elderly group. There was no difference for achieving primary technique effectiveness of RFA in younger or elderly HCC patients. The days required for hospitalization after RFA was comparable in both groups, and the days to discharge are 2

Table 1
Demographic features of patients with hepatocellular carcinoma.

Variable	Younger adults (N = 56)	Elderly (N = 78)	p value
Age, median (IQR)	58 (50–61)	73 (69–78)	< 0.001
Male, No. (%)	42 (75.0)	38 (48.7)	0.004
Child-Pugh classification (A/B/C)	43/10/3	69/9/0	0.060
HCC stage (TNM I/II/III/IV)	31/18/7/0	51/19/8/0	0.497
Prior treatment for HCC, No. (%)	28 (50.0)	30 (38.5)	0.249
Presence of EV or GV, Yes/No	24/21	17/38	0.039
HBV, No. (%)	34 (60.7)	26 (33.3)	0.003
HCV, No. (%)	18 (32.1)	45 (57.7)	0.006
Follow-up, months (median (IQR))	32.0 (18.4–52.2)	38.6 (20.7–59.0)	0.198

Abbreviations: EV, esophageal varices; GV, gastric varices; HBV, hepatitis B virus; HCV, hepatitis C virus; HCC, hepatocellular carcinoma; IQR, interquartile range.

Table 2
Features of radiofrequency ablation treatment sessions and associated demographics of patients at the time of treatment.

Variable	Younger adults (N = 101)	Elderly (N = 165)	p value
Albumin (g/dL)	3.70 (3.26–4.20)	3.78 (3.40–4.10)	0.439
ALT (IU/L)	34 (23–56)	30 (20–47)	0.460
AST (IU/L)	47 (25–66)	39 (27–58)	0.155
Total bilirubin (mg/dL)	1.12 (0.80–1.60)	1.06 (0.70–1.30)	0.004
Platelet ($\times 10^9$/L)	115 (66–163)	121 (89–160)	0.467
PT (sec)	11.5 (10.8–12.6)	11.2 (10.7–11.7)	< 0.001
AFP (ng/mL)	19.19 (8.40–195.50)	12.37 (6.30–44.45)	0.022
Presence of ascites, No. (%)	12 (11.9)	6 (3.6)	0.019
Tumor size (cm)	2.4 (1.6–3.3)	2.1 (1.7–2.8)	0.772
Treated number of tumors	2 (1–3)	1 (1–2)	0.002
Insertion passes	3 (2–4)	2 (2–3)	0.038
Ablation time (minutes)	24 (15–36)	24 (12–36)	0.530
Hospital stay after ablation (days)	3 (1–5)	2 (1–3)	0.036

The value and range are assigned as median (interquartile range).
Abbreviations: AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PT, prothrombin time.

Table 3
Features of radiofrequency ablation treatment sessions and associated demographics of patients at the time of treatment.

Variable	Younger elderly (N = 94)	Older elderly (N = 71)	p value
Age	70 (68–72)	79 (77–82)	< 0.001
Albumin (g/dL)	3.70 (3.40–4.00)	3.90 (3.50–4.23)	0.114
ALT (IU/L)	34.5 (25.3–55)	21 (16–37)	0.001
AST (IU/L)	42.5 (30–67.8)	32 (24–45.5)	< 0.001
Total bilirubin (mg/dL)	1.00 (0.72–1.38)	0.83 (0.61–1.26)	0.121
Platelet ($\times 10^9$/L)	103 (80–141.5)	141 (112–178.5)	< 0.001
PT (sec)	11.2 (10.8–11.8)	10.9 (10.7–11.7)	0.249
AFP (ng/mL)	16.69 (7.99–60.82)	8.43 (3.95–23.02)	0.771
Presence of ascites, No. (%)	4 (4.3)	2 (2.8)	0.945
Tumor size (cm)	2.0 (1.7–2.6)	2.1 (1.8–3.1)	0.209
Treated number of tumors	1 (1–2)	1 (1–2)	0.175
Insertion passes	2 (2–3)	2 (1.5–3)	0.765
Ablation time (minutes)	24 (12–36)	24 (15.5–30)	0.300
Hospital stay after ablation (days)	2 (1–4)	2 (1–2)	0.267

The value and range are assigned as median (interquartile range).
Abbreviations: AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PT, prothrombin time.

days in median (interquartile range, 1 to 4 vs. 1 to 2 days).

3.4. Survival and recurrence of HCC after RFA in elderly

Compared with younger adult group, elder HCC patients had similar survival outcomes (Figure 1A). The one-year, two-year, three-year, and five-year survivals in younger adult group were 90.6%, 84.3%, 68.4%, and 56.1%, and the one-year, two-year, three-year, and five-year survivals in elderly HCC patients were 94.6%, 87.3%, 80.0%, and 61.7%, respectively. The recurrence-free survivals were similar between these two groups (Figure 1B).

The elderly HCC patients were further studied in younger and older elderly, divided by ages 75. We found that older elderly had a shorter recurrence-free survival (Figure 2B, $p < 0.01$). The recurrence probabilities at 3-year derived from Kaplan-Meier method were 50.9% in younger elderly and 83.4% in older elderly. However, older elderly only has slightly shorter survival from the first time of receiving RFA, which is not statistically different compared with that of younger elderly (Figure 2A, $p = 0.12$). The one-year, two-year, three-year, and five-year survivals in younger elderly were 95.7%, 91.1%, 85.8%, and 67.7%; the corresponding survivals in older elderly were 93.2%, 80.3%, 69.6%, and 52.3%. Furthermore, by comparing liver-related outcomes including HCC-related or liver failure related mortalities, the prognosis was similar in both groups (Figure 2C). The one-year, three-year, and five-year survivals in younger elderly were 95.6%, 85.4%, and 66.6%; the corresponding survivals in older elderly were 96.0%, 80.4%, and 65.5%. RFA had comparable effectiveness in HCC treatment across different age groups in terms of prognosis.

4. Discussion

Our present study suggested that elderly patients with HCC can be effectively treated with monopolar RFA. There's no difference in overall survival and recurrence-free survival comparing younger adults and elderly. Although there was a difference in time to recurrence between older elderly and younger elderly patients, the overall survival between these two groups was similar. Generally, monopolar RFA was a well-tolerated and safe treatment for HCC in elders.

Overall, our study suggested that RFA can reach 91.0% primary techniques effectiveness regardless of tumor size or numbers. The reported rates of complete necrosis of HCC after RFA for early stage of HCC was ranged from 91% to 96%.[11–13] The reported overall survival at 3-year after RFA for HCC was ranged from 67% to 80%.[13–16] Therefore, our results showed that the efficacy and outcomes of RFA for HCC in elderly were comparable to previously reported results from various groups.

The leading cause of HCC in Taiwan is HBV infection owing to its high prevalence rate of 15–20% in general population in Taiwan.[17]

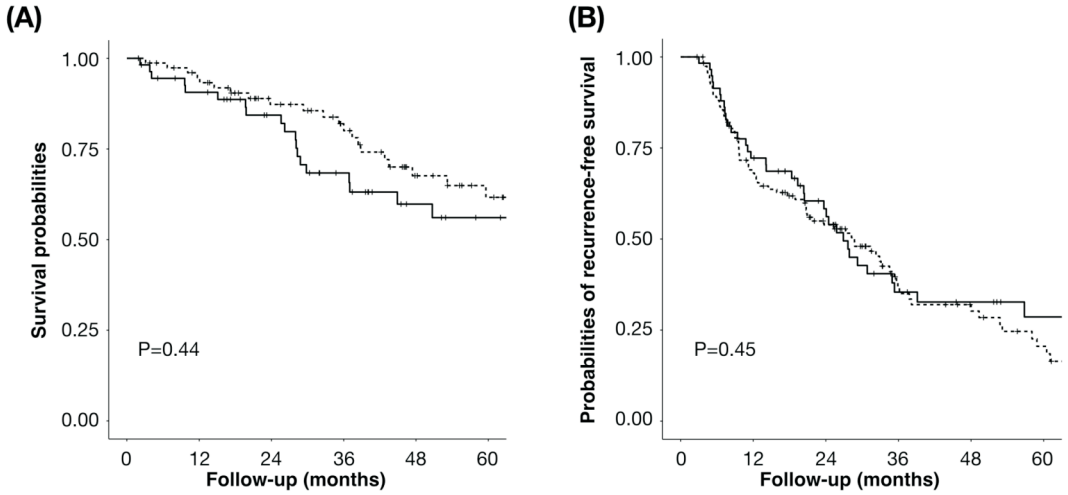

Figure 1. Survival probabilities and recurrence-free survival for elderly or younger adults patients with hepatocellular carcinoma (adults younger than ages 65, solid line; elderly patients, dotted line). (A) A Kaplan-Meier method derived cumulative survival probabilities between the younger adults with elderly older than 65. (B) Both younger adults and elderly showed similar recurrence-free propabilities.

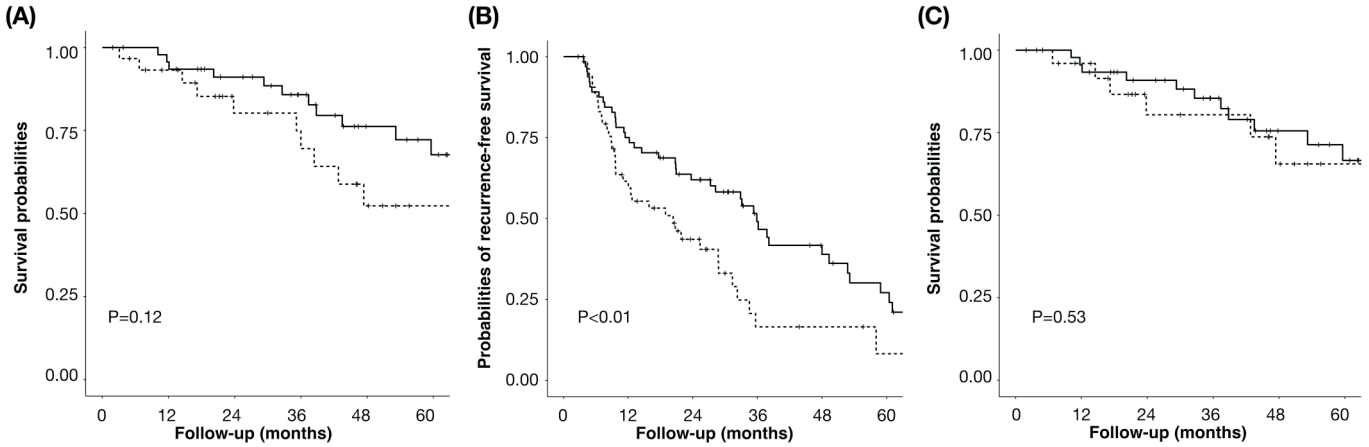

Figure 2. Survival curves and recurrence-free survival curves in elderly patients with hepatocellular carcinoma (younger elderly, solid line; older elderly patients, dotted line). (A) Survival on all-cause related outcomes in younger and older elderly patients, divided with ages 75. (B) Younger elderly had better recurrence-free survival than older elderly. (C) Liver disease related outcomes in both groups were comparable.

Epidemiology studies of HCC showed that the incidence of HBV related HCC begins to rise from ages 55 whereas the incidence of HCV related HCC rises at ages 65.[18] This might explain our data which showed dominance of HBV infection in the younger adults and HCV infection is elderly. Nevertheless, other studies investigated etiologies of HCC in HBV endemic area showed that HBV related HCC peaked at 50–55 years old but incidence of HCV in HCC patient after ages 60.[19] Age and HCV infection were reported as independent prognostic factors for overall survival in HCC patients receiving RFA for HCC.[16]

Other study comparing resection and RFA for patients older than ages 65 with a single HCC less than 5 cm showed that RFA and surgical resection are comparable in overall survival in elderly older than ages 75 and tumor less than 3 cm.[20] A randomized controlled study demonstrated that survival rates in RFA and resection for small HCCs were statistically similar up to 3 year (67.2% vs. 74.8%, respectively). RFA is less invasive and more tolerable than liver resection. Elderly patients are frequently associated with comorbidities. The overall complication rate for elder HCC patients receiving tumor resection was reported as 47% including 19% of cardiopulmonary complications.[21] The incidence of major complications related to percutaneous RFA for HCC was reported as 4.0%, and the most common complication is tumor seeding contributing one third of the major complications.[22] Nowadays, performing tract ablation during withdrawal of needle has an important role in reducing the rate of tumor seeding related to percutaneous RFA for HCC.

Because of comorbidities, treatment modalities especially curative surgical resection were usually less possible for elderly. That potentially leaves elderly to more palliative treatment for HCC. It was previously reported that despite of predominantly early stage of HCC being diagnosed, transcatheter arterial embolization was the predominant treatment.[23] Moreover, for older elderly more than 75 years old, nearly one third of HCC patients received supportive care, and the majority of these patients cannot survive up to 1 year after diagnosis.[23] Our study showed that the survival can be markedly improved with RFA that, even for older elderly HCC patients, the 1-year survival rate was more than 90%. Regarding treatment responses, RFA can achieve similar survival probabilities in either younger or older subgroup of elderly patients with HCC. Therefore, with careful assessment of patient's general condition, senility should not be considered as a primary judgement factor for elderly HCC patient receiving adequate HCC treatment.

This study had several limitations, mostly introduced by its retrospective design. The patient population was heterogeneous especially in the gender and viral factors. In the present study, the younger adults group had a significantly male predominance than

elderly patients in whom the distribution between male and female was nearly equal. Although HCC is generally male predominant,[7] female predominance (male to female ratio as 0.90:1), however, have also been reported in extremely elderly patients.[24] Hepatitis virus such as HBV, environmental factor, and host factors have been proposed to drive the difference of epidemiological differences.[25] Additionally, the RFA treatment may be performed with single or multiple electrodes. However, since different HCCs may have different characteristics, operators might choose optimized ablation system for HCCs intended to ablate. The primary technique effectiveness was similar across different groups in this study which might suggest that the variations in RFA techniques did not lead to difference in effectiveness of RFA.

In summary, RFA is a well-tolerated local ablative therapy across different ages even in elderly. Elderly can have similar technique effectiveness in treating HCC by using RFA. The recurrence and survival were comparable to that of younger adults.

Conflicts of interest statement

No conflicts of interest to disclose.

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