Comparative Study - Retrospective Cohort

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A multicenter case–controlled study on laparoscopic hepatectomy versus microwave ablation as first-line therapy for 3–5 cm hepatocellular carcinoma in patients aged 60 and older

Zhen Wang, MD[a], Hua Zhang, PHD[d], Qiong Meng, MM[o], De-zhi Zhang, MD[j], Song-song Wu, MD[e], Zhi-xian Hong, MD[b], Guang-bin He, MD[g], Hong Yang, MD[h], Bang-de Xiang, MD[i], Xiao Li, MD[c], Tian-an Jiang, MD[k], Kai Li, MD[l], Zhe Tang, MD[m], Fei Huang, MD[n], Man Lu, MD[f], Cun Liu, MD[p], Xiao-ling Yu, MD[a], Zhi-gang Cheng, MD[a], Fang-yi Liu, MD[a], Zhi-yu Han, MD[a], Jian-ping Dou, MD[a], Jie Yu, MD[a,*], Ping Liang, MD[a,*]

Background: There is currently a lack of convincing evidence for microwave ablation (MWA) and laparoscopic liver resection (LLR) for patients $\geq$60 years old with 3–5 cm hepatocellular carcinoma.

Materials and methods: Patients were divided into three cohorts based on restricted cubic spline analysis: 60–64, 65–72, and $\geq$73 years. Propensity score matching (PSM) was performed to balance the baseline variables in a 1:1 ratio. Overall survival (OS) and disease-free survival (DFS) were assessed, followed by a comparison of complications, hospitalization, and cost.

Results: Among 672 patients, the median age was 66 (IQR 62–71) years. After PSM, two groups of 210 patients each were selected. During the 36.0 (20.4–52.4) month follow-up period, the 1-year, 3-year, and 5-year OS rates in the MWA group were 97.6, 80.9, and 65.3% and 95.5, 78.7, and 60.4% in the LLR group (HR 0.98, $P=0.900$). The corresponding DFS rates were 78.6, 49.6, and 37.5% and 82.8, 67.8, and 52.9% (HR 1.52, $P=0.007$). The 60–64 age cohort involved 176 patients, with no a significant difference in OS between the MWA and LLR groups (HR 1.25, $P=0.370$), MWA was associated with a higher recurrence rate (HR 1.94, $P=0.004$). A total of 146 patients were matched in the 65–72 age cohort, with no significant differences in OS and DFS between the two groups (OS (HR 1.04, $P=0.900$), DFS (HR 1.56, $P=0.110$)). In 76 patients aged $\geq$73 years after PSM, MWA provided better OS for patients (HR 0.27, $P=0.015$), and there were no significant differences in DFS between the two groups (HR 1.41, $P=0.380$). Taken together, for patients older than 65 years, the recurrence rate of MWA was comparable with LLR. Safety analysis indicated that LLR was associated with more postoperative bleeding ($P=0.032$) and hypoproteinemia ($P=0.024$).

[a]Department of Interventional Ultrasound, [b]Department of Hepatobiliary Surgery, Fifth Medical Center of Chinese PLA General Hospital, Chinese PLA Medical School, [c]Department of Interventional Therapy, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, [d]Research Center of Clinical Epidemiology, Peking University Third Hospital, Beijing, [e]Department of Ultrasonography, Shengli Clinical Medical College of Fujian Medical University, Fuzhou, [f]Ultrasound Medical Center, Sichuan Cancer Hospital Institute, Sichuan Cancer Center, School of Medicine, University of Electronic Science and Technology of China, Chengdu, [g]Department of Ultrasound, Xijing Hospital, The Fourth Military Medical University, Xian, [h]Department of Ultrasound, The First Affiliated Hospital of Guangxi Medical University, [i]Department of Hepatobiliary Surgery, Guangxi Medical University Cancer Hospital, Nanning, [j]Abdominal Ultrasound Department, The First Hospital of Jilin University, Changchun, [k]Department of Ultrasound Medicine, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang, [l]Department of Ultrasound, Guangdong Key Laboratory of Liver Disease Research, The Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, [m]Department of Surgery, The Fourth Affiliated Hospital, Zhejiang University School of Medicine, Yiwu, [n]Department of General Surgery, The Second Affiliated Hospital of Guangxi Medical University, Nanning, [o]Department of Gynecology, Jinan Zhangqiu District People's Hospital and [p]Department of Ultrasound, Central Hospital Affiliated to Shandong First Medical University, Jinan, People's Republic of China

Zhen Wang and Hua Zhang are listed as co-first author due to comparable contributions to research.

Jie Yu and Ping Liang equally contributed to the article as co-corresponding authors.

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*Corresponding authors. Address: Department of Interventional Ultrasound, Fifth Medical Center of Chinese PLA General Hospital, 28 Fuxing Road, Beijing 100853, People's Republic of China. Tel.: +86 10 66939530; fax: +86 10 68161218. E-mail: liangping301@126.com (P. Liang), and E-mail: jiemi301@163.com (J. Yu).

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Conclusions: MWA was comparable to LLR in patients aged 65 years and older. MWA could be an alternative for the oldest old or the ill patients who cannot afford LLR, while LLR is still the first option of treatments for early-stage 3–5 cm hepatocellular carcinoma in capable elderly's.

Keywords: disease-free survival, elderly patients, hepatocellular carcinoma treatment, laparoscopic liver resection, microwave ablation, overall survival

Introduction

Liver cancer is the third leading cause of cancer-related death worldwide and has become one of the world's major health problems[1]. As the incidence of liver cancer shows an aging trend in many countries and regions[2–5], which indicates more comorbidities in these patients, lower surgical tolerance, and higher treatment risk[6,7]. The WHO defines old age as over 65, while China broadly defines it as 60 and older[8]. To cover more patients, we focused on a wider age range. Although both image-guided microwave ablation and laparoscopic liver resection are currently the main means of liver cancer treatment[9], the major guidelines do not specifically describe the efficacy and minimally invasive nature of the two modalities in the treatment of patients ≥60 years old with 3–5 cm hepatocellular carcinoma (HCC)[10–12], resulting from the lack of reliable direct comparative evidence.

Previous studies have either generally analyzed the effect of hepatectomy on elderly patients without focusing on the more minimally invasive procedure, laparoscopic liver resection (LLR)[13,14], or highlighted solitary HCC with limited sample single-center studies[15–17]. No direct comparison of elderly HCC in the size range of 3–5 cm has been performed to date, which may also be why minimally invasive treatment strategies are not recommended in guidelines for patients with 3–5 cm HCC[10–12]. However, this category of tumors are associated with rapid progression and poor prognosis. Especially for elderly patients, even MWA and LLR with minimally invasive properties present significant therapeutic challenges.

The current study targeted the aging trend of HCC onset, and aims to explore the therapeutic value of the above two minimally invasive techniques in HCC patients aged ≥60 years, hoping to provide a citable basis for clinical treatment.

HIGHTLIGHTS

- Restricted cubic splines analysis showed a nonlinear relationship between overall survival risk and age (60–64 year old: risk increases with age; 65–72 year: risk decreases with age; ≥73 year old: risk increases with age).
- Patients ≥73 years old who receive microwave ablation may have better survival outcomes (HR 0.27, 95% CI: 0.09–0.82, $P=0.015$).
- The rate of intraoperative blood transfusion in laparoscopic liver resection group was significantly higher than that in microwave ablation group ($P<0.001$), and laparoscopic liver resection was associated with more postoperative bleeding ($P=0.032$) and hypoproteinemia ($P=0.024$).

Material and methods

Patients

Six hundred eighty-four participants aged ≥60 were selected from the database of 3385 HCC patients with less than three newly diagnosed lesions (all with the same pathological diagnosis or same enhanced imaging findings) and at least one lesion with a maximum diameter of 3–5 cm admitted to 12 tertiary hospitals in China from January 2008 to October 2019. The inclusion criteria were: 1. Child-Pugh class A or B; 2. Eastern Cooperative Oncology Group (ECOG) score ≤2; 3. At least one lesion in each patient was pathologically confirmed as HCC; 4. No vascular invasion and distant metastasis; 5. No other life-threatening severe comorbidities. With the loss of 12 patients to follow-up (five in the MWA group and seven in the LLR group), there were 672 patients and 851 tumors included in the analysis, comprising 309 in the MWA group and 363 in the LLR group (Fig. 1). Ethical approval for this study (S2019-348-01) was provided by the ethical committee of the primary research unit and conformed to the 1975 Declaration of Helsinki and was registered. The work has been reported in line with the strengthening the reporting of cohort, cross-sectional, and case–control studies in surgery (STROCSS) criteria[18] (Supplemental Digital Content 1, http://links.lww.com/JS9/B811). Part of the patient population was previously reported[16]. Informed consent was waived due to the retrospective nature of the study and the use of deidentified data.

Clinical intervention

Before the therapy, the evaluation on patients was performed by the multidisciplinary team of each hospital covering at least hepatobiliary surgeons, radiologists, interventional radiologists, pathologists, anesthesiologist, and oncologists.

Once any treatment is determined, the corresponding MWA group or LLR group will carefully formulate precise intervention plan and perioperative management strategies combining each patient's physical condition, comorbidities, anesthesia tolerance, and tumor status. The MWA group: I, Based on the total volume of the liver, tumor volume, the adjacent relationship between tumor and vascular, and the type of ablation needle, preoperative three-dimensional planning was carried out for the lesions of the patients, so as to preserve the normal liver tissue as much as possible and ensure enough safe boundary (external expansion of 5 mm) (Supplementary Figure S7, Supplemental Digital Content 2, http://links.lww.com/JS9/B812); II, For lesions adjacent to the gastrointestinal tract, pericardium, kidney and other organs, artificial ascites will be provided during the operation to protection; III, For tumors located in the diaphragmatic fornix, artificial pleural effusion will be provided to assist visualization and protect the diaphragm if required; IV, For lesions difficult to be detected by two-dimensional ultrasound, the operation may be performed under contrast-enhanced ultrasonography (CEUS) or multimodal image fusion navigation (Supplementary Figure S8,

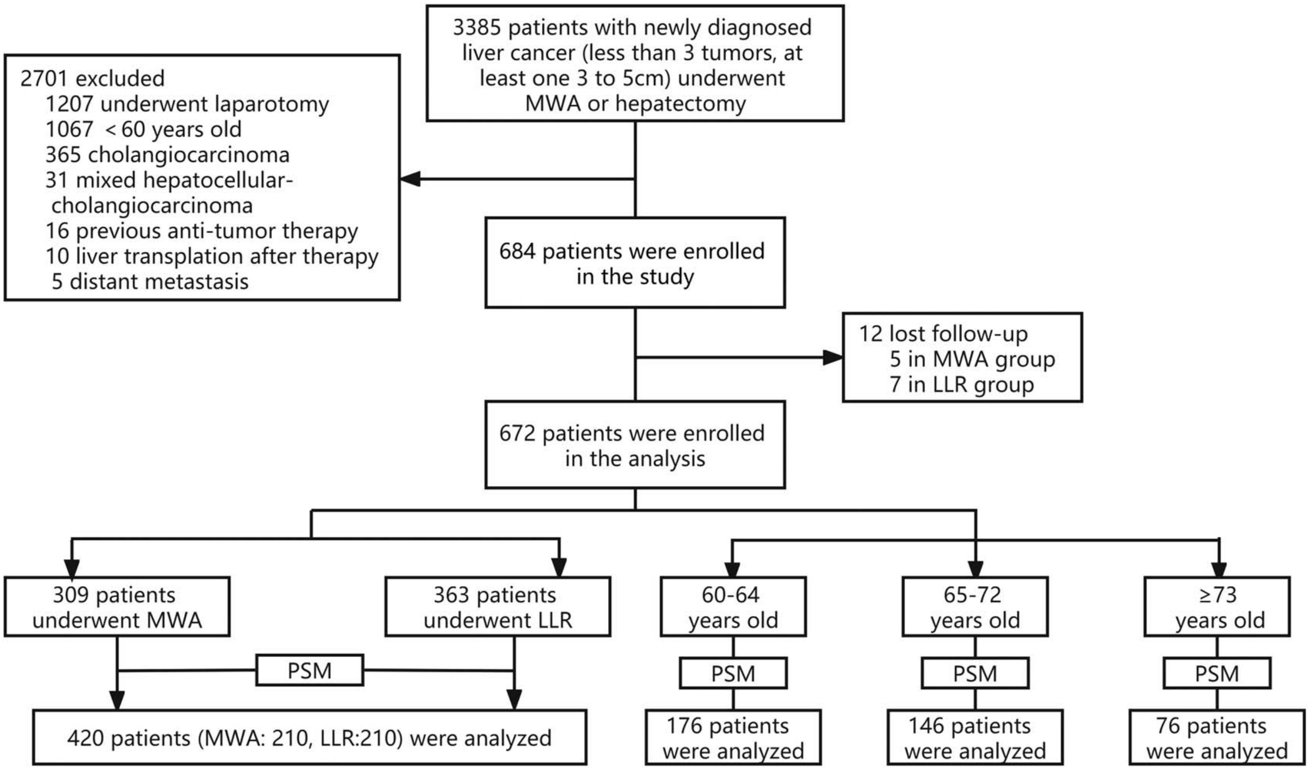

Figure 1. Flow chart. LLR, laparoscopic liver resection; MWA, microwave ablation; PSM, propensity score matching.

Supplemental Digital Content 2, http://links.lww.com/JS9/B812). The MWA system and operational details have been described in the previous literature[16,19], as well as the details of laparoscopic hepatectomy[16,20]. Information of all specialists are provided in the Supporting Appendix 1 (Supplemental Digital Content 2, http://links.lww.com/JS9/B812).

Study end points and follow-up

Overall survival (OS) is the primary study endpoint, defined as time to death from any cause. Disease-free survival (DFS) is a secondary study endpoint defined as the time to recurrence or death, whichever occurs first. Response was evaluated by enhanced image (CT, MRI, or CEUS) based on response evaluation criteria in solid tumors (RECIST) system[21]. The follow-up regimen was similar to the management reported previously[16]. Other outcomes of interest were mortality within 3 months after treatment, serious complications (Class III–IV of the Clavien–Dindo classification system)[22], length of stay, and total inpatient costs.

Statistical analyses

The SPSS 22.0 and R 4.0.3 statistical packages were used to analyze the retrospective data. Multiple imputation was used to deal with missing data, details can be seen in the literature[16].The propensity score was generated by logistic regression analysis. Variables (age, sex, ECOG, cirhosis, HCV, portal hypertension, hypertension, diabetes, cardiac-cerebral vascular disease, hemoglobin, and tumor number) that known or recommended by experts were used as independent variables, and grouped variables were used as dependent variables for model fitting. PSM was performed to reduce bias, and the nearest neighbor matching method was used for matching, the caliper value was 0.2 times the SD, the matching ratio between MWA group and LLR group was 1:1, and the sample size of each group was 210 after matching. We test the equilibrium before and after matching, and calculate the standardized mean difference. Continuous data were described by mean, SD or median, and quartile according to whether they were normally distributed. Frequency and percentage were calculated for count data. Kaplan–Meier (K–M) survival curves method and Cox proportional hazards model were used to analyze OS and DFS. HRs with 95% CIs were estimated using the Cox proportional hazards model. Treatment effects were evaluated among subgroups by adding interaction terms to Cox proportional hazards models. Multivariable models with restricted cubic splines (RCS) were used to analyze the association between age and OS statistical significance was defined as $P < 0.05$ (two-sided).

Results

Grouped by age

RCS was used to analyze the association between age and OS (Fig. 2). According to the results, we grouped by age. Three age cohorts (60–64 years, 65–72 years, ≥ 73 years) were analyzed by the same PSM method, with 176, 146, 78 patients in each cohort after matching (Fig. 1).

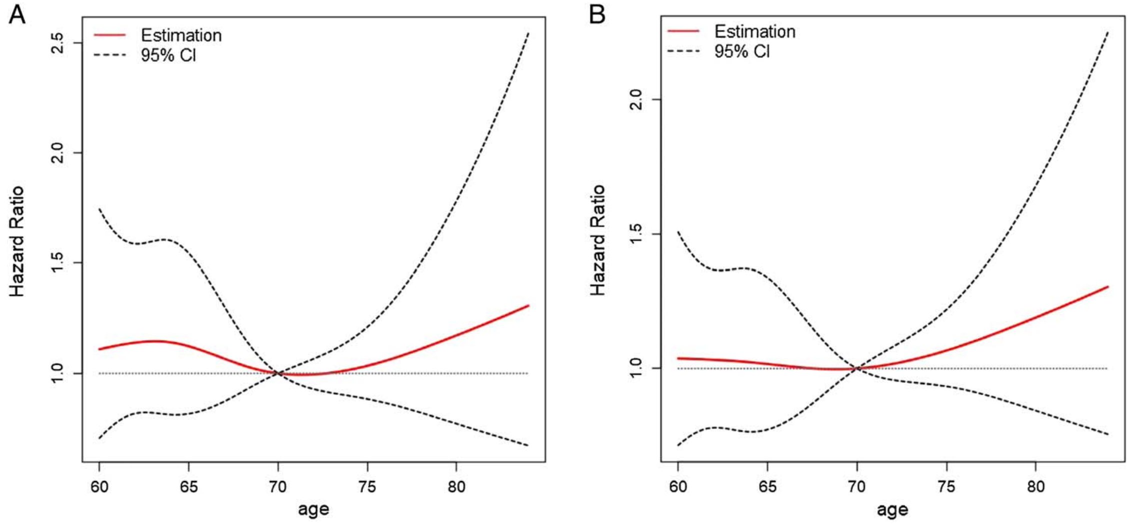

Figure 2. Multivariable models with restricted cubic splines (RCS) were used to analyze the association between age, OS, and DFS. A showed a nonlinear relationship between OS risk and age (60–64 years old: risk increases with age; 65–72 years: risk decreases with age; ≥73 years old: risk increases with age); B indicated age linearly with DFS risk. DFS, disease-free survival; OS, overall survival.

Demographic and clinical characteristics of the total population

The median age of the 672 patients was 66 (62–71) years, with 499 (74.3%) males, 397 (59.1%) exhibiting chronic hepatitis B virus infection, followed by 100 (14.9%) exhibiting chronic hepatitis C virus infection. A total of 495 (73.7%) patients displayed varying degrees of cirrhosis, of whom 86 (12.8%) had complicated portal hypertension. Four hundred forty-three people suffered from one of the following chronic diseases: hypertension, diabetes, cardiovascular, and cerebrovascular diseases. A total of 216 (32.1%) patients exhibited the largest tumor diameter of 4.1–5.0 cm, and 140 (20.8%) patients had multiple tumors. Compared to the LLR group, the MWA group showed a higher median age (68.0 vs. 65.0, $P<0.001$), worse ECOG scores ($P=0.002$), higher rates of HCV infection (21.4 vs. 9.4%, $P<0.001$), cirrhosis (79.0 vs. 69.1%, $P=0.004$), portal hypertension (15.9 vs. 10.2%, $P=0.028$), worse liver function reserve (Child–Pugh B: 5.8 vs. 2.5%, $P=0.028$), and more diabetes (27.5 vs. 16.5%, $P=0.001$). The MWA group included more patients with low hemoglobin (132.0 g/l vs. 142.0 g/l, $P<0.001$) and elevated transaminases (ALT: 26.0 μ/l vs. 22.2 μ/l, $P=0.011$; AST: 27.5 μ/l vs. 25.0 μ/l, $P<0.001$), as well as a higher proportion with multiple tumors (31.1 vs. 12.1%, $P<0.001$). All covariates were subsequently balanced after PSM (Table 1, Supplementary Table S1, Supplemental Digital Content 2, http://links.lww.com/JS9/B812). The baseline details before and after three age-matched cohorts are described in Supplementary Tables S3–5 (Supplemental Digital Content 2, http://links.lww.com/JS9/B812). A detailed description of the definition of portal hypertension is provided in Supplementary Appendix 2 (Supplemental Digital Content 2, http://links.lww.com/JS9/B812).

K–M survival curves of the total population

After 37.1 (22.2–53.7) months of follow-up before PSM, the median OS of 672 patients was 76.4 (60.7–92.0) months in the MWA group and 82.8 (66.7–98.9) months in the LLR group. The overall mortality was 33.0% (102/309) in the MWA group and 28.4% (103/363) in the LLR group. Within 90 days, the mortality was 0.32% (1/309) in the MWA group and 0.28% (1/363) in the LLR group. The 1-year, 3-year, and 5-year OS estimated rates among the MWA group were 97.6, 79.6, and 62.9%, respectively, and the rates among the LLR group were 96.6, 81.9, and 63.4%, respectively (HR 1.11, 95% CI: 0.84–1.46, $P=0.480$) (Fig. 3A). The median DFS of the MWA and LLR groups was 31.0 (24.4–37.7) months and 100.6 (52.3–149.0) months, and the overall recurrence rates were 50.5% (156/309) and 32.5% (118/363), respectively. The corresponding estimated DFS rates of the two groups were 74.7, 45.2, and 32.6% and 85.2, 71.7, and 59.5%, respectively (HR 2.05, 95% CI: 1.61–2.60, $P<0.001$) (Fig. 3C).

After PSM, two groups of 210 patients each were selected. During the 36.0 (20.4–52.4) month follow-up period, the estimated median OS for the MWA arm and LLR arm were 84.1 (67.1–101.1) months and 68.5 (44.3–92.7) months, respectively. Overall mortality in the MWA and LLR groups was 29.0 (61/210) and 30.0% (63/210), respectively. The 90-day mortality rate in both groups was 0.48% (1/210). The 1-year, 3-year, and 5-year OS rates in the MWA group were 97.6, 80.9, 65.3% and 95.5, 78.7, 60.4% in the LLR group (HR 0.98, 95% CI: 0.68–1.40, $P=0.900$) (Fig. 3B). The median DFS of the MWA and LLR groups was 37.2 (27.1–47.2) and 69.9 months, with overall recurrence rates of 44.8 (94/210) and 36.2% (76/210), respectively. The corresponding DFS rates of the two groups were 78.6, 49.6, and 37.5% and 82.8, 67.8, and 52.9%, respectively (HR 1.52, 95% CI: 1.12–2.05, $P=0.007$) (Fig. 3D).

A forest plot of hazard ratios for OS and DFS for all patients and various subgroups based on univariate Cox models is depicted in Supplementary Figure S1 (Supplemental Digital Content 2, http://links.lww.com/JS9/B812).

Table 1

Baseline comparison of patients aged ≥60 years who received microwave ablation or laparoscopic liver resection treatment.

	Before PSM			After PSM		
Variables	**MWA ($n=309$)**	**LLR ($n=363$)**	***P***	**MWA ($n=210$)**	**LLR ($n=210$)**	***P***
Median Age [IQR], years	68.0 (63.0–74.0)	65.0 (62.0–69.0)	< 0.001	65.0 (62.0–72.0)	66.5 (63.0–71.0)	0.698
ECOG, PS, *n* (%)						
0	234 (75.7%)	307 (84.6%)	0.002	172 (81.9%)	171 (81.4%)	0.961
1	66 (21.4%)	42 (11.6%)		32 (15.2%)	32 (15.2%)	
2	9 (2.9%)	14 (3.9%)		6 (2.9%)	7 (3.3%)	
Sex, *n* (%)						
Male	224 (72.5%)	275 (75.8%)	0.335	158 (75.2%)	150 (71.4%)	0.377
Smoking, *n* (%)						
Yes	146 (47.2%)	179 (49.3%)	0.594	102 (48.6%)	104 (49.5%)	0.845
Drinking, *n* (%)						
Yes	138 (44.7%)	158 (43.5%)	0.768	99 (47.1%)	87 (41.4%)	0.238
HBV, *n* (%)						
Yes	182 (58.9%)	215 (59.2%)	0.931	126 (60.0%)	125 (59.5%)	0.921
HCV, *n* (%)						
Yes	66 (21.4%)	34 (9.4%)	< 0.001	36 (17.1%)	30 (14.3%)	0.421
NBNC, *n* (%)						
Yes	61 (19.7%)	114 (31.4%)	< 0.001	48 (22.9%)	55 (26.2%)	0.369
Antiviral treatment, *n* (%)						
Yes	107 (34.6%)	130 (35.8%)	0.749	74 (35.2%)	75 (35.7%)	0.919
Cirhosis, *n* (%)						
Yes	244 (79.0%)	251 (69.1%)	0.004	155 (73.8%)	154 (73.3%)	0.912
Splenomegaly, *n* (%)						
Yes	53 (17.2%)	54 (14.9%)	0.422	29 (13.8%)	33 (15.7%)	0.582
Ascites, *n* (%)						
Yes	29 (9.4%)	32 (8.8%)	0.798	15 (7.1%)	24 (11.4%)	0.130
Portal hypertension, *n* (%)						
Yes	49 (15.9%)	37 (10.2%)	0.028	27 (12.9%)	27 (12.9%)	1.000
Child-Pugh, *n* (%)						
A	291 (94.2%)	354 (97.5%)	0.028	200 (95.2%)	203 (96.7%)	0.458
B	18 (5.8%)	9 (2.5%)		10 (4.8%)	7 (3.3%)	
Comorbidity, *n* (%)						
Hypertension	112 (36.2%)	111 (30.6%)	0.120	71 (33.8%)	70 (33.3%)	0.918
Diabetes	85 (27.5%)	60 (16.5%)	0.001	48 (22.9%)	49 (23.3%)	0.908
Cardiac-cerebral vascular disease	41 (13.3%)	34 (9.4%)	0.109	24 (11.4%)	24 (11.4%)	1.000
Size, *n* (%)						
4.1–5.0 cm	88 (28.5%)	128 (35.3%)	0.061	62 (29.5%)	66 (31.4%)	0.672
Laboratory tests						
Median Hb count [IQR], (×109/l)	132.0 (117.5–142.0)	142.0 (133.0–150.0)	< 0.001	136.0 (124.0–145.0)	137.0 (125.8–146.0)	0.597
Median AFP [IQR], ng/ml	10.3 (3.6–93.9)	13.4 (3.6–162.5)	0.435	8.4 (3.4–66.9)	14.6 (4.1–132.9)	0.129
Median ALT [IQR], μ/l	26.0 (18.3–38.1)	22.2 (16.8–35.0)	0.011	26.0 (17.5–38.5)	22.2 (16.0–35.8)	0.062
Median AST [IQR], μ/l	27.5 (20.9–43.4)	25.0 (19.0–33.0)	< 0.001	26.0 (19.3–41.7)	25.9 (16.0–34.0)	0.244
Median TP [IQR], g/l	67.2 (63.4–71.6)	68.0 (64.2–71.8)	0.071	67.3 (63.1–71.4)	68.0 (63.9–71.4)	0.576
Number, *n* (%)						
1	213 (68.9%)	319 (87.9%)	< 0.001	167 (79.5%)	170 (81%)	0.909
2	71 (23%)	30 (8.3%)		29 (13.8%)	26 (12.4%)	
3	25 (8.1%)	14 (3.9%)		14 (6.7%)	14 (6.7%)	

AFP, alpha-fetoprotein; ALT, alanine transaminase; AST, aspartate aminotransferase; ECOG PS, Eastern Cooperative Oncology Group performance status; Hb, hemoglobin; HBV, hepatitis b virus; HCV, hepatitis c virus; IQR, interquartile range; LLR, laparoscopic liver resection; MWA, microwave ablation; NBNC, non-HBC/HCV; PSM, propensity score matching; TP, the total protein.

K–M survival curves evaluated in 176 patients (patients 60–64 years after PSM)

After a median follow-up of 36.3 (20.0–53.0) months, the median OS was 67.5 (50.1–84.8) months in the MWA group and 70.1 (47.0–93.3) months in the LLR group. Overall mortality rates were 37.5% (33/88) and 34.1% (30/88) in the MWA and LLR groups, respectively, while 90-day mortality rates were 1.1% (1/88) and 0%, respectively. The 1-year, 3-year, and 5-year OS rates in the MWA group were 97.1, 78.3, and 52.1% and 91.6, 76.7, and 61.3% in the LLR group (HR 1.25, 95% CI: 0.76–2.06, $P=0.370$) (Fig. 4A). The median DFS was 28.2 (17.3–38.7) months in the MWA group and was not obtained in the LLR group, with overall recurrence rates of 53.4% (47/88) and 34.1% (30/88), respectively. The corresponding DFS rates of the two groups were 74.1, 40.1, and 29.8% and 79.7, 68.7, and 58.2%, respectively (HR 1.94, 95% CI: 1.22–3.07, $P=0.004$) (Fig. 4D).

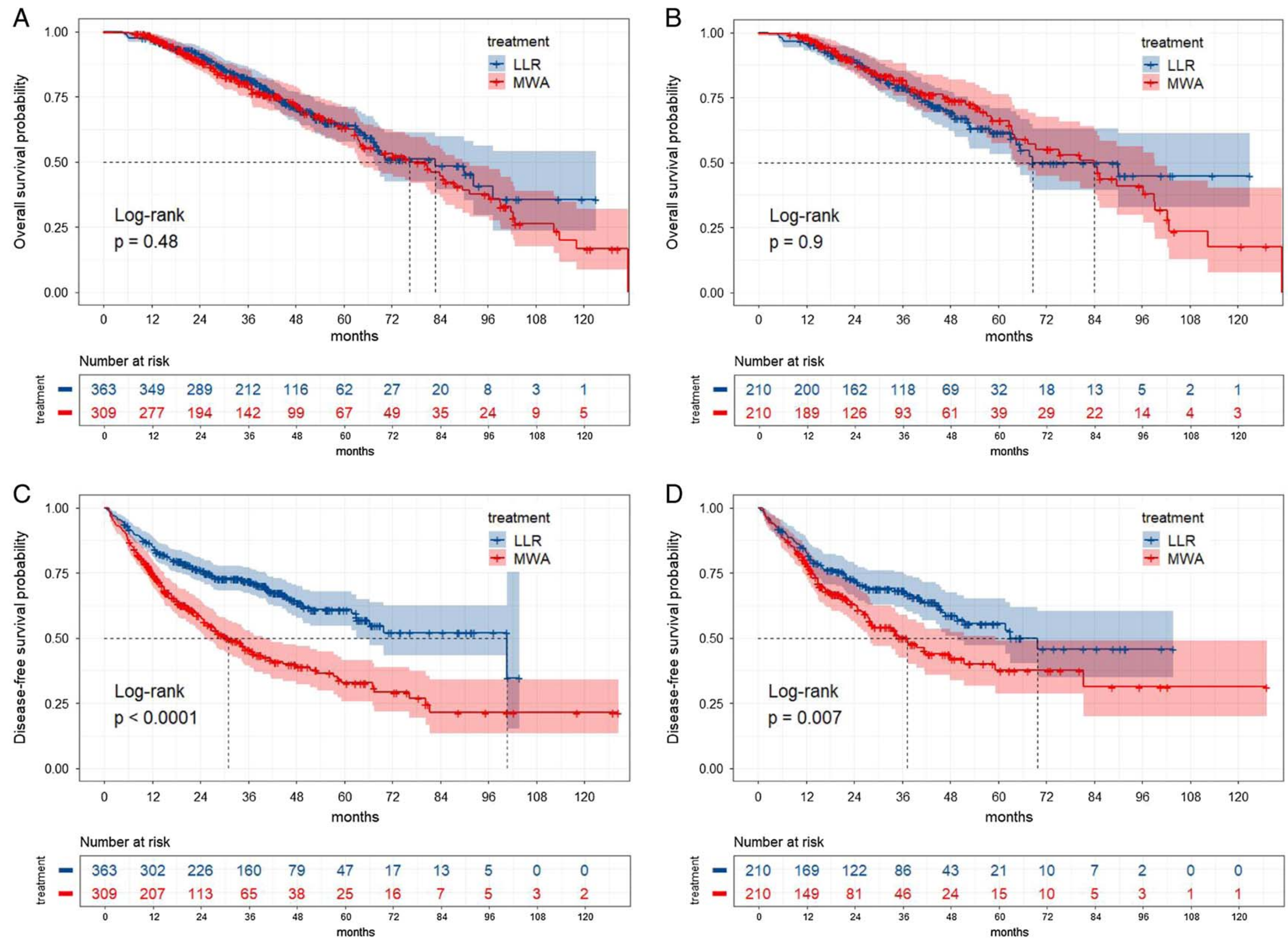

Figure 3. Survival curves before and after PSM for the total population (672). Kaplan–Meier survival curves for (A) OS before PSM in the total population; (C) DFS before PSM in the total population; (B) OS after PSM in the total population; (D) DFS after PSM in the total population. DFS: disease-free survival; LLR, laparoscopic liver resection; MWA, microwave ablation; OS, overall survival.

K–M survival curves evaluated in 146 patients (patients 65–72 years after PSM)

With a median follow-up of 35.0 (19.4–48.9) months, the median OS was 84.1 (54.1–114.1) months in the MWA group and was not reached in the LLR group. The overall mortality was 24.7% (18/73) and 26.0% (19/73) in the MWA and LLR groups, respectively, and the mortality within 90 days was 0 and 1.37% (1/73), respectively. The 1-year, 3-year, and 5-year OS rates in the MWA group were 96.6, 79.9, and 62.3% and 96.3, 80.4, and 59.7% in the LLR group (HR 1.04, 95% CI: 0.55–1.99, $P=0.900$) (Fig. 4B). The median DFS was 28.2 (17.3–38.7) months in the MWA group and was not reached in the LLR group. The recurrence rates were 53.4% (47/88) in the MWA group and 34.1% (30/88) in the LLR group. The corresponding DFS rates of the two groups were 76.8, 55.4, and 37.0% and 83.0, 69.1, and 49.2%, respectively (HR 1.56, 95% CI: 0.90–2.70, $P=0.110$) (Fig. 4E).

K–M survival curves evaluated in 76 patients (patients ≥ 73 year after PSM)

During the 36.8 (23.4–58.4) month follow-up period, the estimated median OS was not reached in the MWA group and was 64.5 (58.4–70.7) for the LLR group. The overall mortality was 13.2% (5/38) in the MWA group and 28.9% (11/38) in the LLR group, and the mortality rate within 90 days was 0% in both groups. The 1-year, 3-year, and 5-year OS rates in the MWA group were 100.0, 93.3, 86.5% and 100.0, 83.8, 61.1% in the LLR group (HR 0.27, 95% CI: 0.09–0.82, $P=0.015$) (Fig. 4C). The median DFS of the MWA group was 58.4 months and was not reached in the LLR group, and the overall recurrence rates were 36.8% (14/38) and 31.6% (12/38), respectively. The corresponding DFS rates of the two groups were 89.0, 52.8, 44.8% and 89.1, 71.8, 50.8%, respectively (HR 1.41, 95% CI: 0.65–3.07, $P=0.380$) (Fig. 4F).

Exploratory subgroup analyses (patients ≥ 65 years after PSM)

Given that tumor size and number are related to the difficulty of local intervention and patient outcome[23], we performed an exploratory stratified analysis of tumor size and number in patients ≥ 65 years of age. A total of 210 patients were eventually included in the MWA and LLR groups for the final analysis.

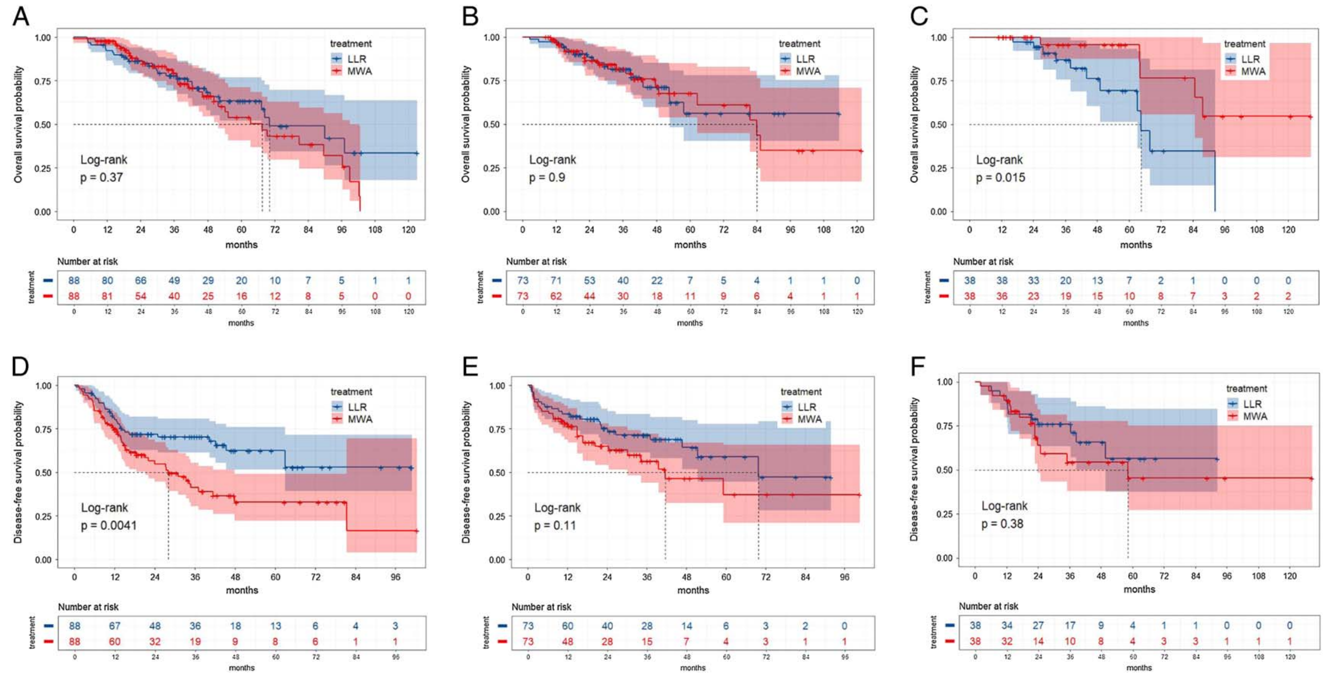

Figure 4. Kaplan–Meier survival curves for the three age cohorts (after PSM). Kaplan–Meier survival curves for (A) OS for the 60–64 year old cohort; (B) OS for the 65–72 year old cohort; (C) OS for the ≥73 year old cohort; (D) DFS for the 60–64 year old cohort; (E) DFS for the 65–72 year old cohort; (F) DFS for the ≥73 year old cohort. LLR, laparoscopic liver resection; MWA, microwave ablation.

Size

The K–M curves indicated no significant difference in OS and DFS between the two treatment groups for either 3.1–4.0 cm or 4.1–5.0 cm HCC [3.1–4.0 cm: OS: (HR 1.36, 95% CI: 0.76–2.46, $P=0.300$); DFS: (HR 1.52, 95% CI: 0.89–2.58, $P=0.110$). 4.1–5.0 cm: OS: (HR 0.59, 95% CI: 0.22–1.59, $P=0.290$); DFS: (HR 1.85, 95% CI: 0.83–4.17, $P=0.130$)] (Supplementary Figure S4, Supplemental Digital Content 2, http://links.lww.com/JS9/B812).

Number

We observed similar trends to tumor size, without a statistically significant difference in the effects of MWA or LLR on either OS or DFS between single and multiple tumors [single: OS: (HR 0.96, 95% CI: 0.55–1.69, $P=0.900$); DFS: (HR 1.42, 95% CI: 0.86–2.36, $P=0.170$). Multiple: OS: (HR 1.95, 95% CI: 0.59–6.41, $P=0.260$); DFS: (HR 2.53, 95% CI: 0.96–6.69, $P=0.052$)] (Supplementary Figure S6, Supplemental Digital Content 2, http://links.lww.com/JS9/B812).

Safety and cost analyses

Table 2 illustrates the significantly higher rate of intraoperative blood transfusion in the LLR group than in the MWA group (1.0 vs. 19.0%, $P<0.001$), and LLR was associated with more postoperative bleeding (0.5 vs. 3.3%, $P=0.032$) and hypoproteinemia (0 vs. 1.9%, $P=0.024$). In all cohorts, MWA was associated with shorter treatment time, shorter hospital stay, and lower total costs (all $P<0.001$) (Table 3).

Type of recurrence and treatment modalities of patients in three cohorts after PSM

The first recurrence types of patients included local tumor progression (LTP), distant intrahepatic recurrence (IR) and extrahepatic metastasis (EM), among which LTP in the LLR group was understood to be a surgical marginal recurrence. From the results shown in Table 4, the recurrence type with the highest incidence was IR, of which 45.5% occurred in the 60–64 year age cohort in MWA group and 28.8% in the 65–72 year age cohort in LLR group. Followed by EM, the highest incidence of MWA group was 14.8% in the 60–64 age cohort, and LLR group was 11.0% in the 65–72 age cohort. The lowest incidence was in LTP, and the highest incidence was 4.1% in both the MWA and LLR groups, in the 65–72 year age cohort.

It was worth noting that after people found tumor recurrence, the vast majority of patients chosen MWA treatment again (up to 29.5%), followed by transcatheter arterial chemoembolization (TACE) (15.1%) or medication (12.5%).

Discussion

In this retrospective multicenter study, we dynamically compared the trend of efficacy changes between MWA and LLR in the treatment of 3–5 cm HCC over 60 years old. Throughout the analysis process, we found a significant nonlinear relationship between population age and OS risk using the RCS method. Therefore, we divided the study population into three age groups: 60–64, 65–72, and ≥73 years old. After strict matching and analysis of the above three groups, it was confirmed again that some of the conclusions were consistent with previous research, and some other interesting results were also found; for example,

Table 2

Incidence of serious complications (grades III–IV) in different age gradients.

	≥ 60 (*n* = 420)			60–64 (*n* = 176)			65–72 (*n* = 146)			≥ 73 (*n* = 76)		
Complications	**MWA**	**LLR**	***P***	**MWA**	**LLR**	***P***	**MWA**	**LLR**	***P***	**MWA**	**LLR**	***P***
Intraoperative blood transfusion, *n* (%)	2 (1.0)	40 (19.0)	< 0.001	0 (0.0)	15 (17.0)	< 0.001	1 (1.4)	18 (24.7)	< 0.001	0 (0.0)	1 (2.6)	0.314
Pneumonia, *n* (%)	1 (0.5)	1 (0.5)	1.000	0 (0.0)	0 (0.0)	–	0 (0.0)	1 (1.4)	0.316	0 (0.0)	0 (0.0)	–
Hypoproteinemia, *n* (%)	0 (0.0)	4 (1.9)	0.024	0 (0.0)	1 (1.1)	0.316	0 (0.0)	3 (4.1)	0.080	0 (0.0)	0 (0.0)	–
Postoperative bleeding, *n* (%)	1 (0.5)	7 (3.3)	0.032	1 (1.1)	0 (0.0)	0.316	0 (0.0)	5 (6.8)	0.023	0 (0.0)	3 (7.9)	0.077
Biliary fistula, *n* (%)	0 (0.0)	0 (0.0)	–	0 (0.0)	0 (0.0)	–	0 (0.0)	0 (0.0)	–	0 (0.0)	0 (0.0)	–
Intestinal fistula, *n* (%)	0 (0.0)	0 (0.0)	–	0 (0.0)	0 (0.0)	–	0 (0.0)	0 (0.0)	–	0 (0.0)	0 (0.0)	–
Pleural and abdominal effusion, *n* (%)	1 (0.5)	4 (1.9)	0.177	1 (1.1)	1 (1.1)	1.000	1 (1.4)	2 (2.7)	0.560	1 (2.6)	0 (0.0)	0.314
Infection, *n* (%)	1 (0.5)	1 (0.5)	1.000	1 (1.1)	1 (1.1)	1.000	0 (0.0)	0 (0.0)	–	1 (2.6)	0 (0.0)	0.314
Needle tract implantation metastases, *n* (%)	1 (0.5)	0 (0.0)	0.317	0 (0.0)	0 (0.0)	–	2 (2.7)	0 (0.0)	0.154	0 (0.0)	0 (0.0)	–
Liver and kidney failure, *n* (%)	2 (1.0)	0 (0.0)	0.156	1 (1.1)	1 (1.1)	1.000	0 (0.0)	0 (0.0)	–	0 (0.0)	0 (0.0)	–

LLR, laparoscopic liver resection; MWA, microwave ablation.

people aged 73 and above in the MWA group showed better survival benefits than those in the LLR group. If this discovery is verified in a well-designed prospective cohort study, a 'more minimally invasive' treatment model for HCC in the elderly population may be more widely accepted.

Previous studies on the treatment options for elderly HCC have mostly focused on early-stage HCC[13,24], or been single-arm study to evaluate the safety and feasibility of MWA[15], or been literature reviews based on published articles[25], which are completely different from the target population and research design of our study. In the present study, we conducted a completely consistent PSM (with the same caliper values and matching variables) for the total population and three age cohorts to increase the reliability of the research conclusions, which was different from the direct stratified analysis of other studies[26]. General stratified analysis is often difficult to ensure a balance between the baseline of the study subjects. Furthermore, the primary endpoint of this study was the OS of patients, with DFS as the secondary endpoint, and the first recurrence patterns and treatment strategies of all patients were tracked to the greatest extent possible to determine the potential impact of MWA and LLR on patient long-term survival.

Studies have confirmed the close relationship between aging and the reduction in liver volume and liver blood flow[27,28]. Even under physiological conditions, the liver weight of elderly men and women in comparison to young people will be decreased by ~6.5 and 14.3%[29], respectively, accompanied by a gradual decrease in pharmacokinetics with age, resulting in a significant reduction in the drug clearance rate of the liver. Zoli *et al.*[30] reported that portal vein blood flow velocity in people over 71 years old was significantly reduced in comparison to that in young people and revealed that liver atrophy in elderly patients was induced by a decrease in the number of hepatocytes instead of a reduction in the size of hepatocytes. This series of studies from a physiological perspective indicates that the livers of elderly patients are generally inferior to those of young people in terms of both physical and biological functions, highlighting the importance of treatment regimens for elderly liver diseases. In the present study, over 70% of the patients were complicated with cirrhosis of varying degrees, reflecting an insufficient liver functional reserve in real clinical patients. This also indicates the significance of retaining as much normal liver tissue as possible for elderly patients with 3–5 cm HCC while undergoing local radical treatment. Both MWA and LLR possess the advantages of minimally invasive treatment; however, for elderly patients, whichever treatment technique is more minimally invasive and can preserve normal liver while treating tumors may result in a high significance for the survival of patients. This is mainly because milder trauma means faster body recovery, and the time

Table 3

Comparison of time and cost in four age cohorts after PSM.

Cohorts	Groups	Intervention time, median min (IQR)	Hospital stay, median days (IQR)	Hospitalization cost, median US$(IQR)
≥ 60 (*n* = 420)	MWA	38 (31–45)	9 (7–12)	6538 (5857–7289)
	LLR	190 (150–240)	15 (10–19)	10715 (7830–13 336)
	P	< 0.001	< 0.001	< 0.001
60–64 (*n* = 176)	MWA	37 (31–48)	9 (8–13)	6520 (5531–7192)
	LLR	190 (146–249)	15 (11–21)	10 153 (7220–12 714)
	P	< 0.001	< 0.001	< 0.001
65–72 (*n* = 146)	MWA	36 (30–48)	9 (7–12)	6538 (6037–7543)
	LLR	210 (145–270)	15 (11–19)	11 476 (8616–13 755)
	P	< 0.001	< 0.001	< 0.001
≥ 73 (*n* = 76)	MWA	39 (33–51)	9 (7–10)	6538 (5513–7080)
	LLR	200 (155–240)	15 (8–19)	10 663 (7681–13 323)
	P	< 0.001	< 0.001	< 0.001

IQR, interquartile range; LLR, laparoscopic liver resection; MWA, microwave ablation; PSM, propensity score matching; US$, United States dollar.

Table 4

The types of first recurrence and treatment modalities of patients in three cohorts after PSM.

TOR and TM Cohorts	60–64		65–72		≥ 73	
	MWA (n = 88)	LLR (n = 88)	MWA (n = 73)	LLR (n = 73)	MWA (n = 38)	LLR (n = 38)
LTP						
n, (%)	3 (3.4)	2 (2.3)	3 (4.1)	3 (4.1)	1 (2.6)	1 (2.6)
TM						
MWA	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)	1 (2.6)	0 (0.0)
Resection	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
RFA	1 (1.1)	1 (1.1)	1 (1.4)	1 (1.4)	0 (0.0)	0 (0.0)
TACE	2 (2.3)	0 (0.0)	1 (1.4)	2 (2.7)	0 (0.0)	1 (2.6)
Medication	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
IR						
n, (%)	40 (45.5)	24 (27.3)	27 (37.0)	21 (28.8)	13 (34.2)	10 (26.3)
TM						
MWA	26 (29.5)	1 (1.1)	16 (21.9)	1 (1.4)	9 (23.7)	2 (5.3)
Resection	1 (1.1)	5 (5.7)	0 (0.0)	2 (2.7)	0 (0.0)	2 (5.3)
RFA	2 (2.3)	4 (4.5)	3 (4.1)	3 (4.1)	2 (5.3)	3 (7.9)
TACE	8 (9.1)	7 (8.0)	5 (6.8)	11 (15.1)	0 (0.0)	3 (7.9)
Medication	3 (3.4)	7 (8.0)	3 (4.1)	4 (5.5)	2 (5.3)	0 (0.0)
EM						
n, (%)	13 (14.8)	6 (6.8)	8 (11.0)	3 (4.1)	2 (5.3)	2 (5.3)
TM						
MWA	2 (2.3)	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)
Resection	0 (0.0)	4 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.6)
RFA	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)
TACE	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)
Medication	11 (12.5)	2 (2.3)	5 (6.8)	3 (4.1)	2 (5.3)	1 (2.6)

EM, extrahepatic metastasis; IR, intrahepatic recurrence; LLR, laparoscopic liver resection; LTP, local tumor progression; MWA, image-guided microwave ablation; PSM, Propensity score matching; RFA, radiofrequency ablation; TACE, transhepatic arterial chemotherapy and embolization; TM, treatment modalities; TOR, type of recurrence.

window for adjuvant treatment can be advanced, which may improve the patient's prognosis[31,32].

From the analysis of 672 patients, no difference was found in the impact of the two treatment modalities on OS, but there was an association of MWA with a higher recurrence rate before and after PSM. This conclusion is consistent with the outcome of our previous studies on solitary HCC[16], possibly due to the 42.9% of patients aged 60 to 64 in the study population. Further analysis of the three age cohorts revealed that MWA gradually overcame the disadvantage of tumor recurrence control when patients were ≥ 65 years (lost statistical difference), showing a potential advantage over LLR in improving OS in patients ≥ 73 years of age. In Table 4, we can clearly see that when patients first experienced recurrence, the proportion of MWA group patients who chose microwave ablation again was much higher than that of LLR group patients who chose resection again. And some studies found that older age was associated with higher treatment compliance[33] but older patients were less likely to undergo aggressive surgery[34]. This finding may suggest that the minimally invasive nature and reproducibility of MWA may benefit the survival of patients, which of course needs to be further confirmed in prospective studies.

Because the goal of this study is to explore the interaction between age and the two treatment methods, we further conducted subgroup analysis on tumor size and number in people aged 65 and above based on DFS results. The results showed that MWA can provide HCC patients with statistically comparable oncological outcomes compared to LLR in different subgroups of size (3.1–4.0 cm or 4.1–5.0 cm) and number (single or multiple) (Supplementary Figure S3-6, Supplemental Digital Content 2, http://links.lww.com/JS9/B812). These results undoubtedly provide a more specific data reference for patients who meet the treatment conditions.

Safety analysis demonstrated that the rate of intraoperative blood transfusion in the LLR group was significantly higher than that in the MWA group, and LLR was related to the incidence of postoperative bleeding and hypoproteinemia, which objectively reflected that MWA was less invasive than LLR in elderly HCC patients. In the comparison of available data on time and economic costs, MWA was associated with shorter treatment duration, shorter hospital stay, and lower overall costs across all cohorts.

This study targeted the aging trend of HCC patients in China and focused on minimally invasive treatment of patients aged over 60 years with 3–5 cm HCC, providing a dynamic observation on the effects of MWA and LLR on survival and recurrence in three age cohorts for the first time. However, there are some limitations of this study. 1. As a retrospective study, despite the same matching variables and caliper values applied in each cohort, there may still be selection and information bias. 2. Since not all patients have undergone three-dimensional planning, precise assessment of specific tumor location, and burden was not performed. 3. No more pathological information could be obtained from patients in the MWA group to evaluate the degree of cirrhosis, thus, it was difficult to grasp the background of liver disease. 4. Since the etiology of HCC in China is mainly based on chronic viral hepatitis infection, whether the conclusions can be applied in other regions requires further evaluation. The above bottlenecks can only be solved in prospective cohort studies. 1. For example, the research design ensures the balance of the baseline of the research object. 2. Unified preoperative three-dimensional planning can visualize the adjacent relationship of tumors and estimate the volume ratio of liver to tumor. 3. With the informed consent of the patient, biopsy can be performed on the normal liver and tumor tissue of the patient to clarify the grading of cirrhosis and the pathological diagnosis of the tumor and to guide subsequent liver protection and antitumor treatment.

Conclusions

In summary, MWA was comparable to LLR in patients aged 65 years and older. MWA could be an alternative for the oldest old or the ill patients who cannot afford LLR, while LLR is still the first option of treatments for early-stage 3–5 cm HCC in capable elderly's. The lower incidence of postoperative bleeding and hypoproteinemia highlights the more minimally invasive nature of MWA. If further confirmed by prospective studies, this conclusion may provide a valid treatment option for HCC patients.

Ethical approval

Ethical approval for this study (S2019-348-01) was provided by the Ethical Committee of the Chinese PLA general hospital, Beijing, China on 26 December 2019.

Consent

Informed consent was exempted due to the retrospective nature and the use of deidentified images.

Author contributions

P.L. and J.Y.: conceptualization; Z.W. and Q.M.: data curation; H.Z. and Z.W.: statistical analysis and visualization; Z.W.: writing and editing. All authors contributed in treatment execution.

Conflict of interest disclosure

All authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

Research registration unique identifying number (UIN)

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Data availability statement

For scientific reasons, raw data may be obtained with the permission of the corresponding author.

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