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Microwave ablation of hepatocellular carcinomas in octogenarians

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Abstract

Aim: To evaluate wether it is safe and meaningful to treat octogenarians with microwave ablation for hepatocellular carcinoma. With an ageing population being healthier than previous generations, old limits for treating disease founded on patient age need to be revised. One of the most common tumour related death causes is hepatocellular carcinoma (HCC). With the development of minimally invasive therapies with curative potential, new ground is being broken offering treatments to older patients in the hope of achieving prolongation and better quality of life.

Methods: In this retrospective single centre study of patients having a first microwave ablation therapy for HCC in a national referral centre for ablative liver treatments, septuagenarians (n = 161, age 70-80) were compared with octogenarians (n = 32, age 80-90).

Results: Octogenarians selected for microwave ablation of HCC at a regional multidisciplinary team conference have similar outcomes as their younger control group. Survival, complications and length of stay are not different.

Conclusion: Octogenarians who are fit for ablative treatment of HCC should not be disqualified on grounds of age, recognising that this group has an obvious immortality, or lead-time, bias as well as a probable selection bias in part explaining their good results.

Keywords: Microwave, ablation, hepatocellular carcinoma, octogenarians, survival, complications

INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide and the fourth most common cause of cancer death according to the 2018 WHO report[1]. During the last 30 years, life expectancy, worldwide, has increased from 63 to 71.7 years with countries such as Japan and South Korea, as well as those in Western European and Northern America having a life expectancy of 80-84 years in 2015[2]. At present, a 70-year-old person in Sweden is expected to live 16.3 more years and a person of 80 has on average 9.2 years left[3].

Curative treatment of HCC is foremost surgical. Postoperative complications increase with age. In a UK study, patients over 75 had a 62% increase in risk of complications and a more than three-fold increased risk of one-year overall mortality compared to patients younger than 65. For one-year overall mortality, the risk was increased by 349% after surgery for colorectal cancer[4]. Leal *et al.*[5] investigated the impact of liver resection for colorectal liver metastases on octogenarians compared to younger patients in a matched cohort study and found twice the morbidity (19% *vs.* 9%) and a 90-day mortality of 7% *vs.* 0%. In a recent review by Cho *et al.*[6], curative intended treatments for hepatocellular cancer with resection or radiofrequency ablation (RFA) was found to be safe in selected patients over the age of 75[5], namely patients who generally had less severe underlying liver disease, were predominantly female and had more well-differentiated tumours, indicating that there was a clear selection bias when comparing the elderly with younger HCC patients. With careful selection, excellent results of resection can be achieved[7-9]. However, with increasing age, comorbidities amass and resective surgery is often not deemed appropriate and patients can be offered local ablative treatments with RFA instead without having age or comorbidities affecting outcome[10,11]. In a recent publication, octogenarians undergoing stereotactic RFA for primary liver tumours were compared to a younger control group using propensity score matching and no significant differences in terms of local recurrence, major complications and overall survival were found[12].

With microwave technology (MWA) entering the scene, with quicker energy delivery and larger ablation volumes compared to RFA[13], the present study aimed to evaluate the results of treating octogenarians with HCC using MWA in comparison with septuagenarians in a highly specialised centre in northern Europe.

METHODS

We retrospectively analysed all patients undergoing microwave ablation for HCC who were seventy years or older at first ablation in a single centre specialised in minimally invasive ablative treatments in Sweden, from June 2010 to December 2018. The collection and publication of data was approved by the regional ethics committee.

All patients were selected for ablative treatment for their HCC at the regional multidisciplinary team conference. Patients without cirrhosis or with cirrhosis without portal hypertension were typically firstly considered for resection, general condition permitting. For the others, with Child-Pugh grade below C and performance status 0-2 as well as with the possibility of curative treatment and largest tumour diameter below 30 mm, ablative treatment was the first choice. The diagnosis was based on radiological LIRADS criteria and not primarily on histology. Microwaves was the energy source of choice for ablative treatment. Tumour targeting was performed with computer-assisted technologies such as ultrasound fused with computed tomography (CT) images or with the aid of computer assisted CT-guided navigation technology (CAS-one, Cascination AG, Bern). Details on the set-up, ablation technique, energy devices and targeting technologies applied were described previously[14].

Patients were followed-up with CT or MRI imaging every three months for one year and according to the national surveillance guidelines[15]. Ablation site recurrence was defined as viable tumour tissue detected

on follow-up imaging within an area of 1 cm surrounding the ablation zone, applying the LIRADS criteria for HCC[16]. In the case of ablation site recurrence or new intrahepatic lesions on follow-up, patients were retreated with minimally invasive microwave ablation whenever possible.

Data on patient and tumour characteristics were extracted from the Swedish Liver registry[17]. Complications were classified according to the Clavien-Dindo classification[18], with major complication defined as a grade 3b or higher within thirty days of treatment. Data on tumour recurrence were extracted from patient's medical records. Overall survival (OS) was calculated from the day of the index treatment, with all patients being followed until death or censored on 15 October 2019.

Descriptive statistics was used to describe baseline characteristics with medians and range for non-normally distributed data. Categorical variables were expressed as total and percentages. Ratios were analysed with the χ^2-test. Overall survival was illustrated using Kaplan-Meier curves and differences in survival analysed with log-rank test. Factors influencing survival were analysed with the Cox proportional hazards method. All statistical computations were made with SigmaPlot 13.0 (Systat software, Inc, San Jose CA)

RESULTS

In total, 193 patients treated with MWA at the age of 70 or above were included in this study. Of these, 32 (17%) were 80 or above years of age and 161 (83%) were 70-80 years of age. Patient and tumour characteristics are outlined in Table 1.

In the group of octogenarians, there was less underlying liver disease with cirrhosis of various reasons (59% *vs.* 80%, $P = 0.021$) and the proportion of females was higher (34% *vs.* 19%, $P = 0.08$). In the other baseline characteristics, and somewhat fewer tumours treated. The age distribution is presented in Figure 1.

Major complications within one month occurred in seven (5%) of the septuagenarians and none of the octogenarians. These were one liver abscess that responded well to drainage and antibiotics, one hematoma, one patient with ascites that was drained, one with a pneumothorax that was evacuated, one patient had a coronary infarction one week after the ablation and one patient had a bleeding oral polyp a week after the ablation. The last developed progressive liver failure with intensive care needs, alas irreversible and died two months after the ablation.

There was no difference in OS between the two groups with a median survival time of 3.9 years for patients between 70 and 80 years of age and 4.3 years for octogenarians ($P = 0.416$). One-, three- and five-year OS were 89%, 59% and 38% (70-80 years of age) and 100%, 100% and 30% (octogenarians), respectively [Figure 2].

In the Cox proportional hazards model, no single analysed factor significantly influenced survival including gender, associated liver disease, ASA-score, Child-Pugh grade, number of tumours treated and largest tumour treated.

Local ablation site recurrence occurred in 19 % (36/194) and 26% (50/194) had a new tumour in another part of the liver within one year of follow-up.

The distribution of repeat treatments is shown in Figure 3. Patients were retreated when there was a chance of cure, not as an upfront palliative measure.

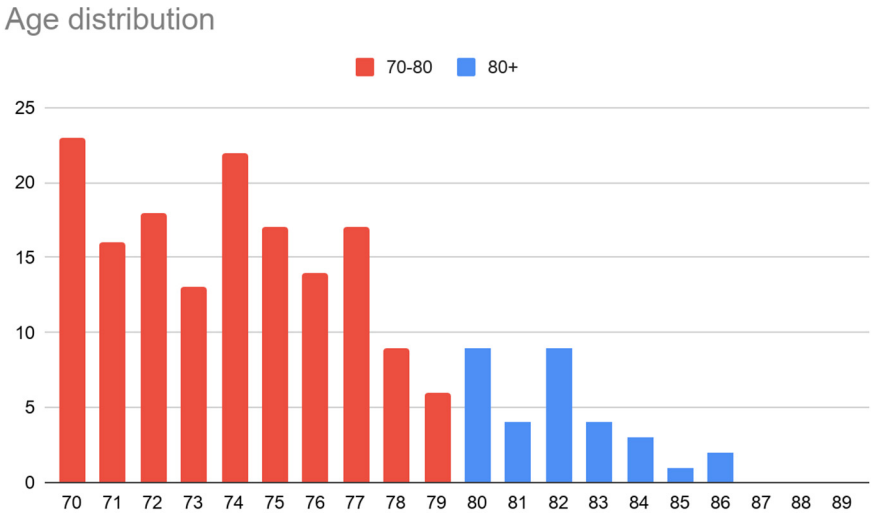
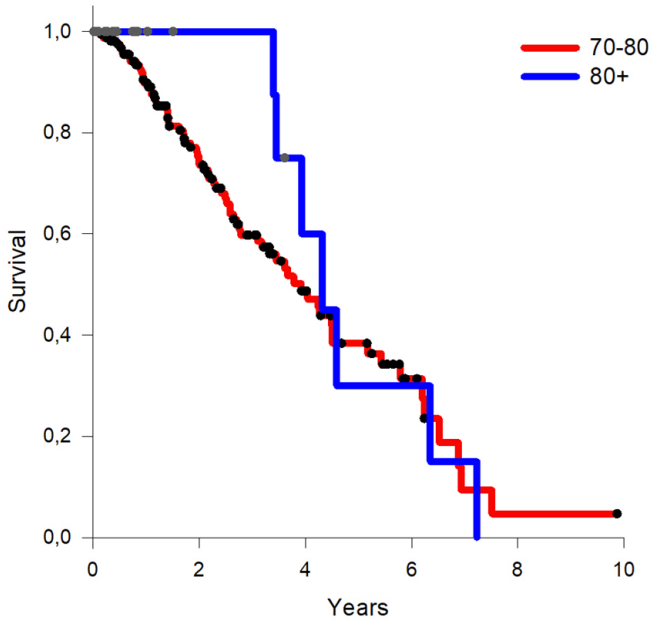


Figure 1. Age distribution of subjects in the study. The Y-axis is the number of patients per age group and the X-axis the age groups

Table 1. Baseline and outcome characteristics

	80+	%	70-80	%	*P*
n	32		161		
Age [median (min-max)]	74.2 (70-79.6)		82.3 (80.1-86.3)		
Male	21	66%	131	81%	0.08
Associated liver disease	19	59%	129	80%	0.021
Alcohol	8	25%	63	39%	0.189
Hemochromatosis	1	3%	5	3%	NS
Hepatitis B	0	0%	4	2%	NS
Hepatitis C	1	3%	34	21%	0.016
NASH	5	16%	25	16%	NS
Porfyria	1	3%	2	1%	NS
Child-Pugh					
A	24	75%	114	71%	NS
B	4	13%	18	11%	NS
C	0	0%	0	0%	NS
Missing	4	13%	28	17%	NS
MELD [median (min-max)]	6.58 (0.86-22.78)		6.26 (0-19.32)		NS
ASA					
1	0	0%	2	1%	NS
2	7	22%	39	24%	NS
3	21	66%	93	58%	NS
4	4	13%	25	16%	NS
Number of tumours					
1	20	63%	88	55%	NS
2	6	19%	34	21%	NS
3+	6	19%	36	22%	NS
Max diameter [median (min-max)]	22 (11-37)		20 (8-58)		NS
Clavien-Dindo class					
0-1	28	84%	142	88%	NS
2	4	13%	12	7%	NS
3a	0	0%	5	3%	NS
3b	0	0%	1	1%	NS
4a	0	0%	1	1%	NS
4b	0	0%	0	0%	NS
5	0	0%	0	0%	NS
Postop stay [median (min-max)]	1 (0-5)		1 (0-32)		NS
Number of subsequent liver treatments	1 (1-6)		2 (1-7)		NS

Baseline characteristics and complications following microwave ablation for hepatocellular carcinoma in elderly patients. Only associated liver disease reached statistical significance with a *P*-value < 0.05. NASH: Non Alcohol Steato Hepatitis; MELD: Model for Endstage Liver Disease; ASA: American Society of Anaesthetists physical status classification



Octogenarians	32	4	2	0
Septuagenarians	86	30	10	2

Figure 2. Overall survival after a first microwave ablation of hepatocellular carcinoma in octogenarians compared to septuagenarians

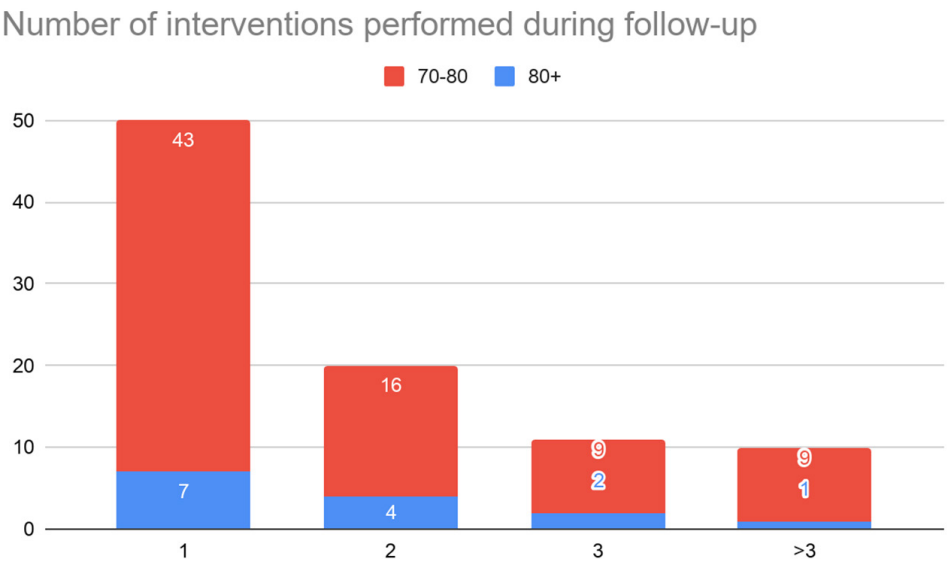


Figure 3. Number of interventions performed during follow-up of the patient cohort grouped into the two age groups. The y-axis represents the number of patients and the x-axis the different strata of interventions

DISCUSSION

The presented data show that microwave ablation of HCC in selected octogenarians can be performed with low morbidity and with results that are equal to those for septuagenarians, which was the primary aim of the study.

This is well in line with previous findings by Shen *et al.*[10] and Zhang *et al.*[11] offering a potentially curative treatment for octogenarians not deemed fit for surgical resection or as a first-line therapy.

Survival in the presented cohort is well comparable to results presented in a meta-analysis of elderly patients resected for HCC by Cho *et al.*[6], but with much shorter length of stay and much fewer complications, where, typically, resected elderly patients stay for 9-18 days in hospital and with 13%-36% having postoperative complications. In a US study from 2012 on RFA[19], the postoperative mortality was worse, as was survival with 72% surviving the first year and 39% and 34% at three and five years compared to the present study's 100%, 69% and 40%, respectively, for the octogenarian group, numbers that are somewhat inferior to what Takahashi *et al.*[20] presented. Numbers are difficult to compare as underlying causes of HCC and expected life span varies greatly among the US, Japan and Sweden.

In the present study, the mean age in the older cohort was 82 with a median survival of 4.3 years and the younger cohort with a mean age of 74 had a median survival of 3.9 years. This is considerably shorter than the average life expectancy for a 74-year-old (13 years) or an 82-year-old (8 years) in Sweden[21].

Selection bias is an obvious disadvantage when analysing this kind of dataset. Associated liver disease and hepatitis C was more prevalent in the younger group.

The small size of the octogenarian cohort could easily mask a Type 2 error. On the other hand, there is the obvious problem with immortality bias as the octogenarians have by necessity survived until 80 and are thus a selected group with a slightly higher life expectancy. This could perhaps in part explain the excellent three-year survival of 100% in that cohort.

In conclusion, as the population steadily has a greater life expectancy, the indications for treating tumours in older and healthier age groups becomes necessary. The results of the present study indicate that ablating hepatocellular carcinomas in octogenarians can safely be performed with good results if no obvious contraindication is present.

DECLARATIONS

Authors' contributions

The author contributed solely to the article.

Availability of data and materials

The data source is a local prospective database where all microwave ablations has been recorded since june 2010.

Financial support and sponsorship

None.

Conflicts of interest

The author declared that there are no conflicts of interest.

Ethical approval and consent to participate

This retrospectiv study was approved by the regional ethics board in preparation of a previous study.

Consent for publication

Not applicable.

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