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ORIGINAL ARTICLE

Effect of Age (over 75 Years) on Postoperative Complications and Survival in Patients Undergoing Hepatic Resection for Hepatocellular Carcinoma

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Abstract

Background Thanks to technical advancement in surgery for hepatocellular carcinoma (HCC), hepatic resection (HR) for elderly HCC patients has become safer. However, elderly patients may have shorter long-term survival after surgery if compared with younger patients because of their expected life span. The aim of the present study was to evaluate clinical outcomes and safety after HR in HCC patients aged >75 years (older) compared with HCC patients aged <75 years (younger).

Method One hundred sixty-eight patients who underwent HR for HCC from 1998 to 2015 in our Center were analyzed using a prospective database. Complications, disease-free survival rates, and cumulative survival rates were compared between the two groups.

Results During the immediate postoperative period, no differences were found about liver-related complications, hospital stay and 90-day mortality. However, older patients had more complications in class II or higher (Clavien classification) ($p = 0.017$). Although disease-free survival in both groups was similar ($p = 0.099$), overall survival was worse in the elderly group ($p = 0.024$). On multivariate analysis, only age ≥75 years was significantly related to overall survival.

Conclusion If elderly patients with liver cirrhosis and HCC are appropriately selected and evaluated, they might have favorable prognoses after HR.

Keywords Hepatocellular carcinoma · Hepatic resection · Liver cirrhosis

Introduction

The high prevalence of hepatocellular carcinoma (HCC) and prolonged life expectancy in the world population has led to an increased number of elderly patients being considered for treatment. It is widely accepted that the risk of developing HCC is age-dependent.[1] Therefore, in Western countries, the diagnosis of HCC is more frequent in patients aged ≥70/75 years.[2] Liver transplantation is probably the treatment of choice for HCCs of less than 5 cm, but the lack of donors limits its application.[3,4] For these reasons, it is necessary to provide further therapy options, especially for elderly patients. International guidelines do not specifically address whether the management and outcomes of HCC in elderly patients are different from those observed in their younger counterpart.[2,5,6] Thanks to technical advancement in surgery for HCC, hepatic resection (HR) for elderly HCC patients has become safer.[7] Although there is no specific age limitation for surgery for HCC, elderly patients may have shorter long-term survival after surgery if compared with younger patients because of their expected life span.[8] In general, elderly patients have a high incidence of comorbidities and they could be considered high-risk patients for HR; therefore, HR is less feasible in elderly patients than in younger patients. In this situation, alternative treatments as radiofrequency ablation (RFA) could be an acceptable solution in selected patients.[9]

The aim of the present study was to evaluate clinical outcomes and safety after HR in HCC patients aged >75 years (older) compared with HCC patients aged <75 years

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(younger). In addition, we also explored the differences of liver conditions and tumor characteristics between the elderly patients and younger patients, aiming to analyze the specific factors affecting the long-term survival between different-age patients.

Materials and Methods

All consecutive patients who underwent HR for HCC (confirmed histopathologically in the resected specimen) from 1998 to 2015 in our Center were analyzed using a prospective database. All patients were assessed for disease staging with a pre-established protocol until 2000[10]; Barcelona Clinic Liver Cancer (BCLC) staging was retrospectively assessed in all patients enrolled before its accessibility.[11]

A multidisciplinary team, which includes surgeons, radiologists, and hepatologists, determined patient's eligibility for an invasive treatment. Criteria for staging and treatment evolved over-time. The diagnosis and staging of HCC was based on the appropriate imaging studies including triple-phase computed tomography (CT) and/or magnetic resonance according to the Barcelona-2000 European Association for the Study of the Liver (EASL) Conference, and histological assessment when required.[12] Eligibility for liver transplantation (according to age, etiology, Child-Pugh, and MELD score) or HR was evaluated. Until 2012 (when the modified BCLC therapeutic algorithm was published[5]), HR was proposed according to BCLC and AASLD guidelines: patients who had a single lesion can be offered surgical resection if they had cirrhosis with preserved liver function. Portal hypertension was not considered a contraindication in all cases.[13] Unlike the BCLC treatment protocol,[5] in the time interval of this study, we did not consider nodule size and number as absolute exclusion criteria from surgical treatment.

In this series, the residual liver function was evaluated using the Child-Pugh classification[14] and MELD (model for end-stage liver disease) score.[15] Comorbidity was assessed using the Charlson's index[16]: according to this score, patients were categorized as having slight (<2) or severe comorbidities (>3). Upon referral, laboratory tests including complete blood cell count, coagulation profile, liver functions, plasma levels of alpha-fetoprotein (AFP), and a chest X-ray were performed.

Patients were included in the present cohort analysis if they fulfilled all of the following criteria on presentation: no previous HR for HCC, single lesion and tumor size less than 5 cm, Child-Pugh class A, and BCLC stage classes A1 to A3. Patient characteristics and follow-up were recorded in a dedicated database.

Treatment

All surgical procedures included intraoperative ultrasonography (IOUS) examinations with intraoperative or laparoscopic probes equipped with a multi-frequency linear-array transducer. Similarly to the histological criteria described by Yamashita et al.,[17] IOUS definition of microinvasive HCC in the Italian subgroup was based according to the presence of portal vein, hepatic vein, bile duct infiltration, and/or intrahepatic metastasis, as previously described.[18] Until 1998, all HR were performed through a subcostal incision. Laparotomy was performed using a standardized technique.[19] Since 1998, the laparoscopic approach has been used in selected patients for limited resection of peripheral HCC <5 cm: laparoscopic HR was the first choice in patients with HCC lesions limited to the left lateral section of the liver or segments IVB, V, and VI.[20,21] Tumor grade was assessed using the system outlined by Edmondson and Steiner,[22] and was based on the area showing the highest grade.[23]

Assessment and Follow-up

Postoperative mortality was defined as occurrence of death within 90 days after treatment. Severity of postoperative morbidity was defined according to the Dindo-Clavien classification of surgical complications.[24] Postoperative liver decompensation was defined by the presence of increased international normalized ratio (INR; or need of clotting factors to maintain normal INR) and/or hyperbilirubinemia and/or ascites and/or encephalopathy.[25]

Liver US and CT (and/or MRI) were performed within 3 months of treatment to assess the response to HR. Patients were further followed locally by an expert hepatobiliary team every 6 months. Physical examination, liver function tests, serum AFP level, liver US (twice a year), and CT (twice a year) were included. Liver decompensation was defined by the presence of ascites, acute encephalopathy, and/or jaundice (bilirubin level more than 3 mg/dl on postoperative biochemical examinations). Follow-up time was defined as the number of months from surgical treatment of HCC to death, or last contact with the patient.

Statistical Analysis

The primary outcome was overall survival. Comparison of continuous variables between and within groups was performed using the Mann–Whitney *U* test and the Wilcoxon matched pairs test. Continuous variables were also compared by one-way analysis of variance (ANOVA) for normally distributed variables between staging groups. Comparison of proportions was performed with the Fisher exact probability test. The Bonferroni correction for multiple comparisons was applied. Data following a normal distribution were expressed as mean ± standard deviation, if data were non-parametric, median and interquartile range values were reported.

To identify patient variables correlated with complications classified as Clavien–Dindo grade 2 or higher, chi-square tests were performed. Factors that emerged in the entire cohort with a p value lower than 0.05 were considered to be significant baseline covariates. They were adjusted by multivariate logistic regression analyses using the forced entry method.

The univariate association of each parameter with survival rates was estimated by comparing actuarial curves according to the Kaplan-Meier product-limit method and log-rank test, which more accurately characterizes the final outcome. The test trend of the survivor function across the ordered groups was also calculated: a relative hazard using the Cox regression-based test was used to evaluate the weight of each subgroup in determining significance.

Initial evaluation and subsequent follow-up data were collected in a dedicated database (FileMaker Pro for Macintosh; FileMaker Inc., Santa Clara, CA, USA) and subsequently analyzed (Intercooled Stata 14.1 for Macintosh, StataCorp., College Station, TX, USA).

The hospital's ethics committee approved the study, and written informed consent for recording and analysis of data was obtained from all patients.

Results

Patients

According to inclusion criteria, 168 out of 341 patients submitted to HR in the same period were included in this analysis: 115 patients (68%) were included in the younger group while the other 53 (32%) patients comprised the older group. Differences in characteristics of patients between the two groups are shown in Table 1. In particular, younger patients showed prevalence of males (77 vs. 57%), higher BCLC staging (A3: 19 vs. 4%), and more esophageal varices (30 vs. 15%). These findings of liver dysfunction are confirmed by the biochemical data, even if all patients were classified as liver function in Child-Pugh A class: younger patients had lower platelets values, higher total bilirubin levels, and higher INR values.

With regards to the characteristic of treatments, 89 younger patients (85 segmentectomies, 4 right hepatectomies) (77%) and 41 older patients (39 segmentectomies, 2 right hepatectomies) (77%) underwent an anatomical resection, while 26 younger patients (23%) and 12 older patients (23%) a non-anatomical resection ($p = 0.995$). In 31 younger patients (27%) and in 14 older patients (26%), a laparoscopic HR was attempted (10% of younger cases and 14% of older patients were converted to laparotomy due to hypercapnia or oncological criteria; $p = 0.287$). Pringle maneuver was used in 62 younger patients (54%) and in 25 older patients (47%; $p = 0.385$). Furthermore, IOUS detected new HCC nodules in five patients (4%) in the younger group and in three patients (6%) in the older group ($p = 0.189$).

Morbidity and Mortality

During the immediate postoperative period, signs of liver decompensation (presence of ascites, encephalopathy, bilirubin levels more than 3 mg/dl) were observed in 25 younger patients (21.7%) and in 15 older patients (28.3%; $p = 0.353$), without influencing postoperative hospital stay (Table 2). However, examining all complications according to Clavien classification, older patients had more complications in class II or higher than younger group ($p = 0.017$).

Univariate analyses showed age ≥75 years, HCV etiology, platelets count inferior to 100.000/mm^3, albumin values inferior to 3.5 g/l, ALT values superior to 52 U/l, operating time superior to 200 min, HR through a open access, Pringle maneuver, estimated blood loss exceeding 200 ml, and blood transfusion during the hospital stay to be characteristics possibly associated with complications classified as Clavien–Dindo grade 2 or higher, with p values higher than 0.05. Multivariate logistic regression analyses demonstrated age ≥75 years, platelets count inferior to 100.000/mm^3, and estimated blood loss exceeding 200 ml as the only independent risk factors (Tables 3 and 4).

In any case, no statistical differences were found for 90-day mortality. Three (2.6%) patients in younger group and four (7.5%) patients in older group died ($p = 0.137$): two for liver failure and one for sepsis in younger patients and two for cardiac failure and two for sepsis in older patients.

Survival and HCC Recurrences

During a median follow-up period of 47 months (IR 24–65.8), overall survival rates at 3 and 5 years were respectively 65 and 46% in the elderly group and 82 and 60% in the younger group (Fig. 1a) ($p = 0.024$).

There was no significant difference in the distribution of causes of death between the two groups. Deaths secondary to cirrhosis or HCC were 19 (36%) in the elderly group and 39 (34%) in the younger group ($p = 0.806$), while deaths unrelated to cirrhosis including those for cardiovascular disease and for other malignant diseases were 11 (21%) and 13 (11%), respectively ($p = 0.104$).

Disease-free survival (DFS) rates at 3 and 5 years were respectively 47 and 22% in the elderly group and 57 and 35% in the younger group (Fig. 1b) ($p = 0.099$). Treatments for HCC recurrences occurred in 42 cases (72%) of younger group and in 18 cases (67%) of older group ($p = 0.588$).

Table 5 shows the survival statistics calculated according to patient characteristics, tumor features, and operative procedures. Age ≥75 years, Child-Pugh class A6, MELD >9, albumin ≤3.5 g/l, ALT ≥52 U/l, CHE ≤5900 U/l, Pringle maneuver, and blood transfusion were the only factors significantly associated with survival on univariate analyses. On multivariate analysis, only age ≥75 years was significantly related to overall survival.

Table 1 Demographic and clinical characteristics of all patients enclosed in the study

	Younger ($n = 115$)	Older ($n = 53$)	p value
Male sex	89 (77%)	30 (57%)	**0.006**
Age (years)	66 ± 7.4	79 ± 3.2	**0.0001**
(median; IR)	(69; 62–72)	(78; 77–82)	
Cirrhosis etiology			0.426
HCV	80 (70%)	38 (72%)	
HBV	20 (17%)	5 (9%)	
Other	15 (13%)	10 (19%)	
Child-Pugh Class A5	84 (73%)	41 (77%)	0.551
Class A6	31 (27%)	12 (23%)	
MELD score	8.5 ± 2.3	8.2 ± 1.7	0.431
(median; IR)	(8; 7–9)	(7; 7–9)	
Charlson's index (≥3)	27 (23%)	14 (26%)	0.680
BCLC[3]			**0.023**
A1	68 (59%)	40 (75%)	
A2	25 (22%)	11 (21%)	
A3	22 (19%)	2 (4%)	
Esophageal varices	35 (30%)	8 (15%)	**0.034**
Diabetes	30 (26%)	16 (30%)	0.081
Recurrent HCC	11 (10%)	9 (17%)	0.168
HCC lesion diameter (mm)	31.1 ± 11.5	30.7 ± 11.4	0.837
(Median, IR)	(30; 21–39)	(29; 22.5–38.5)	
IOUS MI HCC	53 (46%)	30 (57%)	0.205
IOUS vascular infiltration	50 (43%)	28 (53%)	0.259
Platelet count (×100/mm^3)	123 ± 55	142 ± 59	**0.038**
(Median, IR)	(114; 81–160)	(140; 101–179)	
Total bilirubin (mg/dl)	1.1 ± 0.43	0.92 ± 0.36	**0.025**
(Median, IR)	(0.99; 0.76–1.4)	(0.885; 0.7–1.07)	
Serum albumin (g/l)	3.98 ± 0.52	3.99 ± 0.53	0.859
(Median, IR)	(4; 3.6–4.3)	(4.09, 3.6–4.35)	
Prothrombin time (INR)	1.11 ± 0.11	1.06 ± 0.07	**0.0063**
(Median, IR)	(1.09; 1.03–1.17)	(1.05; 1.01–1.11)	
AST (U/l)	62 + 49	62 + 41	0.437
(Median, IR)	(51; 31–92)	(48; 30–77)	
ALT (U/l)	75 + 63	64 + 47	0.257
(Median, IR)	(50; 33–95)	(47; 29–78)	
CHE (U/l)	6285 + 2436	6212 + 1919	0.8488
(Median, IR)	(5872; 4549–7763)	(6130; 5185–7418)	
ALP (U/l)	173 + 127	163 + 95	0.617
(Median; IR)	(130; 85–235)	(130; 91–209)	
alpha-fetoprotein (ng/ml)	120 + 464	117 + 288	0.967
(median, IR)	(8.1; 4.1–37.9)	(5.75; 3.12–47.5)	

Significant results are presented in bold

IR interquartile range, *HCV* hepatitis C virus, *HBV* hepatitis B virus, *MELD* model for end-stage liver disease, *BCLC* Barcelona Clinic Liver Cancer, *HCC* hepatocellular carcinoma, *IOUS* intraoperative ultrasound, *MI* microinvasive, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *CHE* cholinesterase, *ALP* alkaline phosphatase

Discussion

Despite improved surgical results, HR is still a complex surgical procedure with a not-negligible morbidity rate in patients with liver cirrhosis.[26] The aim of the present study was to analyze the influence of age on the outcome of HR in patients with HCC and liver cirrhosis.

The risk of developing HCC is known to be age-dependent, and patients aged ≥75 years with liver cirrhosis may develop HCC. The increased longevity of the population means that

Table 2 Postoperative results

	Younger ($n = 115$)	p value	Older ($n = 53$)
Postoperative mortality: 90-day	3 (2.6%)	0.137	4 (7.5%)
Blood transfusions (U)	7	0.394	5
Patients transfused	7 (6.1%)	0.434	5 (9.4%)
Liver decompesation (ascites, encephalopathy, jaundice, etc.)	25 (21.7%)	0.353	15 (28.3%)
General complications	40 (34.8%)	0.193	24 (45.3%)
General complications (Dindo-Clavien ≥2)	20 (17.4%)	**0.017**	18 (33.9%)
General complications after LPS HR (Dindo-Clavien ≥2) (45 pts)	3 (9.7%)	0.649	2 (14%)
General complications after open HR (Dindo-Clavien ≥2) (123 pts)	17 (20%)	**0.015**	16 (41%)
Postop. hosp. stay (dd)	8.7 ± 4.6	0.538	9.2 ± 5.5

Significant results are presented in bold

HR hepatic resection, *LPS* laparoscopic, *Postop. hosp.* postoperative hospital

more elderly HCC patients are to be expected in the forthcoming future.[2] The management of elderly patients with HCC is significantly more complicated than that of younger ones because of comorbidities including cardiovascular disease, respiratory disease, diabetes mellitus, and renal dysfunction. Furthermore, current guidelines for the management of HCC do not satisfy strategies according to age.[6,11]

In the last years, with technical advancement in hepatic surgery, HR for elderly HCC patients has become safer. Although there is no specific age limitation for HCC surgery, elderly patients may have shorter long-term survival as compared with younger patients because of their expected life span.[8] On the other hand, elderly patients have a high incidence of comorbidities and are considered high-risk patients; therefore, HR may be less feasible in elderly patients than in younger patients in several aspects. For this situation, a percutaneous thermoablation treatment may be an acceptable alternative. However, whether elderly patients with HCC treated with ablative therapies have comparable clinical outcomes as compared with younger patients remains controversial.[27] As suggested in a previous article which used a Markov model comparing RFA with HR,[28] in patients older than 75 years, RFA resulted to be the best treatment option because the

Table 3 Preoperative factors associated with complications classified as Clavien–Dindo grade ≥2

Variables	Univariate OR (95% CI)	p value	Multivariate OR (95% CI)	p value
Age ≥75 years	2.44 (1.08–5.48)	**0.017**	3.68 (1.44–9.39)	**0.006**
Female	1.58 (0.67–3.60)	0.234		
HCV	2.73 (1.01–8.54)	**0.032**	1.25 (0.36–4.33)	0.721
Child A6	1.73 (0.72–4.03)	0.166		
Varices	1.73 (0.72–4.03)	0.166		
BCLC A2-A3	1.88 (0.84–4.19)	0.088		
MELD >9	1.63 (0.64–3.94)	0.242		
Diabetes	1.11 (0.45–2.60)	0.806		
Charlson index ≥3	1.36 (0.54–3.24)	0.459		
Recurrent HCC	0.84 (0.19–2.84)	0.765		
Plt ≤100 (×100/mm^3)	2.44 (1.09–5.46)	**0.016**	3.48 (1.31–9.27)	**0.012**
INR ≥1.2	1.02 (0.27–3.18)	0.971		
Bilirubin ≥1 mg/dl	1.58 (0.70–3.52)	0.223		
Albumin ≤3.5 g/l	2.47 (0.99–5.94)	**0.026**	1.07 (0.38–3.01)	0.902
ALT ≥52 U/l	3.47 (1.50–8.41)	**0.001**	2.27 (0.79–6.51)	0.125
CHE ≤5900 U/l	2.05 (0.91–4.72)	0.058		

Significant results are presented in bold

HCV hepatitis C virus, *BCLC* Barcelona Clinic Liver Cancer, *MELD* model for end-stage liver disease, *HCC* hepatocellular carcinoma, *Plt* platelets, *INR* international normalized ratio, *ALT* alanine aminotransferase, *CHE* cholinesterase

Table 4 Intraoperative factors associated with complications classified as Clavien–Dindo grade ≥2

Variables	Univariate OR (95% CI)	*p* value	Multivariate OR (95% CI)	*p* value
Operating time >200 min	2.30 (1.01–5.44)	**0.030**	1.27 (0.43–3.73)	0.659
Open resection	2.93 (1.02–10.28)	**0.031**	1.76 (0.50–6.26)	0.381
HR ≥2 segments	2.04 (0.49–7.29)	0.221		
Pringle maneuver	2.77 (1.20–6.71)	**0.009**	1.37 (0.45–4.19)	0.583
Intraop. blood loss >250 ml	4.68 (1.94–12.08)	**0.001**	3.55 (1.23–10.27)	**0.019**
Blood transfusion	5.64 (1.41–23.85)	**0.002**	1.67 (0.38–7.34)	0.495

Significant results are presented in bold

HR hepatic resection, *Intraop* intraoperative

risks of local recurrent disease have less influence on the overall survival of the population while the perioperative risks of HR increase significantly. On the other hand, Yazici et al.[29] reported a study of comparison between laparoscopic HR and laparoscopic RFA in elderly patients (aged over 65 years): perioperative morbidity, overall survival, and disease-free survival were similar, but laparoscopic RFA suffered a higher rate of local recurrences ($p = 0.002$).

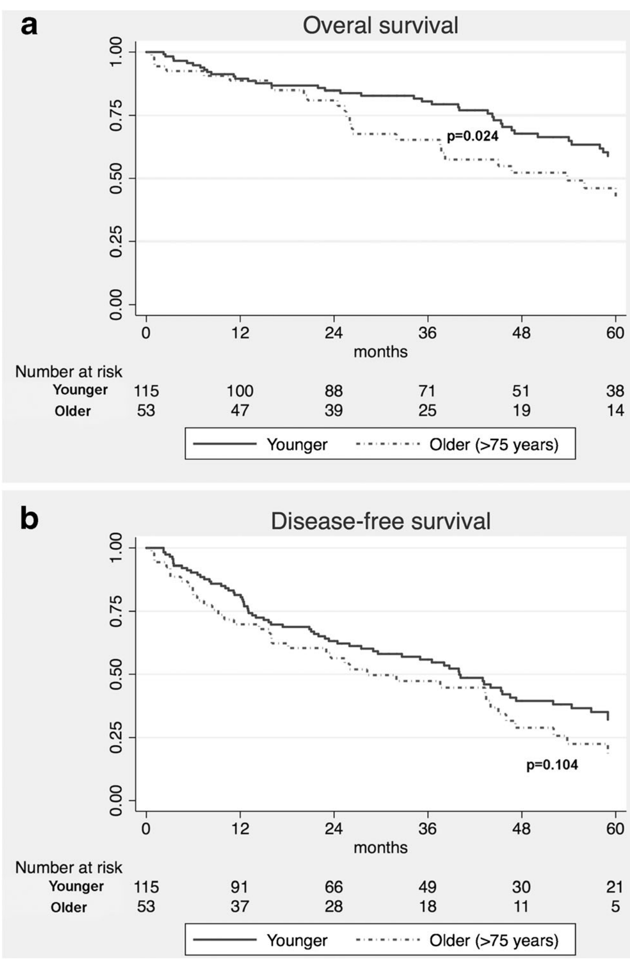

Fig. 1 **a** Cumulative overall survival after liver resection, depending on patient age (cutoff, 75 years). **b** Cumulative disease-free survival after liver resection, depending on patient age (cutoff, 75 years)

In the present study, rates of morbidity and mortality were slightly higher, without a statistical significance, in elderly patients than in younger patients. This finding could be the consequence of the fact that preoperative comorbidities were similar in both age groups, probably because the younger group was not so young with a median age of 69 years. However, more severe complication rates (Dindo-Clavien ≥2) were significantly higher in the elderly group: the concept of "frailty" in a comprehensive geriatric assessment of patients awaiting surgery has drawn deep attention.[30] We do not currently have an established approach for evaluating frailty before the operation: Charlson's index was similar in the two groups and it did not influence postoperative complications rates (see Table 3). Careful perioperative care for elderly patients is essential for improving short-term outcomes of surgery, above all for elderly patients with a "frailty" condition. For patients with resectable HCC, the tolerance of the elderly without preoperative comorbidities or with well-controlled preoperative comorbidities to HR was good enough and similar to that of nonelderly ones.[30]

Another important point that needs to be stressed was that only few patients (3.6%) with major HR (i.e., >3 Couinaud's segments) were included for analysis. It remains uncertain if the same short-term benefits could also be extended if we increased in the elderly the number of major HR that involved a larger parenchymal transection area and longer operating time.[31] Furthermore, about 27% of patients were operated through a laparoscopic approach and it is possible that the short-term benefits of laparoscopic surgery in HR as seen in younger patients continued to be evident in patients with advanced age. If laparoscopic HR should be associated with fewer medical-related morbidity (it is evident in the univariate analysis in Table 2), this would have to be strongly considered in the choice of operative approach in elderly patients with comorbid illnesses.[29,32]

The age of the patient at the time of diagnosis has an important prognostic value in certain cancers. For example, survival is better among younger patients with bladder cancer and papillary thyroid cancer when compared with older

Table 5 Factors associated with overall survival

Variables	Univariate RR (95% CI)	*p* value	Multivariate HR (95% CI)	*p* value
Age: ≥75 vs. <75 years	1.68 (1.06–2.67)	**0.024**	2.08 (1.29–3.36)	**0.003**
Sex: female vs. male	1.28 (0.81–2.02)	0.289		
Etiology: HCV vs. no-HCV	1.17 (0.72–1.90)	0.531		
Child-Pugh: A6 vs. A5	2.34 (1.49–3.70)	**0.0002**	1.71 (0.89–3.28)	0.107
Varices: yes vs. no	1.11 (0.67–1.85)	0.685		
BCLC: A2-A3 vs. A1	1.57 (0.99–2.47)	0.051		
MELD: >9 vs. ≤9	1.92 (1.15–3.19)	**0.011**	1.27 (0.68–2.36)	0.455
Diabetes: yes vs. no	0.99 (0.59–1.63)	0.962		
Charlson index: ≥3 vs. <3	1.34 (0.82–2.18)	0.236		
Recurrent HCC: yes vs. no	0.86 (0.43–1.71)	0.672		
Platelets: ≤100 vs. >100 (×100/mm^3)	1.31 (0.83–2.05)	0.245		
INR: ≥1.2 vs. <1.2	0.92 (0.47–1.79)	0.811		
Bilirubin: ≥1 vs. <1 mg/dl	1.14 (0.72–1.80)	0.579		
Albumin: ≤3.5 vs. >3.5 g/l	2.72 (1.70–4.33)	**0.0001**	1.75 (0.95–3.24)	0.072
ALT: ≥52 vs. <52 U/l	1.68 (1.08–2.62)	**0.021**	1.39 (0.87–2.22)	0.173
CHE: ≤5900 vs. >5900 U/l	1.66 (1.05–2.61)	**0.027**	1.01 (0.58–1.75)	0.967
AFP: >20 vs. ≤20 ng/ml	1.07 (0.67–1.71)	0.781		
Operating time: >200 vs. ≤200 min	1.22 (0.79–1.88)	0.378		
Open resection	1.17 (0.65–2.14)	0.597		
HR: ≥2 vs. <2 segments	0.55 (0.22–1.39)	0.199		
Pringle maneuver: yes vs. no	1.81 (1.15–2.85)	**0.009**	1.56 (0.94–2.58)	0.082
Intraop. blood loss: >250 vs. ≤250 ml	1.33 (0.86–2.06)	0.193		
IOUS microinvasive pattern: yes vs. no	1.27 (0.82–1.95)	0.284		
IOUS vascular microinfiltration: yes vs. no	1.09 (0.71–1.68)	0.679		
IOUS maximum HCC diameter: >20 vs. ≤20 mm	1.61 (0.95–2.75)	0.076		
Blood transfusion: yes vs. no	2.19 (1.14–4.21)	**0.015**	0.85 (0.36–2.01)	0.711

Significant results are presented in bold

HCV hepatitis C virus, *BCLC* Barcelona Clinic Liver Cancer, *MELD* model for end-stage liver disease, *HCC* hepatocellular carcinoma, *INR* international normalized ratio, *ALT* alanine aminotransferase, *CHE* cholinesterase, *AFP* alpha-fetoprotein, *HR* hepatic resection

patients.[33,34] In contrast, survival for colorectal, breast, and gastric cancers is worse among young patients when compared with older patients.[35-37] With regard to HCC, several studies have reported no difference in outcome when comparing HHC patients aged ≥75 years with ones aged <75 years.[26,30,38–41] Thus, there remains considerable controversy as to whether age influences the prognosis. In this study, although DFS in the elderly group was similar to that of the control group, overall survival was worse in the elderly group than in the control group, although the factors that affected DFS and overall survival in the two groups were similar. The incidence of deaths unrelated to cirrhosis or HCC during the follow-up periods was equal to that in the younger group. These results might indicate that preoperative evaluations for the elderly with comorbid illness and patient selection were adequate in our program.

Multivariate analysis confirmed that age is the only prognostic factor for overall survival. Table 6 shows the studies including patients older than 75 years: no differences in survival were found except for our series. In our study, the mean age of elderly group is very high (79 years) and it is evident that elderly group has similar preoperative comorbidities and a better BCLC staging in comparison to younger patients, while important preoperative differences between the selected studies must be outlined. Furthermore, the importance of age is confirmed by a survival analysis using a cutoff of 70 years in our series: no statistical differences were found ($p = 0.8958$) (Fig. 2). On the other hand, Cucchetti et al.[8] showed that for a comprehensive interpretation of the true potential benefit obtained from HR for older patients, survival after surgery should be interpreted within the frame of the life expectancy of individuals who did not develop liver cirrhosis and HCC: elderly patients (aged over 70 years) achieved the lowest number of years of life lost, and this supports the practice of surgery in the elderly.

We believe that the main strength of our study is that, compared with previous studies, hepatic resection could be performed in patients aged over 75 as safely as in younger patients. However, there are certain limitations in this study that could influence the results. Firstly, the retrospective nature makes this

Table 6 Previous studies regarding comparison of clinical outcomes in younger (Y) and elderly (E) patients (aged over 75 years) treated with surgical resection for hepatocellular carcinoma (HCC)

Authors	Year	Mean age		Preoperative findings	OS		DFS	
		Y	E		Y	E	Y	E
Oishi	2009	62	77.5	Y: poorer liver function E: more aggressive tumor	81% (3-year)	77% (3-year)	46% (3-year)	43% (3-year)
Ide	2013	63.7	78	Similar preop. liver function/HCC E: higher rate of comorbidities	68% (5-year)	59% (5-year)	35% (5-year)	34% (5-year)
Nishikawa	2013	63	78.2	Y: more aggressive tumor E: higher rate of comorbidities	77.5% (3-year)	73.3% (3-year)	39.8% (3-year)	38.8% (3-year)
Taniai	2013	62.7	76	Similar preoperative findings	46.6% (5-year)	40.2% (5-year)	21.5% (5-year)	30.8% (5-year)
Liu	2014	59.2	78.9	Y: slight poorer preop. liver function/HCC[a]	66% (5-year)	61% (5-year)	–	–
Kishida	2015	64	77	Y: better renal function E: better performance status	–	–	33% (5-year)	25% (5-year)
Personal	2016	66	79	Similar preop. comorbidities E: better BCLC staging	82%* (3-year) 60%* (5-year)	65%* (3-year) 46%* (5-year)	57% (3-year) 35% (5-year)	47% (3-year) 22% (5-year)

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*$p = 0.024$

[a] After propensity score matching analysis

study vulnerable to potential bias. Patients were included in the present cohort analysis if they fulfilled all of the inclusion criteria. However, the older group had a better BCLC staging than younger patients and this could have influenced the rates of hepatic complications. Secondly, our study was based on a relatively small patient number treated at a single center, and therefore, it is necessary to investigate a larger number of subjects at multiple centers as the next step to confirm our findings. Thirdly, the long period of patients' recruitment could influence the selection criteria, above all for elderly group.

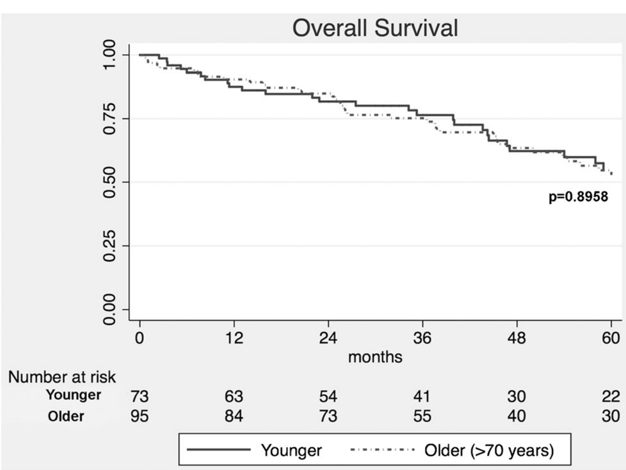

Fig. 2 Cumulative overall survival after liver resection, depending on patient age (cutoff, 70 years)

In conclusion, postoperative complications classified as Clavien–Dindo grade 2 or higher developed more frequently in elderly patients who underwent HR for HCC. However, 90-day postoperative mortality and 5-year recurrence-free survival rates were comparable with those for nonelderly patients. It is true that overall survival is probably influenced by the cutoff of 75 years, but, age alone should not be the only determinant of surgical candidacy for HCC: if elderly patients with liver cirrhosis and HCC are appropriately selected and evaluated not only according to their risk of liver function-related complications, but also according to their general condition, including their cardiovascular, pulmonary condition and psychological state, they might have favorable prognoses after HR.

Compliance with Ethical Standards

Conflict of Interest Roberto Santambrogio, Matteo Barabino, Giovanna Scifo, Mara Costa, Marco Giovenzana, and Enrico Opocher have no conflicts of interest or financial ties to disclose and all authors must meet all of the criteria according the guidelines of the International Committee of Medical Journal Editors (ICMJE).

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