Is Age An Independent Prognostic Factor For Hepatocellular Carcinoma After Surgical Resection?

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Abstract

Purpose: To determine the optimal cutoff for age in predicting prognosis of HCC after surgical resection, and explore its impact on prognosis.

Methods: From 1st January 2012 to 31st December 2015, medical records of patients with HCC and received radical resection were retrospectively reviewed. X-tile was utilized to determine the best cutoff. The primary endpoints were Disease-free survival (DFS) and overall survival (OS). Cox regression analysis was used to discern independent prognostic factors.

Results: 353 patients were enrolled, including 126 in young group (YG; age≤46) and 227 in elder group (EG; age>46), respectively. The YG got a significantly higher proportion of hepatitis B virus infection (p=0.029) and microvascular invasion (p=0.016). The 5-year DFS of YG was lower (38.1% vs. 47.6%，p= 0.046), while 5-year OS showed no significant difference (64.3% vs. 63.5%, p=0.58). Multivariate analysis showed that liver cirrhosis (HR=1.6, p=0.002) and microvascular invasion (HR=1.6, p=0.002) were the independent factors for DFS; microvascular invasion (HR=2.0, p<0.0001) and the tumor site (HR=1.6, p= 0.037) were the independent factors for OS. Age was neither an independent prognostic factor for DFS nor for OS [DFS: HR = 1.3 (0.9-1.7), p = 0.126; OS: HR = 1.1 (0.7-1.5), p = 0.734].

Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver cancer, and the second leading cause of cancer-related deaths worldwide.[1] Chronic infection from hepatitis B virus or hepatitis C virus has been recognized as the two most important etiologic agents of HCC. For HCC within Milan criteria, hepatic partial resection and liver transplantation are considered effective treatments.[2, 3, 4]

The most robust factors related to the prognosis of HCC list as portal vein thrombosis, tumor size, alpha-fetoprotein, and Child-Pugh score. Other factors such as The Cancer of the Liver Italian Program (CLIP) score have also been viewed as independent predictors.[2, 3] However, no consistent conclusion about the relation between age and the long-term prognosis of hepatocellular carcinoma. Some studies have reported that the prognosis of younger patients with HCC is worse than that of elderly patients while others got the opposite conclusion.[3, 5] This dilemma may be caused by the unscientific age classification method.

Therefore, the present study focuses on patients with resectable hepatocellular carcinoma, using an advanced algorithm to stratified young and elderly age patients. The goal is to compare the clinical characteristics and prognosis of the two groups and explore whether age is an independent factor affecting the prognosis of primary hepatocellular carcinoma after surgical resection.

Results

Patients

353 patients were finally enrolled, including 126 in young group (YG; age≤46) and 227 in elder group (EG; age>46), respectively. The median follow-up was 62 months (IQR, 43-85 months). The median age of the groups was: 41 (IQR, 35-44) and 58 (IQR, 53-63 months). The baseline characteristics of the patients were summarized in Table 1, which illustrated the YG got a significantly higher proportion of hepatitis B virus infection (p=0.029) and microvascular invasion (p=0.016) than the EG. Moreover, younger patients had a higher level of red blood cell count (RBC), white blood cell count (WBC), and albumin test (ALB).

Table1. Clinical characteristics of 353 patients

Characteristic	Young (N=126)	Elder (N=227)	P value
Gender			0.235
Male	114 (90.5)	194 (85.5)	
Female	12 (9.5)	33 (14.5)	
Tumor number			1
<2	96 (76.2)	174 (76.7)	
≥2	30 (23.8)	53 (23.3)	
Tumor size (cm)			0.584
5	62 (49.2)	120 (52.9)	
≥5	64 (50.8)	107 (47.1)	
Tumor site			0.603
Central	38 (30.2)	76 (33.5)	
Subcapsular	88 (69.8)	151 (66.5)	
AFP (μg/L)			0.157
<400	77 (61.1)	157 (69.2)	
≥400	49 (38.9)	70 (30.8)	
HBsAg			0.029
+	121 (96.0)	201 (88.5)	
-	5 (4.0)	26 (11.5)	
Cirrhosis			0.495
Yes	70 (55.6)	136 (59.9)	
No	56 (44.4)	91 (40.1)	
Intraoperative blood loss			0.538
>400ml	24 (19.0)	36 (15.9)	
≤400ml	102 (81.0)	191 (84.1)	
Microvascular invasion			0.016
Yes	67 (53.2)	89 (39.2)	
No	59 (46.8)	138 (60.8)	

Differentiation			0.545
Poor	15 (11.9)	21 (9.3)	
Well or moderate	111 (88.1)	206 (90.7)	
WBC (10^9/L)	6.03 (1.7)	5.9(2.3)	0.389
RBC (10^9/L)	5.02 (0.6)	4.74 (0.7)	<0.001
PLT (10^9/L)	190.3 (79.8)	167.1 (78.1)	0.002
ALB (g/L)	43.4 (4.65)	42.5 (4.65)	0.020
ALT (U/L)	40.1 (25.0)	36.9 (28.8)	0.070
AST (U/L)	34.8 (17.6)	35.5 (22.7)	0.718
TBIL (umol/L)	13 (5.25)	12.9 (6.3)	0.994
PT	11.7 (0.9)	11.6 (1.5)	0.996

Survival Analysis

The endpoints of disease-free survival (DFS) and overall survival (OS) between the two groups were calculated via log-rank test, and the Kaplan-Meier method was used to depict the survival curves (Fig 1). The 5-year DFS of young group (YG) was lower than the elder group (EG) (38.1% vs. 47.6%，p= 0.046), while 5-year OS showed no significant difference (64.3% vs. 63.5%, p=0.58).

Prognostic Factors Associated with DFS and OS

Multivariate analysis showed that liver cirrhosis (HR=1.6, p=0.002) and microvascular invasion (HR=1.6, p=0.002) were the independent factors for DFS; and microvascular invasion (HR=2.0, p<0.0001) and the tumor site (HR=1.6, p= 0.037) were the independent factors for OS. The multivariate cox regression analyses could not prove that age was an independent prognostic factor for DFS or OS (DFS: hazard ratio [HR] = 1.3, 95% confidence interval [CI] 0.9-1.7, p = 0.126]; OS: HR = 1.1, 95% CI 0.7-1.5, p = 0.734) (Table 2).

Table2. univariate and multivariate analyses of disease-free survival and overall-survival

Discussion

This study focused on evaluating the prognostic value of age in patients with HCC receiving radical resection. X-tile, a new bio-informatics tool for biomarker assessment and outcome-based cut-point optimization,[7] was used to stratified age, and 46 was identified as the optimal cutoff value. Younger patients (age ≤ 46) have a statistically significant worse DFS (38.1% vs. 47.6%, p = 0.046) than elder patients. Multivariate analysis showed that age was neither an independent prognostic factor for DFS nor for OS [DFS: HR = 1.3 (0.9–1.7), p = 0.126; OS: HR = 1.1 (0.7–1.5), p = 0.734].

Variable	Disease-free survival				Overall-survival			
	univariate		multivariate		univariate		multivariate	
	p	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)
Gender (male)	0.132	1.4 (0.9-2.3)			0.549	1.2 (0.7-2.1)		
Number (multiple)	0.063	1.4 (0.98-1.9)			0.053	1.5 (1.0-2.1)	0.109	1.4 (0.9-2.0)
Size (>5cm)	<0.0001	1.7 (1.3-2.2)	0.245	1.2 (0.9-1.7)	0.003	1.7 (1.2-2.4)	0.081	1.4(1.0-2.0)
Site (capsual)	0.013	1.5 (1.1-2.0)	0.204	1.2 (0.9-1.7)	0.001	2.0 (1.3-3.1)	0.037	1.6 (1.0-2.4)
AFP (>=400ng/mL)	0.493	1.1(0.8-1.5)			0.319	1.2 (0.8-1.7)		
HBsAg	0.053	1.8 (1.0-3.2)	0.096	1.6 (0.9-3.0)	0.116	1.8 (0.9-4.0)		
cirrhosis	0.001	1.7 (1.2-2.2)	0.002	1.6 (1.2-2.2)	0.438	1.2 (0.8-1.6)		
Microvascular invasion	<0.0001	1.7 (1.3-2.2)	0.002	1.6 (1.2-2.1)	<0.0001	2.3 (1.6-3.3)	<0.0001	2.0 (1.4-2.9)
differentiation	0.764	1.1 (0.7-1.7)			0.423	1.3 (0.7-2.2)		
Age (≤46)	0.05	1.3 (1.0-1.8)	0.126	1.3 (0.9-1.7)	0.583	1.1 (0.8-1.6)	0.734	1.1 (0.7-1.5)
WBC (<4.0×10⁹/L)	0.318	1.3 (0.8-2.2)			0.626	1.2 (0.6-2.2)		
RBC (<4.3×10¹²/L)	0.501	1.1 (0.8-1.7)			0.672	1.1 (0.7-1.8)		
PLT (<100×10⁹/L)	0.186	1.4 (0.8-2.4)			0.888	1.1 (0.5-2.1)		
ALB (<35g/L)	0.373	1.4 (0.7-2.8)			0.089	1.9 (0.9-4.2)	0.172	1.7 (0.8-3.7)
ALT (>50U/L)	0.504	1.1 (0.8-1.5)			0.622	0.9 (0.6-1.3)		

AST (>40U/L)	0.05	1.3 (1.0-1.8)	0.601	1.1 (0.8-1.5)	0.296	1.2 (0.8-1.7)
TBIL (>17.1umol/L)	0.974	1.0 (0.7-1.4)			0.252	1.3 (0.8-1.9)
PT (prolongation>3s)	0.539	1.1e-07 (0-Inf)			0.651	1.1e-07 (0-Inf)

The previous research didn't propose an optimized method to determine the cutoff value of age. Some studies determined the cutoff value as 40 based on the European or American guidelines' recommendation.[8–10] However, hepatocellular carcinoma in non-hepatitis B virus endemic areas, including Europe and America, is rare in patients younger than 40 years of age.[11] This classification is not suitable for the hepatitis B virus endemic areas such as East Asia and sub-Saharan Africa. The imbalance in number of cases between each age group limited the impact of this cutoff value. Others selected the cuf-off value of 55 based on the median of the sample data.[12] Selection bias may exist in these studies. We use the X-tile software to evaluate the robustness of the relationship between age and DFS by the construction of a two-dimensional projection of every possible division, which theoretically can produce a cutoff that will optimally divide the cohort.

The previous studies had inconsistent results about the relation between age and the long-term prognosis of hepatocellular carcinoma. Some studies reported that the overall survival of younger patients with HCC and received radical resection is worse than that of elderly patients,[8,12–15] while others got the opposite conclusion.[11,16–17] The difference may be caused by their choice of cutoff value. Besides, with the age increasing, more and more lethal factors would occur except for HCC, so the evaluation of overall survival of HCC would be more difficult. Therefore, we chose disease-free survival as the primary endpoints and overall survival as the second endpoint.

Wang JH et al,[17] Liu et al,[18] and Yang, G et al[19] found that although ablation performed less intraoperative blood loss, shorter operative time, lower incidence of complications and shorter length of stay, radical resection offered a lower incidence of recurrence. Combining our study, to reduce the frequency of hospitalizations caused by recurrence, the first choice for young patients with resectable HCC should recommend surgical resection. 46 years of age may be an appropriate cutoff value. Meanwhile, most patients with intrahepatic recurrence have the opportunity to receive repeated ablation.[18, 20] Ablation may be an effective and safe alternative for intrahepatic recurrence or liver metastases. Besides, clinical doctors should pay more attention to the education of regular follow-up to younger patients.

Some studies proposed age was an independent prognostic factor.[8] But more studies disagreed with this.[5, 12, 14] The results of our study did not support that age was an independent prognostic factor. The seemingly worse prognosis of young age may be a "dilution" caused by the negligence of important counfounding factors. WXiao H et al[21] also found similar phenomenon. In our stue found that a higher proportion of young patients had microvascular invasion (p = 0.016) than elder patients, which was one of

the independent factors for DFS (HR = 1.6, p = 0.002). dy, analysis of patients subgroup with microvascular invasion showed the difference in DFS between the two age groups were insignificant, which support the hypothesis that microvascular invasion was a potential confounding factor.

In our study, we found that the YG got a significantly higher proportion of hepatitis B virus infection, and worse tumor condition (higher proportion of microvascular invasion), but better liver function than the EG. It`s consistent with the previous published study.[8–10, 12] Ha SY et al[15] conducted a gene expression analysis and found 69 differentially expressed genes between the young and old patients. Most of the genes were relative to the cell cycle or cell division, and the mitotic rate was significantly higher in HCC of young patients, which means more aggressive tumor biology. Further exploration from the cellular and molecular levels is necessary to determine whether there are mechanism differences related to the occurrence of HCC in different age groups.

Fidler MM et al[22] pointed out that the global incidence of cancer in 20–39 years old in 2012 was 43.3 per 100 000 people per year, and the corresponding mortality was 15.9 per 100 000 people per year. Although the data was not as terrifying as in the elder group, it's of great importance to increase awareness and resources for this neglected sub-population. Currently, risk stratification and treatment protocols are not clear for younger patients because lack of corresponding clinical trials. Screening and early detection programs might have a significant effect at a limited cost.

There are some limitations to the study. First, the study was single-center research and the sample size was relatively small, selection bias may exist. Larger sample validation is needed. Second, this study did not fully adjust for potentially unknown confounding factors that may affect the results. Third, the study lacked the exploration of the molecular level. Lastly, cox regression could not statistically prove that age was an independent risk factor for either DFS or OS, indicating that the problem needs further study.

Methods

Patients

patients with HCC and received radical resection at the Sun Yat-Sen University cancer center (SYSUCC) from 1st January 2012 to 31st December 2015 were retrospectively selected. The inclusion criteria were: (a) the age of patients ranged from 18 to 75 years old; (b) tumors corresponded with BCLC A/B stage; (c) patients underwent radical surgical resection (R0 resection, negative surgical margin identified by the microscope). The exclusion criteria were: (a) patients received non-surgical anti-cancer treatment before the resection, such as ablation, transcatheter arterial chemoembolization (TACE), systemic chemotherapy, portal vein embolization or radiotherapy, etc; (b) patients were complicated with major organ failure or autoimmune diseases; (c) patients with other malignant tumors beside hepatocellular carcinoma (HCC); (d) patients lost to follow-up. The protocol of resection procedure was carried out according to our previous article.[7] All methods were carried out in according to the treatment strategy of hepatocellular carcinoma.[23]

This study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the ethical review committee of the Sun Yat-sen University Cancer Center. And informed consent was obtained from all cases.

Follow-up Data Collection And Endpoints

All patients underwent regular postoperative follow-up. Each follow-up includes physical examination, serum alpha-fetoprotein (AFP) level test, and at least one imaging scan (ultrasound, abdominal CT, or MRI). The first follow-up was scheduled 3–4 weeks after resection to determine potential postoperative complications. The follow-ups were arranged every 3 months for the first two years after resection, and every 3–6 months thereafter, until death or loss to follow-up. Recurrence was confirmed by the imaging scan (CT/MRI) and serum alpha-fetoprotein (AFP) level. The primary endpoints were disease-free survival (DFS, time from treatment initiation to disease recurrence) and overall survival (OS, time from treatment initiation to death for any reason).

Statistical Analysis

Evaluated the cutoff value by a specific software named “X-tile” based on the disease-free survival (DFS) and divided patients into two groups: young group (YG, age ≤ 46) and elder group (EG, age > 46). Continuous variables were compared using the independent-samples t-test or the Mann-Whitney test; categorical variables and ordinal variables were assessed by the chi-square test and Kruskal-Wallis test, respectively. Disease-free survival (DFS) and overall survival (OS) were analyzed by log-rank test and the survival curves were depicted using the Kaplan-Meier method. Cox regression analysis was used to discern independent prognostic factors for DFS and OS. Variables with P value less than 0.1 in univariate analysis were added to the multivariate analysis, and variables with P value less than 0.05 in the multivariate analysis were thought as independent factors.

The statistical analyses were performed using the IBM SPSS Statistics 25 and R 4.0.5. P-values less than 0.05 were considered statistically significant, and all tests were two-tails.

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Figures

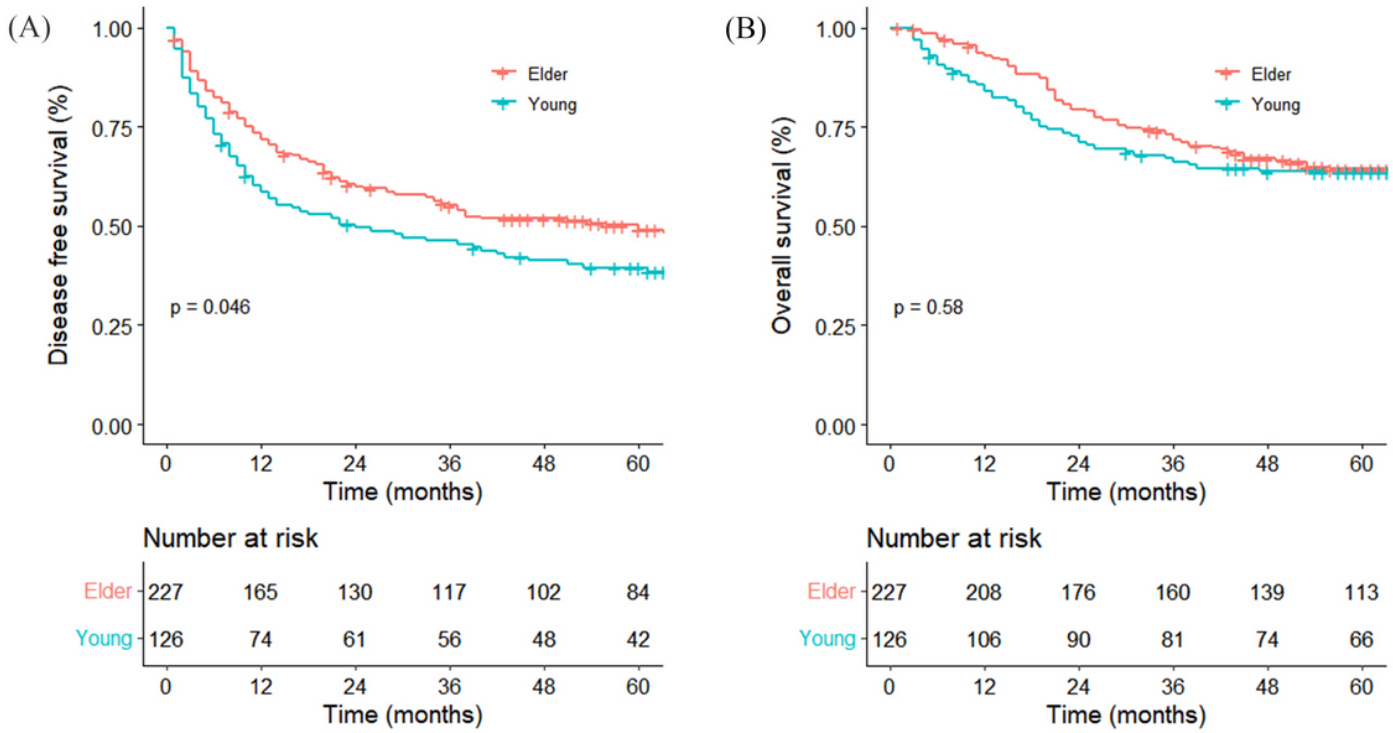

Figure 1

comparison of 5-year disease-free survival (A) and 5-year overall-survival (B) between YG and EG via Kaplan-Meier survival curve

Supplementary Files

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