Long-term outcome of elderly patients (75 years or older) with hepatocellular carcinoma

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Running head: Outcomes of elderly patients with HCC

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Abstract

Background: The aim of this study was to evaluate the long-term outcome of elderly patients with hepatocellular carcinoma aged 75 years or older.

Methods: The study included 422 patients with hepatocellular carcinoma, who were divided into two age groups: 75 years or older (n=140) and younger than 75 (n=282). Outcomes were compared between the two groups.

Results: The number of elderly patients treated with supportive care alone (33 patients; 24%) was significantly higher than younger patients (30 patients; 11%, $p<0.01$). The 1-, 3-, 5-, and 7-year overall survival rates of the elderly patients (81%, 55%, 39%, and 23%, respectively) were worse than those of younger patients (85%, 64%, 49%, and 36%, respectively, $p=0.042$). However, the overall survival rate of the elderly group after excluding 63 patients treated with supportive care alone, was similar to that of the younger group ($p=0.615$). Multivariate analysis identified age, total bilirubin levels, albumin levels, serum DCP levels, tumor size, number of HCC nodules, vascular invasion, extra-hepatic metastasis, and treatment modality as independent and significant factors of overall survival.

Conclusion: Advanced age is a negative prognostic factor in patients with hepatocellular carcinoma due to the tendency for frequent use of conservative treatment rather than locoregional or surgical treatment.

Key words: elderly, hepatocellular carcinoma, prognosis, therapy.

Introduction

The average life expectancy at birth has been increasing in many countries. The average life expectancy in Japan is longest in the world, being 79 years for males and 86 years for females(1). With the aging of the society in Japan, the number of elderly patients with hepatocellular carcinoma (HCC) has been increasing(2, 3). Thus, treatment strategy needs to be tailored for elderly patients with HCC. Various studies have examined the effectiveness of surgical treatment(4-8), percutaneous ethanol injection(9), radiofrequency ablation (RFA)(10-12), transarterial chemoembolization (TACE)(13, 14), and sorafenib(15) for elderly patients with HCC. With advances in diagnostic and biomedical technologies, most of the studies have shown that treatment of elderly patients with HCC is as safe and effective as younger patients, with overall post-treatment survival rates similar to those of younger patients(4-13, 15-17). However, unintentional bias in the selection of patients may have occurred in the above studies with inclusion of patients with good liver function or those without severe concomitant diseases for the aggressive treatments of HCC. To our knowledge, only a few studies have evaluated the long-term outcome of elderly patients with HCC including considerable number of patients treated with supportive care alone. In the present study, we investigated the survival rates of elderly patients with HCC aged 75 years or older who underwent treatment for HCC to clarify treatment strategy for elderly patients with HCC.

Materials and Methods

Patients

Between January 2001 and October 2009, 440 patients were diagnosed with HCC at the Department of Internal Medicine, Kurume University Medical Center. The diagnosis of HCC was established either by histopathology or typical appearance of HCC on two sets of imaging studies (ultrasonography, computed tomography, angiography, and magnetic resonance imaging), and/or based on high plasma levels of tumor markers such as alpha-fetoprotein (AFP) and des-gamma-carboxy prothrombin (DCP)(18). Of these, 10 patients had insufficient pretreatment data and 8 patients were lost to follow-up, and these patients were excluded from the present study. Thus, the study included 422 patients with HCC. The patients were divided into two groups according to age: ≥75 years (n=140) and <75 years (n=282).

Treatment strategy

When a diagnosis of HCC was established at Kurume University Medical Center, the following treatment options were assessed. *1)* Surgical resection was assessed especially for patients with localized HCC and preserved hepatic reserve capacity. Liver transplantation (LT) was considered based on HCC meeting the Milan criteria(19) with Child-Pugh class C cirrhosis. *2)* Non-surgical treatments, such as, RFA, TACE, combination of TACE and RFA, hepatic arterial infusion chemotherapy, systemic chemotherapy, and radiotherapy were assessed when surgical treatment were contraindicated or the patient refused surgical treatment. *3)* Patients who received supportive care alone comprised those in whom locoregional therapies were considered inappropriate due to the presence of concomitant diseases such as

cardio-pulmonary diseases, psychiatric disorders, and renal insufficiency, as well as those with poor hepatic function or performance status, and those who categorically refused any treatment for HCC. Outcomes were compared between the two groups.

Statistical analysis

We used the χ^2, Fisher exact, and Mann-Whitney U tests, where appropriate, to evaluate differences in clinical features of patients and in tumor characteristics. Cumulative survival was analyzed by the Kaplan-Meier method and survival curves were compared by the log-rank test. A Cox proportional-hazards model was used to identify independent clinical factors or groups that influenced survival. Survival was confirmed up to April 30, 2013. The Statistical Package for Social Sciences for Windows (version 15.0, SPSS Inc., Chicago, IL) was used for data analysis. A *p* value of <0.05 was considered significant. Written informed consent was obtained from all patients before treatment and best supportive care. This study was conducted in accordance with the Declaration of Helsinki.

Results

Clinical and tumor characteristics

Table 1 summarizes the profiles of the two groups of patients with HCC. Elderly patients had higher frequency of hepatitis C virus (HCV)- and hepatitis B virus (HBV) -unrelated liver disease (p=0.02) than younger patients. Elderly patients had better hepatic reserve capacity (higher albumin levels [p=0.018] and prothrombin activity

[p<0.01], lower total bilirubin levels [p<0.01], and higher frequency of Child-Pugh class A [p<0.01]) than younger patients. The two groups were comparable with regard to gender, serum AFP levels, serum DCP levels, number of HCC nodules, presence of extra-hepatic metastasis, Milan criteria for HCC, and tumor stage. However, elderly patients had a tendency for larger tumor size (34.5 vs. 26.0 mm; p=0.028) and lower frequency of vascular invasion (p=0.038).

Treatment of HCC

With regard to the treatment, the treatment modalities provided included surgical resection (n=14), RFA (n=42), combination of TACE and RFA (n=32), TACE (n=8), chemotherapy or radiotherapy (n=11), and supportive care alone (n=33) for elderly patients; and surgical resection (n=22), LT (n=1), RFA (n=102), combination of TACE and RFA (n=75), TACE (n=14), chemotherapy or radiotherapy (n=38), and supportive care alone (n=30) for younger patients. The number of patients treated with supportive care alone was significantly higher in the elderly patients (33 patients; 24%) than in the younger patients (30 patients; 11%) (p<0.01).

Survival rates

Of the 140 elderly patients, 91 died while the remaining 49 were censored. Of the 282 younger patients, 171 died and the remaining 111 were censored. The median survival time of elderly patients was 1,129 days (range; 21-4,442 days), compared with 1,427 days (range; 9-4,341 days) for younger patients. Figure 1 shows the cumulative survival rate curves according to age. The 1-, 3-, 5-, and 7-year overall survival rates

of the elderly patients (81%, 55%, 39%, and 23%, respectively) were worse than those of younger patients (85%, 64%, 49%, and 36%, respectively, p=0.042). However, excluding 63 patients treated with supportive care alone, the 1-, 3-, 5-, and 7-year overall survival rates of the elderly (93%, 67%, 49%, and 33%, respectively: n=107) were comparable to those of the younger patients (88%, 69%, 52%, and 41%, respectively: n=252, p=0.615) (Figure 2). Univariate analysis indicated that age (p=0.042), total bilirubin levels (p<0.01), albumin levels (p<0.01), serum AFP levels (p<0.01), serum DCP levels (p<0.01), tumor size (p<0.01), number of HCC nodules (p<0.01), vascular invasion (p<0.01), extra-hepatic metastasis (p<0.01), and treatment modality (p<0.01) correlated with overall survival (Table 2). Among the 10 factors tested, multivariate analysis identified age [p=0.016, RR 1.391 (95% CI 1.062-1.821)], total bilirubin levels [p<0.01, RR 1.828 (95% CI 1.333-2.507)], albumin levels [p=0.012, RR 1.403 (95% CI 1.078-1.825)], serum DCP levels [p=0.010, RR 1.472 (95% CI 1.098-1.975)], tumor size [p=0.029, RR 1.529 (95% CI 1.044-2.241)], number of HCC nodules [p<0.01, RR 1.737 (95% CI 1.320-2.285)], vascular invasion [p<0.01, RR 2.774 (95% CI 1.810-4.251)], extra-hepatic metastasis [p<0.01, RR 2.771 (95% CI 1.508-5.092)], and treatment modality [p<0.01, RR 4.092 (95% CI 2.922-5.731)]as independent and significant factors of overall survival (Table 2).

Causes of death

Table 3 lists the causes of death for both groups. More than 70% of the elderly patients died from HCC, but the HCC-related death rate in the elderly (73%) was not different from that of the younger patients (73%). Death unrelated to liver disease

included death from pneumonia (n=2), psychiatric disorders (n=3), cardiovascular diseases (n=1), cerebral vascular disorder (n=1), cancer in other organs (n=2), hemothorax (n=1), and unknown causes (n=4) in the elderly patients; and pneumonia (n=5), psychiatric disorder (n=1), cerebral vascular disorders (n=3), cancers in other organ (n=4), renal disorders (n=4), acute pancreatitis (n=2), infection with *Vibrio vulnificus* (n=1), bleeding of gastric ulcer (n=1), and unknown causes (n=3) in the younger patients. Treatment-related deaths occurred in relation to treatment of liver cirrhosis or refractory ascites following treatment of HCC (n=3); complication of splenectomy (n=1 elderly patient), complication of peritoneo-venous shunt (n=1), and complications associated with LT in a younger patient (n=1).

Discussion

In aging societies, the treatment strategy of malignant diseases in elderly patients is a global issue, especially patients with HCC, because various non-surgical treatment modalities have been developed and surgical techniques have also greatly improved. Moreover, aging was strongest risk for development of HCC in chronic hepatitis C patients treated with interferon based therapy(20).

Our study examined the long-term outcome of elderly patients with HCC aged ≥75 years, including considerable number of patients treated with supportive care alone. The number of patients treated with supportive care alone was significantly higher in the elderly patients (33 patients; 24%) than in the younger patients (30 patients; 11%, $p<0.01$). Poon et al reported that the surgical treatment rate was lower in elderly patients with HCC than in younger patients(13). Collier and Tsukioka also reported

that elderly patients with HCC were more likely to receive conservative treatment compared to younger patients(17, 21). Despite progress in treatments of HCC, better care of liver cirrhosis and better care of concomitant diseases, elderly patients with HCC tend to more likely receive less invasive or conservative treatments than younger patients.

In the present study, although elderly patients had better hepatic reserve capacity and similar Milan Criteria for HCC and tumor stage compared to younger patients, the overall survival rates in the elderly patients were worse than those of younger patients (5-year; 39% vs. 49%, 7-year; 23% vs. 36% p=0.042, Figure 1). Multivariate analysis identified age, total bilirubin levels, albumin levels, serum DCP levels, tumor size, number of HCC nodules, vascular invasion, extra-hepatic metastasis, and treatment modality as independent and significant factors of overall survival (Table 2).

Advanced age was one of the adverse prognostic factors in patients with HCC. This result was similar to the recent report(22), but different from most other studies in whom patients were treated surgically or received locoregional treatment of HCC(4-13, 15-17). Suda et al analyzed 740 patients with HCC including 38 patients treated with supportive care alone. They stressed that aging was an adverse significant factor affecting overall survival for patients with HCC, however when the survival benefit was evaluated on the basis of percent survival to life expectancy, therapeutic approach should not be restricted due to patient age(22). Interestingly, our analysis of data of the elderly group after excluding those of 63 patients treated with supportive care alone, showed comparable overall survival rate in the elderly and young patients (5-year; 49% vs. 52%, p=0.615, Figure 2). Treatment modality was the most powerful

prognostic factor in patients with HCC in the multivariate analysis [RR 4.092 (95% CI 2.922-5.731)], and elderly patients with HCC were more likely to receive supportive care alone compared to younger patients. Despite the advances in diagnostic and biomedical technologies, advanced age remains today a negative prognostic factor for patients with HCC due to the tendency for use of supportive treatment alone, rather than locoregional or surgical treatment.

To clarify the treatment strategy for elderly patients with HCC, the cause of death is an important issue (Table 3). In the present study, more than 70% of elderly patients died from HCC, and the HCC-related death rate in the elderly patients (73%) was similar to that of younger patients (73%). HCC is considered to be a life-limiting factor in elderly patients with HCC similar to younger patients. Therefore, aggressive treatment of HCC might improve the survival of elderly patients with HCC, similar to younger patients, if such treatment is feasible in relation to the clinical status and the concomitant diseases.

In conclusion, the present study demonstrated that advanced age is a negative prognostic factor in patients with HCC due to the tendency for frequent use of conservative treatment rather than locoregional or surgical treatments. The therapeutic strategy for elderly patients with HCC should be as same as for younger patients, because the efficacy of treatment in the elderly patients was not much different from that of younger patients.

Acknowledgements

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Figure Legends

Figure 1. Kaplan-Meier survival curves of 422 patients with HCC according to age. The 1-, 3-, 5-, and 7-year overall survival rates of the elderly patients were worse than those of younger patients (p=0.042).

Figure 2. Kaplan-Meier survival curves of 359 patients with HCC who received surgical or locoregional treatment according to age. The 1-, 3-, 5-, and 7-year overall survival rates of the elderly patients were comparable to those of the younger patients (p=0.615).

Table 1. Clinical profile of 422 patients with hepatocellular carcinoma.

	Elderly patients (age ≥75 years)	Younger patients (age <75 years)	p value
Number of patients	140	282	
Gender (Male / Female)	82 / 58	193 / 89	0.051
Age [median (range)]	78.5 (75-96)	66 (36-74)	<0.01
Background [HCV / HBV / HCV (-) and HBV (-)]	113 / 5 / 22	228 / 32 / 32	0.02
Prothrombin activity [%; median (range)]	77 (43-100)	71 (16-100)	<0.01
Total bilirubin [mg/dl; median (range)]	0.8 (0.3-19.6)	1.0 (0.2-9.8)	<0.01
Albumin [g/dl; median (range)]	3.8 (2.1-4.9)	3.6 (1.8-4.8)	0.018
Child-Pugh class (A / B or C)	105 / 35	163 / 119	<0.01
AFP [ng/ml; median (range)]	26 (2-431000)	42 (3-1000000)	0.221
DCP (mAU/ml; median (range))	85 (7-187000)	54 (7-943000)	0.153
Tumor size [mm; median (range)]	34.5 (11-180)	26.0 (7-200)	0.028
Tumor number (1 / ≥2)	78 / 62	150 / 132	0.678
Vascular invasion (yes / no)	10 / 130	40 / 242	0.038
Extra-hepatic metastasis (yes / no)	7 / 133	8 / 274	0.273
Milan criteria (In / Out)	76 / 64	169 / 113	0.295
Tumor stage (I or II / III or IV)	79 / 61	162 / 120	0.917
Therapy [Aggressive treatment / Supportive care alone]	107 / 33	252 / 30	<0.01

HCV; hepatitis C virus, HBV; hepatitis B virus, AFP; alpha-fetoprotein, DCP; des-gamma-carboxy prothrombin.

Table 2. Factors related to survival of 422 patients with hepatocellular carcinoma.

	n	Univariate p value	Multivariate p value	RR (95%CI)
Gender (Male / Female)	275 / 147	0.791		
Age (<75 / ≥75)	282 / 140	0.042	0.016	1.391 (1.062-1.821)
Background (Viral / Non-viral)	378 / 44	0.079		
Prothrombin activity (<80 / ≥80%)	305 / 117	0.360		
Total bilirubin (<1.5 / ≥1.5 mg/dl)	344 / 78	<0.01	<0.01	1.828 (1.333-2.507)
Albumin (<3.5 / ≥3.5 g/dl)	167 / 255	<0.01	0.012	1.403 (1.078-1.825)
AFP (<100 / ≥100 ng/ml)	286 / 136	<0.01	0.133	1.233 (0.938-1.621)
DCP (<100 / ≥100 mAU/ml)	242 / 180	<0.01	0.010	1.472 (1.098-1.975)
Tumor size (<50 / ≥50 mm)	322 / 100	<0.01	0.029	1.529 (1.044-2.241)
Tumor number (1 / ≥2)	228 / 194	<0.01	<0.01	1.737 (1.320-2.285)
Vascular invasion (yes / no)	50 / 372	<0.01	<0.01	2.774 (1.810-4.251)
Extra-hepatic metastasis (yes / no)	15 / 407	<0.01	<0.01	2.771 (1.508-5.092)
Therapy [Treatment (+) / Supportive care alone]	359 / 63	<0.01	<0.01	4.092 (2.922-5.731)

AFP; alpha-fetoprotein, DCP; des-gamma-carboxy prothrombin, 95%CI: 95% confidence interval.

Table 3. Comparison of causes of death between two groups.

	Elderly patients (n=91)	Younger patients (n=171)
HCC related death (%)	66 (73)	124 (73)
Liver failure or rupture of EV (%)	10 (11)	21 (12)
Death unrelated liver disease (%)	14 (15)	24 (14)
Treatment related death (%)	1 (1)	2 (1)

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HCC; hepatocellular carcinoma, EV; Esophageal varices.

Figure 1

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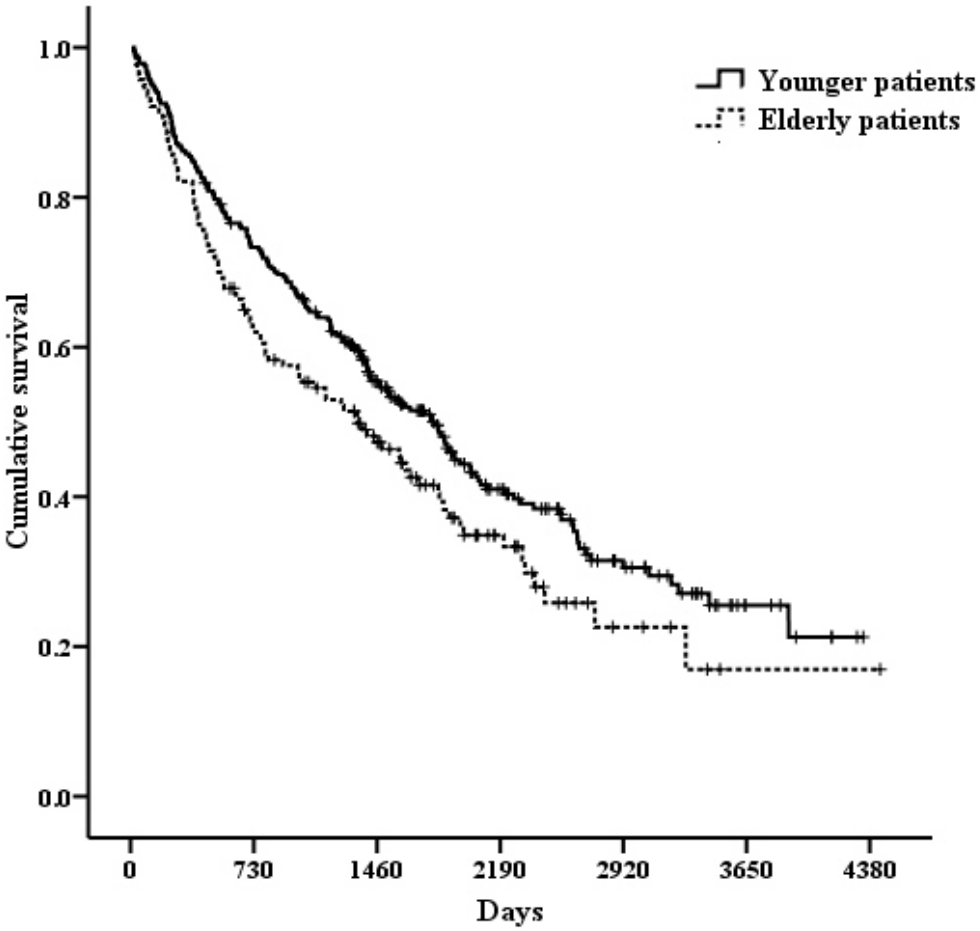
Younger patients
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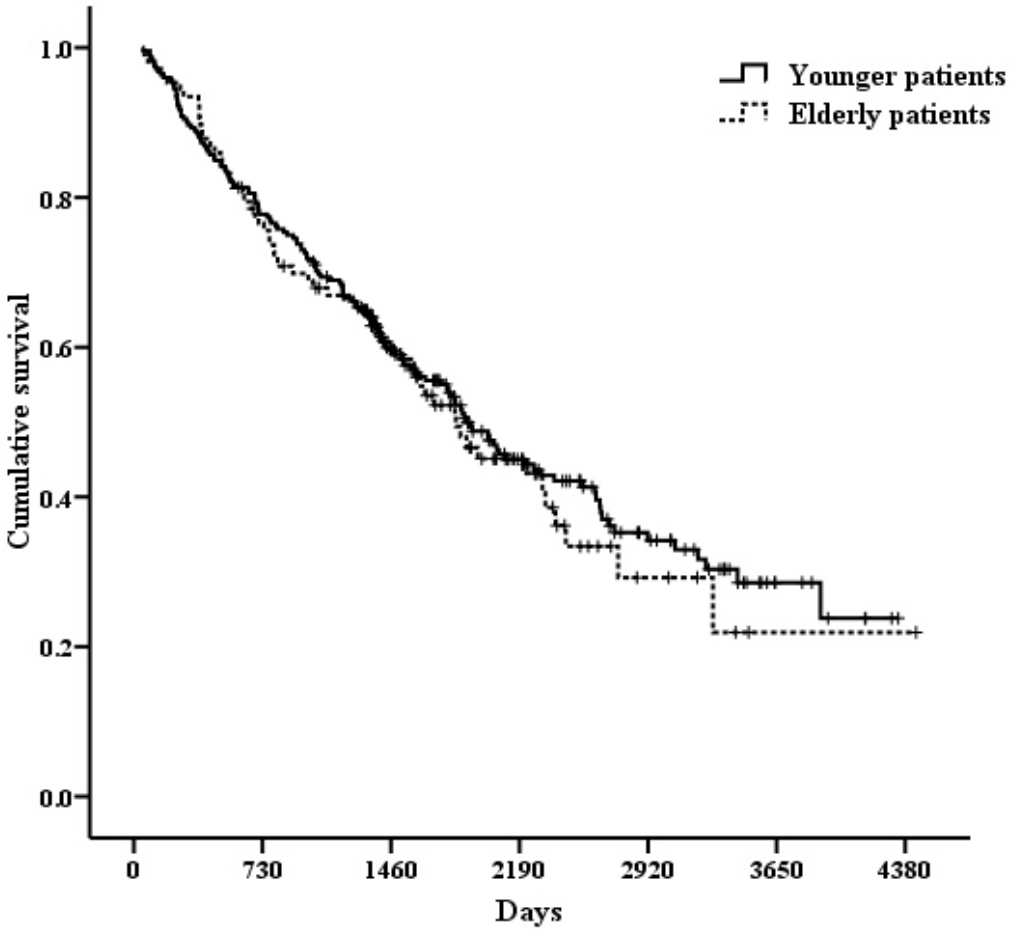
Figure 2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