Review

Treatment for Hepatocellular Carcinoma in Elderly Patients: A Literature Review

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Abstract

An aging society means that the number of elderly patients with cancer is predicted to rise in the future. Hepatocellular carcinoma (HCC) usually develops in patients with hepatitis B virus infection, hepatitis C virus infection, or alcoholic liver disease. The risk of developing HCC is also known to be age-dependent and elderly patients sometimes present with HCC. The increased longevity of the population thus means that more elderly HCC patients are to be expected in the coming years. In general, many elderly patients are not receiving optimal therapy for malignancies, because it is often withheld from them because of perceived minimal survival advantage and the fear of potential toxicity. Comprehensive data with regard to treatment of elderly patients with HCC are currently limited. Furthermore, current guidelines for the management of HCC do not satisfy strategies according to age. Thus, there is urgent need for investigation of safety and clinical outcomes in elderly patients who receive therapy for HCC. In this review, we primarily refer to current knowledge of clinical characteristics and outcome in elderly patients with HCC who underwent different treatment approaches (i.e., surgical resection, liver transplantation, locoregional therapies, and molecular-targeting therapy).

Key words: Hepatocellular carcinoma, Elderly patients, Cancer treatment, Clinical characteristics; Clinical outcome.

Introduction

Hepatocellular carcinoma (HCC) ranks fifth among the most prevalent cancers worldwide, and is the third most common cause of cancer-related death. Therefore, it is a major global health problem [1–5]. Most cases of HCC are attributable to chronic liver disease resulting from chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infection [1–5]. A recent report by Chung et al. demonstrated that the HCC-related mortality rate in Japan has steadily increased over the past 50 years and >30 000 patients died of HCC every year and the age at death increased [6].

An aging society means that the number of elderly patients with cancer is also predicted to rise in the future [7]. In Japan, 75-year-old men and women have an average expected life span of around 5 and 10 years, respectively, and Japan has the greatest longevity in the world [8]. The risk of developing HCC is known to be age-dependent, and patients aged ≥75 years sometimes present with HCC [9, 10]. The increased longevity of the population means that more elderly HCC patients are to be expected in the coming years. In Japan, the adjusted HCC mortality has increased in recent years [11]. Moreover, the average age of HCC patients in Japan is increasing as well as the proportion of elderly HCC patients [12]. In the United States, latest estimates suggest that HCC incidence peaks above the age of 70 years [13]. Notably,

together with the increase in the average lifespan, the number of HCC patients who are very old (i.e. >80 years) has been steadily increasing [14].

The number of elderly patients with HCC is expected to increase partly because of the following epidemiological reasons: (1) the rising incidence of liver cirrhosis (LC) unrelated to hepatitis virus, such as non-alcoholic steatohepatitis (NASH)-related LC, which develops over a long period of time; and (2) the delayed effect of antiviral therapy, such as nucleoside analogs for chronic hepatitis B and interferon (IFN) for chronic hepatitis C, on the development of HCC [3–5, 15, 16]. In addition, HCV infection is generally acquired during adult life. The incidence of HCV infection is closely associated with age, although the total number of cases is gradually decreasing because of the effect of antiviral therapy and the screening for HCV antibody in blood donors [17–20]. In patients with HCV infection, old age is associated with more severe histological findings and the presence of LC [10]. One of the most essential issues in clinical settings lies in the increasing number of elderly patients with HCV infection. HCV infection thus constitutes a major part of the etiology in elderly patients with HCC.

The management of elderly patients with HCC is significantly more complicated than that of younger patients because of comorbidity including cardiovascular disease, respiratory disease, diabetes mellitus, renal dysfunction, and altered drug pharmacokinetics [21–34]. In general, many elderly patients are not receiving optimal therapy for malignancies, because it is often withheld because of perceived minimal survival advantage and the fear of potential toxicity [30–35].

The treatment of HCC has significantly improved in the past few decades. The current treatments for HCC with established efficacy include: (1) surgical resection (SR)/liver transplantation (LT); (2) transcatheter arterial chemoembolization (TACE); (3) percutaneous radiofrequency ablation (RFA); (4) percutaneous ethanol injection (PEI); (5) percutaneous microwave coagulation therapy (PMCT); and (6) molecular-targeted therapy (MTT; e.g., sorafenib) [1–5, 36–40]. The optimal therapy should be selected for individual patients with HCC based on the assessment of performance status (PS), tumor-related factors, liver-function-related factors and comorbidity [1–5, 36–40]. However, current guidelines for the management of HCC do not satisfy strategies according to age [41, 42].

As described earlier, the proportion of elderly patients with HCC and their average age is increasing in Japan [6, 10–12]. These trends have led to a rising demand in our country for investigations related to clinical characteristics and outcomes of therapy in elderly patients with HCC. In this review, we mainly refer to current knowledge of clinical characteristics and outcome in elderly patients with HCC who underwent different treatment approaches (i.e., SR, LT, locoregional therapies and MTT).

Clinical characteristics of HCC in elderly patients

The clinical course of liver diseases in elderly patients may differ in several aspects from that in younger patients, although there are no liver diseases specific to those of advanced age [43]. The process of liver carcinogenesis in elderly patients seems to be a distinctive factor. In previous studies, elderly patients with HCC were more likely to be women [14, 21–34, 44]. This may have been associated with a larger female elderly population because of their longer life expectancy. In other words, the proportion of women in the population is known to gradually increase with age [8]. The peak age of HCC occurrence in women is delayed by around 5 years as compared with that in men [45]. Furthermore, in many studies, elderly patients with HCC were more likely to be HCV carriers [14, 21–33, 44]. This finding may be explained by the fact that most HBV carriers acquire the virus via vertical transmission in the perinatal period, whereas most HCV carriers are infected at a later stage in life. HCC is therefore manifested as one of the complications of HCV carriers much later than in HBV carriers [14, 21–33, 44]. The peak age of HCC occurrence thus varies considerably worldwide because of the different distribution of etiological factors. The average age at onset of HBV-related HCC is reported to be 10 years younger than that of HCV-related HCC [46].

Oishi et al. reported that the proportion of elderly HCC patients negative for both hepatitis B surface antigen and HCV antibody (NBNC-HCC) was larger than that of younger HCC patients [47]. Factors other than hepatitis virus or alcohol, or genetic disturbance may be related to the development of HCC in some elderly patients [47]. Patients with NASH-related HCC are more likely to be older than those with hepatitis-virus-related HCC [48, 49]. A large proportion of cases with cryptogenic LC represent end-stage liver disease of NASH [50]. The background liver disease in elderly patients with NBNC-HCC may thus be considerably related to NASH [48, 49].

The prevalence of a normal liver in elderly patients with HCC is reported to be higher than that in younger patients [24–33, 43]. These observations suggest that aging itself is a risk factor linked to liver

carcinogenesis. A previous report revealed that the telomere length in the liver is shortened with the progression of liver fibrosis and/or aging, increasing the risk of HCC development [51]. Aberrant DNA methylation, which is observed in the normal aging process, may also be associated with HCC development in elderly patients [52]. A recent report by Miki et al. demonstrated that HCV patients who received a blood transfusion at an older age developed HCC sooner despite their lower grade of liver fibrosis than those at a younger age [46]. Their results also indicate that aging itself is a risk factor for HCC development.

Several studies reported that the number of HCC nodules in elderly patients was smaller than that in younger patients [24–34, 43, 53–55]. Multicentric liver carcinogenesis is associated with the degree of background liver fibrosis [56, 57]. Less advanced liver fibrosis in elderly patients may explain these observations.

In summary, elderly patients with HCC are more likely to female and HCV carriers compared with younger patients. The degree of background liver fibrosis and tumor-related factors may differ considerably between the two groups. Aging is closely associated with liver carcinogenesis.

SR

Along with LT, SR is regarded as a curative treatment approach for resectable HCC [2, 4, 5, 15, 16, 41, 42, 58]. Furthermore, with technical advancement in surgery for HCC, SR for elderly HCC patients has become safer [59]. Although there is no specific age limitation for surgery for HCC in Japan, elderly patients may have shorter long-term survival after surgery as compared with younger patients because of their expected life span [8, 24–33, 53, 60]. SR for HCC in elderly patients thus deserves serious consideration. According to the European Association for the Study of the Liver (EASL) guidelines, SR is indicated in HCC patients with a single tumor not exceeding 2 cm in diameter, PS 0, Child–Pugh class A, and no portal hypertension [41]. SR is considered the initial first-line treatment for resectable HCC because of its generally good outcome, and the lack brain-dead liver donors in Japan [12]. There have been several studies regarding the outcome and safety in elderly patients with HCC treated with SR [24–33, 47, 53–55, 61, 62].

Sato et al. studied the mortality and complication rates for hepatectomy for HCC in a large sample, using a nationwide Japanese database [Diagnosis Procedure Combination (DPC) database] [61]. Their multivariate logistic regression analyses for in-hospital mortality after hepatectomy for HCC revealed that, with age <60 years as a reference, 60–69 years [hazard ratio (HR), 2.12], 70–79 years (HR, 3.12) and >80 years (HR, 2.48) were significantly associated with in-hospital mortality [61]. This suggested that increased age was closely associated with mortality in patients who underwent surgery for HCC.

Kaibori et al. retrospectively studied the clinicopathological data and outcomes for 333 patients aged <70 years and 155 aged ≥70 years who underwent SR [55]. The overall survival (OS) rates at 3, 5 and 7 years were 69.7%, 57.3% and 44.0%, respectively, in the younger group and 70.3%, 54.6% and 35.8% in the elderly group ($P = 0.7940$). The corresponding 3-, 5- and 7-year disease-free survival (DFS) rates were 38.5%, 22.5% and 18.9%, respectively, in the younger group and 29.9%, 21.1% and 18.1% in the elderly group ($P = 0.1856$). In terms of surgery-related complications, there was no significant difference in the two groups ($P = 0.7614$) [55]. They therefore concluded that clinical outcomes of SR for HCC were similar in younger and elderly patients with HCC [55].

In our comparative studies of clinical outcomes and safety between elderly patients who underwent curative SR (≥75 years, n = 92) and younger patients (<75 years, n = 206), the 1-, 3- and 5-year OS rates after surgery were 90.0%, 73.3% and 43.0%, respectively, in the elderly group and 91.0%, 77.5% and 64.4% in the control group ($P = 0.188$). The corresponding recurrence-free survival (RFS) rates were 66.3%, 38.8% and 26.2%, respectively, in the elderly group and 66.3%, 38.8% and 22.2% in the control group ($P = 0.634$). There was no significant difference between the two groups in terms of surgery-related serious adverse events (SAEs) ($P > 0.999$) [29]. Thus, we concluded that SR appears to be a safe and feasible procedure for the treatment of HCC in elderly patients.

Portolani et al. demonstrated in a multivariate analysis of 175 elderly HCC patients who received surgery that major resection was an adverse predictor linked to OS ($P = 0.021$) [62]. They concluded that major resection in elderly patients with HCC must be reserved for selected cases, although they claimed that limited liver resection is a valid option for the treatment of HCC in elderly patients.

Interestingly, there is one report from Japan regarding the outcome of repeat hepatectomy for recurrent HCC in elderly patients with HCC [34]. The authors reported that there was no significant difference in the incidence of postoperative complications or the duration of postoperative hospital stay between elderly (≥75 years, n = 33) and younger (<75 years, n = 88) patients. The 3-year OS rates for the younger and elderly groups were 83% and 73%, respectively ($P = 0.51$). The 3-year DFS rates for the younger and el-

derly groups were 35% and 38% (*P* = 0.88) [34]. Repeat hepatectomy may be a safe procedure in some elderly patients with HCC.

In summary, elderly patients with HCC who underwent SR had comparable prognosis compared with younger patients, and SR for elderly patients with HCC may be safe. Previous studies regarding comparison of survival of SR in elderly patients and younger patients are summarized in Table 1.

LT

LT is considered as an important treatment option in western countries even in patients with decompensated cirrhosis of various causes [4, 63–65]. Given the Milan criteria are satisfied, living-donor partial LT for the treatment of decompensated cirrhosis complicated with HCC has been covered by the national health insurance system in Japan since 2004 [66]. Living-donor LT is the major choice of treatment because of the shortage of brain-dead donors in Japan [4, 63–67].

There is an arbitrary age limit for LT because of the increased comorbidity in elderly patients [68]. In general, HCC patients aged >65–70 years are not considered as potential candidates for LT [69]. However, there are several data regarding clinical outcomes in elderly patients with or without HCC who underwent LT [60, 68–72].

Randell et al. reported that for LT recipients aged >65 years, the annual death rate per 1000 patients at risk rose from 49 in 1991 to 185 in 2000 [71]. They emphasized that although elderly patients should not be completely excluded as candidates for LT, careful consideration during the evaluation process is required. Zetterman et al. also demonstrated that recipient age was a significant predictor for survival in patients with HCV infection [72].

Table 1. Previous studies regarding comparison of clinical outcomes in younger and elderly patients treated with surgical resection for hepatocellular carcinoma.

Author/ year/country	Treatment	Definition of elderly patient	No. of patient		OS		R(D)FS		Morbidity rate		Mortality rate	
			Y	E	Y	E	Y	E	Y	E	Y	E
Takenaka et al /1994/Japan [33]	Surgery	≥70 years	229	39	51.6% (5-year)	75.9%** (5-year)	31.0% (5-year)	30.4%** (5-year)	2% (LF only)	10%* (LF only)	1.0%	5.0%**
Poon et al /1999/China [27]	Surgery	≥70 years	299	31	51% (3-year)	58%** (3-year)	38% (3-year)	27%** (3-year)	40%	48%**	6%	10%**
Cescon et al /2003/Italy [53]	Right hepatectomy	≥70 years	99	23	53.9% (3-year)	64.2%** (3-year)	NA	NA	32.3%	39.1%**	2.0%	0%**
Yeh et al /2004/Taiwan [28]	Surgery	≥70 years	398	34	45.5% (3-year)	64.3%** (3-year)	26.5% (5-year)	28.7%** (5-year)	NA	NA	7.7%	10.5**
Zhou et al. /2006/China [30]	Surgery	≥65 years	125	54	49.1% (3-year)	56.8%** (3-year)	33.8% (3-year)	36.0%** (3-year)	NA	NA	2.4%	0%**
Kondo et al /2008/Japan [24]	Surgery	≥70 years	199	95	NA	NA**	NA	NA	43.8%	41.3%**	NA	NA
Kaibori et al /2009/Japan [55]	Surgery	≥70 years	333	155	69.7% (3-year)	70.3% (3-year)	38.5% (3-year)	29.9%** (3-year)	19%	18%**	4%	3%**
Oishi et al /2009/Japan [47]	Surgery	≥75 years	504	62	81% (3-year)	77%** (3-year)	46% (3-year)	43%** (3-year)	19%	22%**	1%	0%
Huang et al /2009/China [25]	Surgery	≥70 years	268	67	39.9% (3-year)	54.6%* (3-year)	40.8% (3-year)	57.7%** (3-year)	4.5%	9%**	1.1%	1.5%**
Shirabe et al /2009/Japan [54]	Surgery	≥80 years	43	307	84.4% (2-year)	75.6%** (2-year)	NA	NA	22%	26%**	0%	0.3%**
Mirici-Cappa et al /2009/Italy [32]	Surgery	≥70 years	43	142	61.6% (3-year)	67.3%** (3-year)	NA	NA	NA	NA	NA	NA
Portolani et al /2011/Italy [62]	Limited resection	≥70 years	276	175	NA	NA**	41.9% (3-year)	37.1%** (3-year)	16.7%	16.0%**	4.2%	3.2%**
Su et al /2012/Taiwan [26]	Surgery	≥55 years	700	374	67.3% (3-year)	66.4%* (3-year)	NA	NA**	NA	NA	NA	NA
Nishikawa et al /2013/Japan [29]	Surgery	≥75 years	206	92	77.5% (3-year)	73.3%** (3-year)	38.8% (3-year)	38.8%** (3-year)	15.5%	16.3%**	NA	NA

OS; overall survival, R(D)FS; recurrence (disease)-free survival, Y; younger patients, E; elderly patients, LF; liver failure, NA; not available, * statistically significant, ** statistically not significant.

Taner et al. reported in 13 patients (aged ≥75 years) who underwent orthotopic LT that there were no intraoperative or perioperative deaths and seven patients are still alive with a mean survival period of 65 months [68]. They concluded that advanced age itself is not considered a contraindication for LT. A recent report from Canada demonstrated in 822 patients who received deceased donor LT (197 donors aged >60 years) that HCV infection and recipient age were the only adverse predictors for graft and patient survival in those receiving an older graft [70].

With regard to LT for patients with HCC, a recent report from Switzerland revealed in 30 HCC patients experiencing post-transplant HCC recurrence that time from transplant to HCC recurrence (*P* = 0.001) and history of rejection (*P* = 0.043) were independent predictors linked to post-recurrence survival, and advanced age was not a significant predictor associated with survival [60].

Overall, although LT for elderly patients is not always contraindicated, thoughtful consideration for LT and careful observation after LT are needed.

Percutaneous treatment

Since its introduction in Japan in 1999, RFA has rapidly gained popularity because of its excellent antitumor effect, safety and low invasiveness. Now, RFA is the first-line percutaneous treatment for HCC [1–5, 21, 39, 73–78]. The current EASL guidelines recommend percutaneous RFA for HCC with PS 0–2, Child–Pugh class A or B, and ≤3 unresectable tumors of ≤3 cm diameter. Even in patients with unresectable tumors >3 cm, percutaneous RFA in combination with TACE is recommended to expand the ablated area [42, 79]. More recently, several investigators have used RFA to treat selected patients with resectable HCC with favorable clinical outcomes, and RFA is gradually gaining popularity in the treatment of resectable HCC in many countries, in addition to Japan [78].

In general, elderly patients have a high incidence of comorbidity such as cardiovascular disease, diabetes mellitus and chronic renal disease, and are considered high-risk patients for SR [22–34, 53–55, 62]. Thus, radical SR of HCC may be less feasible in elderly patients than in younger patients in several aspects, and RFA therapy may be an acceptable alternative [74–80].

Sato et al. studied the mortality and complication rates for RFA of HCC in a large sample, using a nationwide Japanese database (DPC) [61]. Their multivariate logistic regression analyses for in-hospital mortality after RFA for HCC revealed that, with age <69 years as a reference, 70–79 years (HR, 7.05) and >80 years (HR, 8.12) were significantly associated with in-hospital mortality. This suggested that increased age was closely associated with mortality in patients who underwent RFA for HCC, as well as in those who underwent surgery.

Shiina et al. conducted a large single-center retrospective study involving 1170 HCC patients [269 (23.0%) >75 years old] who underwent RFA [76]. In their multivariate analysis, increasing age was significantly associated with OS [HR, 1.03; 95% confidence interval (CI), 1.02–1.04; *P* < 0.0001] [76].

Takahashi et al. conducted a retrospective comparative study between younger (<75 years, n = 354) and elderly (≥75 years, n = 107) patients who underwent curative RFA [22]. The cumulative OS rates at 3 and 5 years were 82% and 61%, respectively, in the elderly group and 80% and 63% in the younger group (*P* = 0.824). The cumulative RFS rates were 49% at 3 years in the elderly group and 49% at 3 years in the younger group (*P* = 0.594). The major complication rates were 2.8% (3/107) in the elderly group and 3.67% (13/354) in the younger group. They concluded that RFA treatment might be safe and effective in elderly patients, as well as younger HCC patients [22]. In our recent comparative study (n = 368: 130 HCC patients aged ≥75 years and 238 HCC patients aged <75 years), the 1- and 3-year OS rates after RFA were 90.0 and 64.1%, respectively, in the elderly group, and 97.6 and 83.7% in the younger group (*P* = 0.001) [21]. The corresponding RFS rates after RFA were 66.9% and 21.3%, respectively, in the elderly group and 80.5% and 40.0% in the younger group (*P* = 0.001). The 1- and 3-year local tumor progression rates after RFA were 15.0% and 43.0%, respectively, in the elderly group and 8.3% and 26.3% in the younger group (*P* = 0.002). In terms of SAEs related to RFA, there was no significant difference between these two groups (*P* = 0.670). We concluded that clinical outcomes in the elderly group were poorer than those in the younger group, although RFA in the elderly patients was a safe procedure.

Overall, whether elderly patients with HCC treated with ablative therapies have comparable clinical outcomes as compared with younger patients remains controversial. Previous reports with regard to comparison of survival of ablative therapies in elderly patients and younger patients are summarized in Table 2.

TACE

TACE is a procedure whereby an embolizing agent after intra-arterial injection of an anticancer drug is injected into the hepatic artery to deprive the

tumor of its major nutrient source via embolization of the nutrient artery, resulting in ischemic necrosis of the tumor [81–88]. TACE is the most frequently used treatment for unresectable HCC in Japan where it was originally developed [82, 85–88]. The EASL guidelines recommend TACE for unresectable, Child–Pugh class A or B multiple HCC with no vascular invasion, whereas in Japan, TACE is recommended even for HCC patients with vascular invasion if radiological portal invasion (Vp) is Vp1 or Vp2 [41, 42].

Previously, old age was considered to be a contraindication for TACE in the treatment of HCC [89]. However, a recent study demonstrated that the prognostic factors affecting the survival of HCC patients treated with TACE included: (1) tumor stage; (2) tumor markers; and (3) hepatic functional reserve [82]. Advanced age was not an adverse predictor in patients with HCC treated with TACE.

Yau et al. conducted a large comparative study in 1040 HCC patients treated with TACE (197 aged ≥70 years and 843 <70 years) [44]. Both the overall median survival (14.0 *vs.* 8.1 months, *P* < 0.003) and disease-specific survival (15.2 *vs.* 8.7 months, *P* < 0.001) were significantly higher in elderly than young patients and no significant difference was observed in terms of TACE-related mortality between the young and elderly patients (3% *vs.* 4%, *P* = 0.49). They concluded that elderly patients with HCC treated with

TACE had comparable efficacy and tolerability to those in younger patients.

Likewise, Cohen et al. conducted a prospective cohort study regarding TACE for HCC including 102 HCC patients (34 aged ≤65 years, 45 aged 65–75 years, and 23 aged ≥75 years) [14]. Their results revealed that OS rates at 1, 2 and 3 years were 74%, 37% and 31%, respectively, in patients aged <65 years; 83%, 66% and 48% in patients aged 65–75 years; and 86%, 41% and 23% in patients aged ≥75 years (*P* = 0.19). Advanced age was not associated with the rate of adverse events.

A recent study from Italy compared the outcomes among elderly (≥70 years, n = 128) and younger patients (<70 years, n = 197) with unresectable HCC who received radioembolization [90]. It demonstrated that radioembolization was equally well tolerated in the two groups and there was no significant difference in survival between the two groups (*P* = 0.942). This suggested that radioembolization is well-tolerated and effective for elderly as well as younger patients.

Overall, elderly patients with unresectable HCC treated with TACE had comparable clinical outcomes compared with younger patients and TACE for elderly patients with unresectable HCC seems to be a safe procedure. Previous studies comparing survival of TACE for HCC in elderly and younger patients are summarized in Table 2.

Table 2. Reports of previous studies regarding of comparison of clinical outcomes in younger and elderly patients treated with locoregional therapies for hepatocelluar carcinoma.

Author /year/country	Treatment	Child-Pugh	Definition of elderly patient	No. of patient		OS		R(D)FS		Morbidity rate		Mortality rate	
				Y	E	Y	E	Y	E	Y	E	Y	E
Tateishi et al /2005/Japan [77]	RFA	A/B	≥68 years	160	159	79.2% (3-year)	76%** (3-year)	NA	NA	NA	NA	NA	NA
Takahashi et al /2010/Japan [22]	RFA	A/B	≥75 years	354	107	80% (3-year)	82%** (3-year)	49% (3-year)	49%** (3-year)	3.7%	2.8%**	0%	0%**
Mirici-Cappa et al /2010/Italy [32]	RFA or PEI	A/B/C	≥70 years	230	195	52.9% (3-year)	53.4%** (3-year)	NA	NA	NA	NA	NA	NA
Kao et al /2012/Taiwan [23]	RFA	A/B	≥65 years	100	158	87% (3-year)	83.1%* (3-year)	39.8% (3-year)	21.9%* (3-year)	NA	NA	NA	NA
Nishikawa et al /2012/Japan [21]	RFA	A/B	≥75 years	238	130	83.7% (3-year)	64.1%* (3-year)	40.0% (3-year)	21.3%* (3-year)	1.3%	2.3%**	0%	0%**
Poon et al /1999/China [27]	TACE	A/B	≥70 years	317	67	18% (3-year)	25%** (3-year)	NA	NA	26%	24%**	5%	7%**
Yau et al /2009/China [44]	TACE	A/B/C	≥70 years	843	197	14.9% (3-year)	23.2%* (3-year)	NA	NA	27%	24%**	3.5%	4.7%**
Mirici-Cappa et al /2010/Italy [32]	TACE	A/B/C	≥70 years	396	158	32.0% (3-year)	36.4%** (3-year)	NA	NA	NA	NA	NA	NA
Cohen et al /2013/Israel [14]	TACE	A/B/C	≥75 years	38(<65yr)/ 41(65-75yr)	23	31%/ 48% (3-year)	23%** (3-year)	NA	NA	NA	NA	NA	NA

OS; overall survival, R(D)FS; recurrence (disease)-free survival, Y; younger patients, E; elderly patients, RFA; radiofrequency ablation, PEI; percutaneous ethanol injection, TACE; transcatheter arterial chemoembolization, NA; not available, * statistically significant, ** statistically not significant.

Molecular-targeted therapy (sorafenib)

There has long been a lack of concrete evidence to support systemic chemotherapy for unresectable advanced HCC [91]. However, after the clinical efficacy of a molecular-targeted drug, sorafenib, for unresectable advanced HCC was shown in two RCTs (SHARP trial and Asia–Pacific trial), this drug was approved for the treatment of unresectable advanced HCC in Japan in 2009 [92, 93]. The EASL guidelines recommend sorafenib for unresectable, advanced, Child–Pugh class A or B HCC with PS 0–2 and vascular invasion or distant metastasis [41]. According to the Japanese guidelines, sorafenib is recommended for unresectable, advanced, Child–Pugh class A HCC with vascular invasion or distant metastasis, as well as for patients intolerant to TACE or in whom the procedure of TACE is anatomically unsuitable [42, 94, 95].

Systemic chemotherapy for advanced cancer is often either modified or withheld for the management of elderly patients with advanced cancer for fear of potential toxicity [96–98]. Furthermore, several adverse events associated with sorafenib have been reported [92–95, 99–105]. Especially in elderly patients with advanced HCC who undergo sorafenib therapy, caution is needed for the expected SAEs, because they have higher comorbidity and poorer PS, and SAEs cause treatment discontinuation [96–98].

Wong et al. compared the efficacy and tolerability of sorafenib elderly (age ≥70 years, n = 37) and younger (age <70 years, n = 135) patients with advanced HCC [96]. The median progression-free survival time was similar in the elderly and younger groups (2.99 months *vs.* 3.09 months; P = 0.275), as was the OS time (5.32 months *vs.* 5.16 months; P = 0.310). Grade 3 or 4 SAEs were observed in 68.6% of the elderly and 62.7% of the younger patients (P = 0.560). They concluded that the survival benefits and overall treatment-related SAEs of sorafenib are comparable in elderly and younger patients with advanced HCC. Likewise, a study from Italy investigated the impact of age on the effects of sorafenib therapy in patients with HCC and LC [97]. In 150 patients [90 in the younger group (<70 years) and 60 in the elderly group (≥70 years)], the median time to progression (TTP) and OS were longer in the elderly than the younger group (12 *vs.* 8 months and 16 *vs.* 12 months, respectively), although the differences were not significant. Grade 3 and 4 SAEs were more frequent in the younger than the older group (15.7% *vs.* 9.2%, respectively; P = 0.0146), suggesting that elderly patients with HCC and LC tolerate sorafenib therapy compared with younger patients with HCC and LC.

On the contrary, Morimoto et al. reported that the discontinuation rate of sorafenib therapy for advanced HCC because of SAEs was more frequent among patients aged ≥75 years (41.7%) than among those aged <75 years (15.0%) with the standard dose of sorafenib (800 mg daily) (P = 0.047) [106].

There is one report about the usefulness of a reduced starting dose of sorafenib in elderly patients with advanced HCC [98]. In 60 elderly patients with HCC aged ≥70 years who received reduced dose sorafenib, median TTP was 7.0 months (95% CI, 5.2–8.7 months) and median survival was 10.0 months (95% CI, 5.0–14.9 months). Quality of life did not show any significant change during the study. The results emphasized the usefulness of reduced dose sorafenib in elderly patients with HCC.

However, there is still a lack of sufficient evidence of clinical usefulness and safety of sorafenib therapy in elderly patients with advanced HCC. Further cumulative clinical evidence is needed.

Conclusion

We reviewed the clinical characteristics and outcomes of each therapy in elderly patients with HCC. Etiology of background liver disease, male to female ratio, degree of liver fibrosis, proportion of patients with comorbidity, and tumor characteristics differ considerably between elderly and younger patients with HCC. In each therapy for HCC, that is, SR, LT, ablative therapies, TACE and MTT, some elderly patients with HCC may have comparable clinical outcomes and safety compared with younger patients. However, further clinical evidence is needed to confirm these results.

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Conflict of interest

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