The number of elderly patients with hepatocellular carcinoma (HCC) has been increasing. Characteristics of elderly HCC patients are a higher proportion of females, a lower rate of positive hepatitis B surface antigen, and a higher rate of positive hepatitis C antibodies. Careful patient selection is vital for performing hepatectomy safely in elderly HCC patients. Treatment strategy should be decided by not only considering tumor stage and hepatic functional reserve, but also physiological status, including comorbid disease. Various assessment tools have been applied to predict the risk of hepatectomy. The reported mortality and morbidity rates after hepatectomy in elderly HCC patients ranged from 0% to 42.9% and from 9% to 51%, respectively. Overall survival rate after hepatectomy in elderly HCC patients at 5 years ranged from 26% to 75.9%. Both short-term and long-term results after hepatectomy for strictly selected elderly HCC patients are almost the same as those for younger patients. However, considering physiological characteristics and the high prevalence of comorbid disease in elderly patients, it is important to assess patients more meticulously and to select them strictly if scheduled to undergo major hepatectomy.

Core tip: The number of elderly patients with hepatocellular carcinoma (HCC) has been increasing. Careful patient selection is vital for performing hepatectomy safely in elderly HCC patients. Treatment strategy should be decided by not only considering tumor stage and hepatic functional reserve, but also physiological status, including comorbid disease. Both short-term and long-term results after hepatectomy for strictly selected elderly HCC patients are almost the same as those for younger patients. However, considering physiological characteristics and the high prevalence of comorbid disease in elderly patients, it is important to assess patients more meticulously if scheduled to undergo major hepatectomy.

Key words: Hepatocellular carcinoma; Hepatectomy; Elderly

INTRODUCTION
Hepatocellular carcinoma (HCC) is the third-leading cause of death worldwide. Age-standardized incidence
rates in Eastern Asia are 35.5 per 100000 in males and 12.7 per 100000 in females. An estimated 748300 new liver cancer cases and 695000 cancer deaths occurred worldwide in 2008\[1\]. Hepatitis B virus (HBV) infection or hepatitis C virus (HCV) infection is recognized as the major risk factor for development of HCC. In fact, it has been estimated that HBV infection is associated with 50%-80% of HCC cases worldwide, whereas HCV infection is implicated in the pathogenesis of 10%-25% of HCC cases. The incidence of HCC in cirrhotic liver associated with HBV or HCV infection is between 1% and 7% per year. Another cause of cirrhosis in which HCC can develop is alcohol abuse. Non-alcoholic steatohepatitis-related cirrhosis is also a risk factor for the development of HCC. A recent study has suggested that aging itself might be a factor affecting hepatocarcinogenesis\[2\].

Average life expectancy at birth has been increasing worldwide. In Japan, 75-year-old men and women have average expected life spans of around 5 and 10 years, respectively. An 80-year-old male has an average life expectancy of 8.26 years, while a female aged 80 years can expect to live another 11.04 years\[3\].

The number of elderly HCC patients has been increasing\[4,5\]. The average age of HCC patients and the proportion of elderly HCC patients in Japan are increasing. A recent report showed that the mean ages at diagnosis of HCC were 66.4 years in males and 69.9 years in females\[6\]. Another recent report showed that patients over 70 years of age constitute more than 50% of those undergoing hepatectomy for HCC\[7\]. HCC is considered to be a life-limiting factor even in very old patients. Therefore, in patients with good liver function and performance status (PS), hepatectomy for HCC might improve the survival rate, even in very old patients\[8\]. Aging causes several problems due to a decline in the functional reserve of multiple organ systems and the high prevalence of comorbidity in the treatment of HCC.

This review summarizes the physiology, characteristics, preoperative risk assessment, and clinical outcomes in elderly HCC patients undergoing hepatectomy.

**DEFINITION OF ELDERLY**

The “elderly” are not clearly defined as a homogeneous population because different age subsets, divided with ages ranging from 65 to 80 years, are mixed. Elderly individuals have been defined in reports as individuals of ages ranging from 65 to 80 years, are mixed. Elderly individuals have been defined in reports as individuals of ages ranging from 65 to 80 years, are mixed. Elderly in the reserve of multiple organ systems and the high prevalence of comorbidity in the treatment of HCC.

**PHYSIOLOGICAL ALTERATION OF THE LIVER CAUSED BY AGING**

Aging changes biological functions in many organs. Several vital proteins such as albumin, prothrombin, and fibrinogen are produced in the liver; albumin maintains the isotonic environment of the blood (with serum albumin level being a good indicator of the nutritional index in elderly people), prothrombin is related to coagulation ability, and fibrinogen is related to hemostasis by helping blood clots to form. With advancing age, the ability to synthesize proteins (especially albumin) and the metabolic function of the liver generally declines. Furthermore, the volume and blood flow of the liver in elderly people is decreased\[9\].

The liver is a characteristic organ that is able to regenerate itself after hepatic resection\[10,11\]. It is known that after hepatic resection, the remaining liver expands in volume to compensate for lost tissues. The volume of the liver after remnant liver regeneration is not different between elderly and young people. However, findings after surgical resection have revealed that the effect of aging on the liver is delayed and there is reduced proliferation immediately after loss of liver mass\[12\]. The liver in living-related older donors does not regenerate as quickly as those in younger donors\[13\]. In an animal experiment, it was found that synthesis of DNA isolated from regenerating livers of aged rats was reduced and delayed compared with that of DNA from young rats\[14\].

An early study demonstrated that major hepatectomy for elderly patients with primary liver cancer resulted in a high mortality rate (23%), with the main cause of death being hepatic insufficiency. It was reported that cirrhosis led to an unacceptable mortality rate of 44% after hepatic resection of 5 or more segments of the liver\[15\]. The loss of regenerative capacity in older livers may cause serious problems in recovery after major hepatectomy in elderly patients. However, a recent study showed that mortality rate in elderly patients (70 years of age or more) who underwent major hepatectomy was 7.9%, which was not so different from that in younger patients (5.4%), although most patients enrolled in that study had metastatic cancer\[16\].

**COMORBID DISEASE**

In general, the proportion of comorbid disease such as cardiovascular, cerebrovascular, pulmonary disease, renal disease, hypertension, and diabetes mellitus is higher in elderly patients than in younger patients\[17-19,21-23,33-35\]. The proportion of comorbid disease in elderly patients...
is double that of younger patients. More than 80% of cancer patients over 65 years of age have at least one comorbid disease requiring treatment[16].

Nanashima et al[1] demonstrated that preoperative comorbidity significantly increased with age in HCC patients who underwent hepatectomy. Huang et al[4] reported that most comorbidities in elderly HCC patients were well-controlled before hepatectomy, although elderly patients did present with a significantly higher frequency of preoperative comorbidities than in younger patients. Especially for elderly patients, it is necessary to assess comorbid disease and to consider the balance with treatment effect of hepatectomy and the risk of morbidity after hepatectomy. The presence of comorbid diseases has been shown to be an important risk factor of mortality or morbidity after surgical procedures in various surgical risk models mentioned below[36-39].

Diabetes mellitus is also a frequent comorbid disease in elderly patients. Diabetes mellitus increases the risk of HCC development[38]. Moreover, diabetes mellitus in HCC patients after hepatectomy is related to a higher rate of postoperative morbidity and poorer postoperative survival rates[39]. A recent report warns liver surgeons against shocking results of major hepatectomy for patients with metabolic disorders. Postoperative mortality in patients undergoing right hepatectomy with two or more metabolic disorders including diabetes mellitus, hypertension, dyslipidemia, and obesity reached 30%. Moreover, the mortality rate in patients with three or more metabolic disorders reached 54%[37]. Although it is essential to control metabolic disorders medically before hepatectomy, the indication of major hepatectomy for patients with serious metabolic disorders should be reconsidered.

Table 1  General surgical risk model in hepatectomy

| Table 1 General surgical risk model in hepatectomy |
|---------------------------------------------------|
| **Physiological parameters** | **E-PASS** | **APACHE II score** |
| Age | | |
| Cardiac history | | |
| Respiratory history | | |
| Blood pressure | | |
| Pulse rate | | |
| Glasgow Coma scale | | |
| Hemoglobin level | | |
| White cell count | | |
| Urea concentration | | |
| Serum sodium level | | |
| Serum potassium level | | |
| Serum creatinine | | |
| Electrocardiography | | |
| Physiological and operative severity score for the enucleation of the primary tumor (POSSUM) | Blood loss/body weight | |
| Multiple procedures | Operation time | |
| Total blood loss | Extent of skin incision | |
| Peritoneal seeping | | |
| Presence of malignancy | | |
| Mode of surgery | | |
| Operative parameters | | |

The treatment strategy for HCC patients is decided mainly according to their physiological status, hepatic functional reserve, and tumor stage. Hepatectomy for HCC patients, especially for elderly HCC patients, is still a risky procedure with significant morbidity and mortality. The prevalence of HCC in a series of elderly patients undergoing hepatectomy ranged from 22.7% to 46.7%[40,41]. Patient with poor physiological status are not candidates for such invasive procedures as hepatectomy. Careful patient selection is vital to achieving acceptable outcomes after hepatectomy (Table 1).

According to the guidelines of clinical practice for HCC in Japan[42], treatment strategies should be decided by considering both the tumor factor and hepatic functional reserve. There is no restriction for age or PS in said guidelines. Barcelona-Clinic Liver Cancer staging classification and treatment schedule classifies HCC patients by variables related to tumor stage, liver functional status, physical status, and cancer-related symptoms. With regard to physical status, hepatectomy is indicative for a patient with PS 0, 1, or partial 2.

Evidence-based, patient-specific risk prediction is valuable in the decision-making process. Although age by itself is not a strong risk factor of mortality or morbidity, when considering other physiologic factors[43], age may be a proxy for physiological reserve[44,45] and a surrogate marker for undeclared comorbidity. Thus, we have to determine candidates for hepatectomy by not only considering tumor stage and hepatic functional reserve, but also via the use of physiological assessment tools. The variety of scoring systems for surgical procedures indicates how numerous the variables are that can be analyzed to derive mortality and morbidity rates.

The American Society of Anesthesiologists (ASA) score, which is widely used, is a useful indicator of morbidity after abdominal surgery in elderly patients[46], and is incorporated in a number of other scoring systems. The advantages of the ASA score are that it can be simply applied and is better for risk stratification, while the disadvantages are that it is not designed as an operative risk score, and it is not specific or predictive[47].

Physiological and operative severity score for the enumeration of mortality and morbidity (POSSUM score)[48] and Portsmouth POSSUM (P-POSSUM)[49], and estimation of physiologic ability and surgical stress (E-PASS) score[50,51] have been reported as measures for surgical audit to objectively evaluate the operative risk by the preoperative condition of the patient and the surgical stress.

POSSUM and P-POSSUM provide information on predicted risk in terms of morbidity and mortality. Clinical parameters included in POSSUM/P-POSSUM and E-PASS scoring are shown in Table 1. Both scoring systems consist of physiologic and operative parameters. At present, the predicted mortality and morbidity rates from the POSSUM or P-POSSUM scoring systems can be eas-
There are a few scoring systems, in which age of the patient or physiological status is factored, that are specific to HCC patients for hepatectomy to estimate the risk of in-hospital death after hepatectomy. Recently, Simons et al. developed a simple risk scoring system to estimate the risk of in-hospital death after resection of HCC. The five patient characteristics used to predict in-hospital mortality after hepatectomy include age group, sex, Charlson comorbidity score group, procedures for HCC, and teaching hospital status. The strongest predictors of in-hospital death were a Charlson score of 3 or more (indicating at least 2 comorbid conditions or those of greater severity) and a more invasive procedure (lobectomy). The total possible score was 22. They graded the patients into 4 groups: low, scores from 0 to 4; low to moderate, scores from 5 to 9; moderate to high, scores from 10 to 14; and high, scores from 15 to 22. The estimated mortality rates in these 4 groups were 1.48%, 3.98%, 10.33%, and 28.30%, respectively. The risk score for patients older than 75 years was 3 (Table 2).

A preoperative nomogram using a population-based database in the USA to predict perioperative mortality risk after liver resections for malignancy has recently been developed[50]. The risk factors of this nomogram include age, race, gender, liver primary, coagulopathy, renal failure, congestive heart failure, cardiac arrhythmias, and other major comorbidities. The nomogram was successfully validated by a high-volume center and is the only clinical tool that has been externally validated to predict preoperative mortality after liver resections for malignancy[57].

**CHARACTERISTICS OF ELDERLY HCC PATIENTS WHO UNDERWENT HEPATECTOMY**

The characteristics of elderly HCC patients are a higher proportion of females, a lower rate of positive hepatitis B surface antigen (HBs-Ag), better liver functional reserve, and a higher proportion of normal livers[8,58] (Table 3).

The hepatic resection rate for elderly HCC patients ranged from 0% to 14%; 12% -28% in younger HCC patients[8,10,34,58]. Hepatic resection rates for elderly HCC patients were lower than those for younger HCC patients. Very old patients did not frequently receive surgical treatment and were more likely to receive conservative treatment[8].

A summary of the characteristics of previously reported elderly HCC patients who underwent hepatectomy is shown in Table 3. Similarly to the characteristics of all elderly HCC patients, five studies have shown that the proportion of females in elderly HCC patients is higher than that in younger HCC patients[10,14,9,2,59]. Four of those studies were recent. The reasons for the higher proportion of females in elderly HCC patients are that the average life expectancy at birth for females is longer than that of males, and thus the proportion of females is higher than that of males in the elderly population. Moreover, the peak age of occurrence of HCC in females is 5
not different in elderly HCC patients compared to younger HCC patients\(^{[60,11,13,17,19,20,25,33,62,64]}\). Similarly, most studies have shown that the values of indocyanine-green retention rate at 15 min (ICG-R15) are not different in elderly compared to younger HCC patients\(^{[9,11,13,15,17,19,20,24,25,59,62,64]}\), while two studies showed that the values of ICG-R15 in elderly HCC patients with hepatectomy were higher than those in younger HCC patients\(^{[21,23]}\). Hepatic functional reserve in elderly HCC patients was almost the same as that in younger HCC patients. Surgeons therefore have the same treatment policy for evaluating hepatic functional reserve before hepatectomy in both elderly and younger patients.

Regarding tumor factors, Huang et al\(^{[10]}\) reported that there was a significantly higher frequency of tumor encapsulation in elderly HCC patients than in younger patients. Tumor encapsulation has been reported to be a favorable prognostic factor for HCC\(^{[65]}\). In addition, a higher incidence of tumor encapsulation indicates a higher differentiation of HCC and a lower incidence of vascular invasion\(^{[12]}\). It was suggested that a higher frequency of tumor encapsulation might be an indicator of less malignant disease in elderly patients with HCC\(^{[57]}\).

### SHORT-TERM OUTCOME OF HEPATECTOMY FOR ELDERLY HCC PATIENTS

The mortality rate after hepatectomy for elderly HCC patients ranged from 0% to 42.9% (Table 4). However, due to recent advances in surgical procedures and perioperative management, most recent studies have shown that mortality rates after hepatectomy in both elderly and younger patients are similar\(^{[14-17,20,21,23,24,25,33,35,59,61,63,64]}\). Child-Pugh B and C are risk factors of operative death for elderly HCC patients\(^{[66]}\). Regarding major hepatectomy, although the degree of liver regeneration at one month after right lobectomy in elderly patients is not different from that in younger patients, the incidence of hospital death due to hepatic failure after right lobectomy in elderly HCC patients is extremely high\(^{[68]}\). It is possible that remnant liver regeneration immediately after major hepatectomy in elderly patients is impaired\(^{[67]}\) (Table 4).

The morbidity rate after hepatectomy for elderly HCC patients ranged from 9% to 51%. Despite the high rate of comorbidity disease in elderly patients, as mentioned above, most studies have shown that morbidity rates of elderly patients are not different from those in younger patients. On the other hand, Ferrero et al\(^{[15]}\) reported that postoperative morbidity rate was lower in elderly HCC patients. Moreover, Kondo et al\(^{[14]}\) reported that the frequency of pneumonia is the only difference in postoperative complications.

Meanwhile, the mortality and morbidity rates after hepatectomy in elderly patients with colorectal liver metastasis (CLM) range from 0% to 8% and 14.2% to 52.5%, respectively. The rates in elderly patients with CLM are not different from those in elderly patients with HCC\(^{[60]}\).

### Table 2 Risk assessment specific for elderly patients undergoing hepatectomy

| Simple Risk Score | Nomogram |
|-------------------|----------|
| Physiological parameters | Point | Point |
| Age | Point | Age |
| ≤ 55 | 0 | 18-54 |
| 55-75 | 1 | 55-70 |
| > 75 | 4 | ≥ 70 |
| Sex | Point | Sex |
| Women | 0 | Women |
| Men | 1 | 1 |
| Hospital type | Point | Race |
| Teaching | 0 | White |
| Nonteaching | 3 | Non white |
| Charlson comorbidity score | Absolute type | Admission type |
| 0 | 0 | Elective |
| 1 | 3 | Urgent/Emergent |
| 2 | 4 | Liver primary |
| ≥ 3 | 8 | No |
| | | Yes |
| | | 25 |
| | | Hypertension |
| | | Yes |
| | | 0 |
| | | No |
| | | 61 |
| | | Coagulopathy |
| | | No |
| | | 0 |
| | | Yes |
| | | 100 |
| | | Renal failure |
| | | No |
| | | 0 |
| | | Yes |
| | | 87 |
| | | Congestive heart failure |
| | | No |
| | | 0 |
| | | Yes |
| | | 49 |
| | | Cardiac arrhythmias |
| | | No |
| | | 0 |
| | | Yes |
| | | 47 |
| | | Liver disease |
| | | No |
| | | 0 |
| | | Yes |
| | | 41 |
| | | Fluid and electrolyte disorders |
| | | No |
| | | 0 |
| | | Yes |
| | | 52 |
| | | COPD |
| | | No |
| | | 0 |
| | | Yes |
| | | 17 |
| | | Other neurological disorders |
| | | No |
| | | 0 |
| | | Yes |
| | | 95 |
| Operative parameters | Procedure type | Procedure type |
| Procedure type | RFA/enucleation | 0 |
| Lobectomy | 2 | Lobectomy |
| 6 | 27 | 27 |

Most studies have shown that serum albumin levels are lower in elderly patients with HCC than in younger HCC patients\(^{[12,14-17,19,20,23,33,64]}\). There are many HBV-related HCC patients in China, with lower HBs-Ag rates in elderly HCC patients being reported even in China. On the other hand, the rate of positive HCV antibody (HCV-Ab) is higher in elderly HCC patients than in younger HCC patients\(^{[10-13,17,19,20,25,33,39,62,64]}\).

Most studies have shown that serum albumin levels are lower in elderly patients with HCC than in males\(^{[60]}\).
LONG-TERM OUTCOME OF HEPATECTOMY FOR ELDERLY HCC PATIENTS

Overall survival rates after hepatectomy in elderly HCC patients at 5 years ranged from 62% to 75.9%, whereas those in younger HCC patients ranged from 31.4% to 68% [9-13,15,16,19,20,23-25,34,59,61,63,64]. Most reports demonstrated that overall survival rates after hepatectomy at 5 years are not different in elderly patients compared to younger patients [11]. Only one study showed better overall survival rates after hepatectomy at 5 years in elderly patients [33]. In that study, the overall 5-year survival rates after hepatectomy were 43.2% in the elderly group and 31.4% in the younger group, whereas 5-year disease-free survival rate in the elderly group was not significantly different from that in the younger group. Thus, it was suggested that elderly patients with HCC possibly had longer tumor-bearing survival than that of younger patients because HCC in the elderly patients was less advanced and less aggressive [27] (Table 4).

Since the majority of elderly patients have various comorbidities, deaths unrelated to HCC may have affected the survival rate in the elderly group. However, long-term results for elderly HCC patients who underwent hepatectomy were almost the same as those for younger patients. One possible explanation is that elderly patients who undergo hepatectomy might be strictly selected before referring to hospitals because hepatectomy is a more invasive procedure than other gastrointestinal surgeries.

Postoperative recurrence of HCC is the most important factor affecting survival of patients who have undergone radical resection. Repeated hepatectomy has been suggested to be the most effective treatment for recurrent HCC [20]. Even for elderly patients with recurrent HCC, repeated hepatectomy has been recommended to achieve better survival if the tumors are resectable and hepatic functional reserve is preserved [17]. Tsujita et al. [11] reported that the criteria of initial therapy for recurrent HCC are identical to those of initial treatment for primary HCC, even in elderly patients.

Overall survival rates at 5 years in elderly patients with CLM are 16% to 38%. The outcomes for elderly patients undergoing hepatectomy for HCC are better than those for elderly patients undergoing hepatectomy for CLM [20].

CONCLUSION

The average life expectancy at birth and number of elderly HCC patients have been increasing worldwide. Thus, the necessity of invasive treatments including hepatectomy for elderly patients has been increasing. Hepatectomy can now be performed safely for strictly selected elderly patients. With strict preoperative evaluation, both short-term and long-term results after hepatectomy for elderly HCC patients are almost the same as those for younger patients. Considering physiological characteristics and the high prevalence of comorbid disease in elderly patients, it is important to assess patients more meticulously and to plan an elective operation in detail for elderly patients scheduled to undergo major hepatectomy.
Table 4 Outcome of hepatectomy for elderly hepatocellular carcinoma patients

| Ref. | Year | Country | Age | Number of patients | Mortality rate (%) | Morbidity rate (%) | OS at 5 years (%) |
|------|------|---------|-----|--------------------|-------------------|-------------------|------------------|
|      |      |         |     |                    | Y     | E     | Y     | E     | Y     | E     | Y     | E     |
| Takenaka et al[9] | 1994 | Japan   | 70  | 229                | 1     | 5     | 50   | 51   | 51.6  | 75.9 |
| Yamamoto et al[10] | 1997 | Japan   | 70  | 40                 | 7     | 2.8   | NA   | NA   | NA    | NA   |
| Poon et al[11]     | 1999 | China   | 70  | 299                | 31    | 6     | 10   | 10   | 51.6  | 58.1 |
| Wu et al[12]       | 1999 | Taiwan  | 80  | 239                | 21    | 2.1   | 15.5 | 14.3 | 59.3  | 40.9 |
| Hanazaki et al[13] | 2003 | Japan   | 70  | 283                | 103   | 6     | 9.7  | 9.7  | 42.2  | 42.2 |
| Yeh et al[14]      | 2004 | Taiwan  | 70  | 398                | 34    | 7.7   | 10.5 | NA   | NA    | 39.6 |
| Ferrero et al[15]  | 2005 | Italy   | 70  | 177                | 64    | 9.6   | 3.1  | 3.1  | 32.3  | 48.6 |
| Zhu et al[16]      | 2006 | China   | 65  | 125                | 54    | 2.4   | 0    | NA   | 38.6  | 50.1 |
| Kondu et al[17]    | 2008 | Japan   | 70  | 210                | 109   | 2.9   | 3.7  | 43.8 | 41.3  | NA   |
| Kaibori et al[18]  | 2009 | Japan   | 70  | 333                | 155   | 4     | 3    | 19   | 18    | 57.3 |
| Oishi et al[19]    | 2009 | Japan   | 70  | 502                | 64    | 1     | 2    | 19   | 22    | 64   |
| Huang et al[20]    | 2009 | China   | 70  | 268                | 67    | 1.1   | 1.5  | 4.5  | 31.4  | 43.2 |
| Mirici-Cappa et al[21] | 2010 | Italy   | 70  | 142                | 43    | NA    | NA   | NA   | 32.4  | 44.8 |
| Tsuji et al[22]    | 2010 | Japan   | 70  | 77                 | 23    | 1     | 0    | NA   | NA    | 83  |
| Portolani et al[23] | 2011 | Italy   | 70  | 276                | 175   | 4.3   | 3.4  | 16.7 | 16    | NA   |
| Yamada et al[24]   | 2012 | Japan   | 80  | 267                | 11    | 0     | 0    | 3.3  | (LF)  | 43   |
| Tsuji et al[25]    | 2012 | Japan   | 80  | 385                | 23    | 0.8   | 4.3  | NA   | NA    | 84.8 |
| Nishikawa et al[26] | 2013 | Japan   | 75  | 206                | 92    | NA    | NA   | 15.5 | 16.3  | 64.4 |
| Hirokawa et al[27] | 2013 | Japan   | 70  | 120                | 100   | 2     | 2    | 35   | 32    | 64   |
| Ide et al[28]      | 2013 | Japan   | 75  | 192                | 64    | 3.1   | 3.1  | 29   | 33    | 68   |
| Isono et al[29]    | 2013 | Japan   | 75  | 186                | 66    | 1     | 0    | 19   | 26    | NA   |
| Tanai et al[30]    | 2013 | Japan   | 75  | 353                | 63    | 2.8   | 6.3  | 22.9 | 30.2  | 46.6 |
| Wang et al[31]     | 2014 | China   | 70  | 152                | 56    | 1.3   | 3.6  | 47.4 | 53.6  | NA   |

1 Represents significant difference; 2 Represents OS at 3 years. Y: Younger patients; E: Elderly patients; O5: Overall survival rate; NA: Not available; L5: Liver failure.

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| Yamada et al[33]   | 2012 | Japan   | 80  | 267                | 11    | 0     | 0    | 3.3  | (LF)  | 43   |
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P- Reviewer: Abdul-Wahed NM, De Nardi P, Zezos P
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