

## Management of hepatocellular carcinoma in the elderly

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### Abstract

Mean age of hepatocellular carcinoma (HCC) patients has been progressively increasing over the last decades and ageing of these patients is becoming a real challenge in every day clinical practice. Unfortunately, international guidelines on HCC management do not address this problem exhaustively and do not provide any specific

recommendation. We carried out a literature search in MEDLINE database for studies reporting on epidemiology, clinical characteristics and treatment outcome of HCC in elderly patients. Available data seem to indicate that in elderly patients the outcome of HCC is mostly influenced by liver function and tumor stage rather than by age and the latter should not influence treatment allocation. Age is not a risk for resection and older patients with resectable HCC and good liver function could gain benefit from surgery. Mild comorbidities do not seem a contraindication for surgery in aged patients. Conversely, major resection in elderly, even when performed in experienced high-volume centres, should be avoided. Both percutaneous ablation and transarterial chemoembolization are not contraindicated in aged patients and safety profile of these procedures is acceptable. Sorafenib is a viable option for advanced HCC in elderly provided that a careful evaluation of concomitant comorbidities, particularly cardiovascular ones, is taken into account. Available data seem to suggest that in either elderly and younger, treatment is a main predictor of outcome. Consequently, a nihilistic attitude of physicians towards under- or no-treatment of aged patients should not be longer justified.

**Key words:** Hepatocarcinoma; Epidemiology; Cirrhosis; Elderly; Treatment

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**Core tip:** The number of elderly patients with cancer is expected to rise in the next future, and facing with elderly cirrhotic patients with hepatocellular carcinoma (HCC) will characterize liver oncology scenario in the near future. International guidelines do not specifically address how to approach HCC in aged patients and no recommendations are available on age threshold to which clinical decisions should refer. Available data seem to rule out an intrinsic negative impact of age itself on HCC prognosis, and treatment allocation should be decided mainly according to HCC stage, liver residual function and general conditions. Indeed, a nihilistic

attitude to restrict treatment in this population is not longer justified.

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## INTRODUCTION

In Western countries, the number of elderly subjects is increasing, and 75 years old people may have an expected life expectancy of 5-10 years<sup>[1]</sup>. The progressive ageing of population also means that the number of elderly patients with cancer is expected to rise in the next future<sup>[2-4]</sup>. It is widely accepted that the risk of developing hepatocellular carcinoma (HCC) is age-dependent<sup>[5]</sup>; hence, in our countries, the diagnosis of HCC is more frequent in patients aged  $\geq 70$  years<sup>[6]</sup>. In fact, over the last two decades, the mean age of HCC patients at first diagnosis has progressively increased from 60 years in the mid-nineties to 70 years in more recent series<sup>[6-11]</sup>. Thus, facing with elderly cirrhotic patients with HCC is becoming a routine in clinical practice, and clinicians should be aware of the scenario that will characterize liver oncology in the near future. Therefore, investigations on the approach to HCC in aged patients are urgently warranted. International guidelines do not specifically address whether the management and outcomes of HCC in elderly patients are different from those observed in their younger counterpart<sup>[12-16]</sup>. In fact, elderly patients are usually under-represented in clinical trials or in seminal studies, which represent the key evidence to support the recommendations on HCC management. Therefore, a gap between guidelines and clinical practice may arise. In particular, no recommendations are available on age threshold to which clinical decisions should refer and older patients are merely defined as difficult-to-treat or fragile patients<sup>[17-19]</sup>. Establishing an "a priori" age threshold for HCC treatment could be viewed as unethical; in daily practice, however, age plays a critical role in the decision making process of HCC treatment, with particular reference to liver transplantation and resection.

In this brief review, we will focus on some relevant issues associated with the management of HCC in elderly patients, with the aim of providing physicians with some scientific information useful to approach the management of these patients. An extensive literature search in MEDLINE was performed with different combinations of the following keywords: "hepatocellular carcinoma" AND ["surgery" OR "hepatectomy", OR "resection", OR "radiofrequency", OR "percutaneous ablation", OR "chemoembolization", OR "TACE", OR "radioembolization", OR "sorafenib"] AND "meta-

analysis", "randomized controlled trial", "prospective study" or "retrospective study" AND "elderly". We restricted the time interval for literature search regarding overall survival and disease free survival in specific treatment approach from January 2000 to October 2014, because several international guidelines on management of HCC have been produced worldwide in that period. However, we included few articles published before, because of their relevance on general epidemiology and changing population scenario of HCC. In addition, bibliographies of review articles were hand-searched to identify additional relevant studies and randomized controlled trial on therapeutic outcome in elderly, which were considered for analysis. Only articles published in full text and in English language were considered. Abstracts were not included. The title and abstract of studies identified in the search were reviewed by two authors independently (Borzio M and Dionigi E) to exclude studies that did not address the specific research question of interest. After this initial screening, a cross-checked to identify discrepancies was done. If multiple publications from the same cohort were found, the most recent report was considered. The latest electronic search date was the 30 October 2014.

## ELDERLY: DEFINITION OF AND CLINICAL IMPLICATION

The concept of "elderly" has become more difficult to define. Definition of elderly is still uneven, mostly because the life expectancy varies from different geographical areas. Therefore, there is no general agreement on the age at which a person should be considered old<sup>[20]</sup>. Moreover, chronological age is not necessarily a synonymous of biological age, and this latter may be different in men as compared to women. In general, the chronological age of 65 years-roughly equivalent to retirement age - is currently accepted as a threshold to define an "elderly" person. In scientific literature on liver disease, and in particular in papers dealing with HCC, the most used threshold is 70 years<sup>[21-23]</sup>. More recently, clinical studies adopting a threshold of 75/80 years have been published<sup>[24-26]</sup>.

The increasing age of the HCC population brings some drawbacks to HCC treatment, due to the occurrence of comorbidities which can be associated with reduced treatment tolerability and an increased risk of severe toxicity. In a recent survey on naïve HCC patients by our group, the prevalence of relevant comorbidities in aged patients was  $> 60\%$ <sup>[6]</sup>. Comorbidities could also limit the access to proper treatment and may represent a barrier hampering the adherence to therapeutic flow-charts recommendations by international guidelines. Moreover, comorbidities make difficult the correct staging of HCC in elderly patients. According to the classification of the barcelona clinic for liver cancer (BCLC), which is the most widely-adopted staging system worldwide, Eastern Cooperative Oncology Group Performance Status that

quantizes constitutional syndrome due to tumour burden is one of the key variables which determine disease stage and, consequently, influence treatment allocation<sup>[27]</sup>. In particular, according to BCLC, patients with a PS  $\geq$  1 are excluded from curative treatments regardless of tumour extension. However, the difference between PS 0 and 1 is very narrow, and it is based only on the ability to carry out heavy works. It appears intuitive that this ability could deteriorate simply because of ageing and/or presence of comorbidities, and it may be independent from disease stage. This problem has been recently addressed and adjustments of BCLC staging system are warranted<sup>[28]</sup>. Another problem frequently encountered in elderly patients is the reluctance of relatives in approving to invasive therapies, erroneously considered too risky. In this context, the final therapeutic decision should be taken within a multidisciplinary setting and be shared with relatives who should be made aware of survival benefit and risks of treatment balanced to life expectancy.

## EPIDEMIOLOGIC CONSIDERATIONS

Older population with HCC is characterized by a higher prevalence of females<sup>[29,30]</sup>. This likely simply reflects the longer life span in this gender. 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.

In many studies, elderly patients with HCC were more likely to be hepatitis C virus (HCV) carriers<sup>[30-43]</sup>. In fact, unlike HBV infection, most HCV infections are acquired late in life and HCV-related carcinogenesis needs a long-time interval to accomplish. Nonalcoholic steatohepatitis (NASH) is another etiologic condition frequently associated with HCC in elderly. NASH-related carcinogenesis is indeed characterized by a long-lasting and insidious development. Patients with NASH-related HCC are generally older than those with virus-related HCC<sup>[44,45]</sup>. Given that a relevant proportion of cirrhosis previously classified as cryptogenic are indeed NASH-related<sup>[46]</sup>, it must be argued that a large proportion of non-viral, non-alcoholic HCC in elderly are related to longstanding NASH, in particular when associated with diabetes<sup>[44,45]</sup>.

With respect to the gross pathology of HCC at presentation, several studies reported that in elderly patients HCC is more frequently mono-pauci focal and it is frequently associated with less advanced fibrosis. It is well-known that multifocal liver carcinogenesis is associated with the degree of liver fibrosis while, with ageing, carcinogenesis has much more time to progress even in the absence of relevant inflammation and fibrosis<sup>[26,34-42,47-52]</sup>.

It has been reported that HCC in elderly patients was more frequently encapsulated<sup>[35]</sup>. It is well known

that encapsulation is a favorable prognostic factor for HCC being indicative of higher differentiation of HCC and a lower incidence of vascular invasion<sup>[37,38]</sup>.

## HCC OUTCOME IN ELDERLY

Prospective studies specifically designed to compare the outcomes of HCC in older and younger patients are lacking. Available data on HCC outcome in elderly patients mainly derive from retrospective sub-analyses of observational, in-field surveys performed in the last decades and designed to follow HCC patients prospectively. These studies showed that short-term survival was unaffected by age and it was primarily predicted by cancer stage and the underlying cirrhosis<sup>[24,29,41]</sup>. Conversely, long-term survival in elderly patients is mostly dependent on their expected shorter life-span and occurrence of comorbidities. Kim *et al.*<sup>[29]</sup>, in a large series of Korean HCC patients, showed that non-liver related mortality was significantly higher in older patients (> 70 years) than in younger subjects, although the overall survival was similar to that found in non-aged patients.

Available data seem to rule out an intrinsic negative impact of age itself on HCC prognosis, suggesting that treatment allocation should be decided according to HCC stage, liver residual function and general conditions, rather than to age of patients. In addition, hepatic functional reserve in elderly HCC patients was almost the same as that in younger HCC patients.

Consequently, as for younger patients, in older patients the early diagnosis of HCC is mandatory and aged cirrhotic patients should not be excluded from ultrasound screening/surveillance programs. The evidence that elderly patients undergoing treatment displayed a similar survival rate compared with younger patients, and the survival rate depended solely on whether treatment was initiated, further support the role of treatment itself as an independent predictor of outcome irrespective of age<sup>[29]</sup>. Results from a sub-analysis on data collected from a large cohort of "real-life" Italian cirrhotic patients (CLIP cohort), prospectively followed over a period of twelve years, showed that being under treatment was an independent predictor of better prognosis for elderly patients<sup>[41]</sup>. This would mean that a nihilistic attitude to restrict treatment does not appear justified in this population.

## RESECTION

Hepatic resection is considered a first-line curative therapy for early HCC in patients with well-compensated cirrhosis, and in those with large tumours and without cirrhosis. However, elderly patients have long been considered unfit for surgery due to their intrinsic fragility. Moreover, practical guidelines do not specify any age limit for surgery. In the last decades, however, technical progresses have made surgery for HCC in elderly patients safer and feasible<sup>[53]</sup>. Studies comparing the outcome of HCC resection in old and young patients

**Table 1** Outcome of elderly and younger patients with hepatocellular carcinoma undergoing resection

Ref.	Age limits (yr)	O/Y	Survival (%)			DFS		
			1 yr	3 yr	5 yr	1 yr	3 yr	5 yr
Yeh <i>et al</i> <sup>[38]</sup>	70	30/398	85	64	39	NA	NA	29
Zhou <i>et al</i> <sup>[39]</sup>	70	55/124	89	57	50	74	31	30
Kondo <i>et al</i> <sup>[34]</sup>	70	109/210	80	49	38	63	34	16
Kaibori <i>et al</i> <sup>[50]</sup>	70	155/333	78	45	42	NA	NA	NA
Oishi <i>et al</i> <sup>[25]</sup>	70	62/504	79	52	47	NA	30	21
Huang <i>et al</i> <sup>[35]</sup>	70	67/268	NA	70	55	NA	38	23
Poon <i>et al</i> <sup>[23]</sup>	75	62/504	NA	77	58	NA	43	30
Tsujita <i>et al</i> <sup>[47]</sup>	75	23/77	NA	81	64	NA	46	28
Su <i>et al</i> <sup>[36]</sup>	70	31/299	83	55	43 <sup>b</sup>	69	58	47
Nishikawa <i>et al</i> <sup>[51]</sup>	70	92/206	72	40	31	65	41	36
			79	58	29	57	27	27
			75	51	40	54	38	24
			95	70	NA	60	38	NA
			96	83	NA	61	35	NA
			87	66	51	NA	NA	NA
			82	67	59	NA	NA	NA
			90	73	43	66	39	26
			91	78	64	66	39	22

<sup>b</sup> $P < 0.01$ . Data on younger patients are reported in italics. Only articles reporting on either survival and disease free survival (DFS) were considered. O/Y: Old/young.

performed in the last 15 years indeed documented encouraging results<sup>[25,26,34-39,42,47-50]</sup> (Table 1).

Many authors agree that age is not a risk factor for resection and those older patients with HCC and good liver functional reserve could gain benefit from surgery. In surgical series, the rate of HCCs diagnosed in the background of non-cirrhotic liver ranged from 0.3% to 30% approximately<sup>[37,54]</sup>. It cannot be excluded that this bias of selection may have influenced the final favourable outcome in aged patients treated with surgical resection. However, these findings may simply reflect the more scrupulous and restrictive criteria as to liver function reserve adopted in these fragile patients before allocating them to liver surgery.

Opposite conclusions were in two independent studies from different geographical areas, multivariate analysis revealed that age was an independent negative predictor of outcome after liver resection<sup>[55,56]</sup>.

Data on survival and disease free survival in old and young patients undergoing HCC resection are reported in Table 1. Post-operative mortality in elderly patients was reported to range from 0 to 3.2%<sup>[25,34-42,48-50,55-57]</sup>.

In two retrospective studies from Far East, surgery-related in-hospital morbidity and mortality were not significantly different in older as compared to younger patient<sup>[26,50]</sup>. A surprisingly high mortality (10.5%) was found in aged (> 70 years) resected patients which, however, was not so different from that observed in younger patients (7.7%).

Mild comorbidities do not seem a contraindication for surgery in aged patients. Poon *et al*<sup>[23]</sup>, in their retrospective analysis on aged patients ( $\geq 70$  old) undergoing hepatic resection for HCC, concluded that surgery is safe in well-selected patients even in presence

of comorbidities. In the study by Huang *et al*<sup>[35]</sup>, a better post-surgical overall survival was reported in the elderly group despite a higher prevalence of comorbidities.

Conversely, chronic renal diseases and cardiovascular diseases were significantly associated with higher mortality in elderly in Sato *et al*<sup>[54]</sup> study.

Comorbidities such as cardiovascular diseases or chronic renal diseases should be therefore carefully evaluated before present aged patients as a candidate to hepatic resection, in particular if HCC is associated with cirrhosis.

Comorbidities were among the five characteristics included in a recently proposed simple risk score, to predict in-hospital mortality after hepatectomy for HCC. 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)<sup>[58]</sup>.

Major resection (> 3 segments) should be considered with caution in older patients. Portolani *et al*<sup>[56]</sup>, in a multivariate analysis on 175 elderly patients undergoing surgery, showed that major resection was an adverse predictor of overall survival (OS). Similar results were reported by Reddy *et al*<sup>[40]</sup> who found that increasing age (> 60 years) was independently associated with postoperative mortality after major hepatic resection even when performed in experienced, high-volume centres. The authors concluded that major resection in elderly patients should be avoided or limited to selected cases and possibly performed by experienced.

Attitude to perform liver resection in older patients is indeed another variable influencing the outcome. High-volume hospitals seem to be characterized by lesser morbidity and in-hospital mortality<sup>[55]</sup>.

**Table 2 Outcome of elderly and younger patients with hepatocellular carcinoma undergoing radiofrequency ablation**

Ref.	Age limits (yr)	O/Y	Survival (%)			DFS		
			1 yr	3 yr	5 yr	1 yr	3 yr	5 yr
Tateishi <i>et al</i> <sup>[62]</sup>	68	159/160	NA	76	NA	NA	NA	NA
			NA	79	NA	NA	NA	NA
Mirici-Cappa <i>et al</i> <sup>[41]</sup>	70	159/230	90.1	53.4	29	NA	NA	NA
			89.9	52.9	35.1	NA	NA	NA
Nishikawa <i>et al</i> <sup>[31]</sup>	75	130/238	90	64.1	44.8	66.9	21.3	19
			97.6	83.7	64 <sup>b</sup>	80.5	40	19.5 <sup>b</sup>
Takahashi <i>et al</i> <sup>[32]</sup>	75	107/354	NA	82	61	NA	49 <sup>2</sup>	56 <sup>2</sup>
			NA	80	63	NA	49 <sup>2</sup>	56 <sup>2</sup>
Kao <i>et al</i> <sup>[33]</sup>	65	158/100	NA	NA	81.3	NA	NA	NA
			NA	NA	65.4	NA	NA	NA
Hiraoka <i>et al</i> <sup>[63]</sup>	75	63/143	93	83	50 <sup>1</sup>	NA	NA	NA
			93	78	58	NA	NA	NA

Data on younger patients are reported in italics. Only articles reporting on either survival and disease free survival (DFS) or overall recurrence<sup>2</sup> were considered. <sup>b</sup>P = 0.001; <sup>1</sup>Not significant. O/Y: Old/young; NA: Not available.

Overall, available data should reassure surgeons and hepatologists on the feasibility of curative resection even in elderly patients. On a patient-by-patient approach, surgery should be offered to well-selected cases following a multidisciplinary discussion and after a careful evaluation of resection benefit, risks of treatment and expected life span.

### LIVER TRANSPLANTATION

Orthotopic liver transplant (OLT) is a curative treatment for HCC. Due to the organ shortage, access to OLT is still narrowed and age is one of the most important variables limiting access to the waiting list. Living donor transplant (LDT) may be a reliable option even for older patients but LDT programs are still limited or not available in many countries. Although there is not an established age limit for OLT, an arbitrary threshold of > 65-70 years is generally adopted worldwide. Elderly patients are considered poor candidates due to the frequent presence of ischemic heart disease and diabetes, which are known to adversely affect post OLT course.

OLT outcome in patients ≥ 70 years has been only seldom documented. In the study by Taner *et al*<sup>[57]</sup>, 13 transplanted patients ≥ 75 years experienced a favorable outcome and seven of them experienced a mean survival of 65 mo. A large-scale survey from Switzerland concluded that advanced age was not a significant predictor of survival<sup>[58]</sup>. However, in clinical practice, patients older than 65 years are seldom listed for OLT. In countries where paucity of organ donors is a problem, OLT for HCC in elderly remains an unrealistic option.

### RADIOFREQUENCY ABLATION

Percutaneous thermal ablation is recommended as a curative treatment for single unresectable HCC < 3 cm or multiple HCC (till 3 nodules < 3 cm). Since its introduction in the early 90's, radiofrequency has gained

popularity being, in early HCC, equally effective, safer and less invasive than resection. In a population-based survey carried out in United States which addressed temporal changing of therapeutic interventions to HCC in clinical practice, a 43% increase of RFA over time was found, and this change was particularly evident in aged patients<sup>[60]</sup>.

Studies on outcome after radiofrequency ablation (RFA) in elderly patients yielded conflicting results (Table 2). In two retrospective studies performed on large series from Japan, old age emerged as an independent predictor of poor prognosis at multivariate analysis<sup>[61]</sup>. In the study by Nishikawa *et al*<sup>[26]</sup>, the reduction in OS observed in elderly patients compared with their younger counterpart was primarily due to the higher rate of early recurrence. Conversely, other studies have reported that old age was not an independent predictor of reduced survival after RFA<sup>[60-62]</sup>. Good safety profile of RFA is maintained in elderly and the rate of major complications was found to be similar in elderly and in younger cirrhotic patients<sup>[32]</sup>. Comorbidities seem unlikely to impact on the post-RFA outcome.

Overall, RFA as well as other ablative techniques such as percutaneous alcohol injection and microwaves could be used in elderly subjects with satisfactory results and outcome and may represent a valid alternative to surgery for early HCC being less risky and largely preferred in these fragile patients. Moreover, percutaneous ablation is by far the most frequently used treatment for HCC recurrence. Clinicians should be therefore trained in these procedures, particularly when facing with patients aged 75 years or more.

### TRANSHEPATIC ARTERIAL CHEMOEMBOIZATION

The efficacy of transarterial chemoembolization (TACE) for unresectable HCC in cirrhotic patients emerged from two meta-analyses published during the last ten years. For these reasons, American and European guidelines

approved TACE as the treatment of choice of HCC in intermediate stage in cirrhotic patient with preserved liver function. There are only few studies addressing the use of TACE in elderly and its use in this setting is still debated. In two retrospective cohort studies, TACE was less frequently offered to older patients mainly because this technique was considered less feasible and potentially risky in elderly patients<sup>[24,41]</sup>. More recent studies did not confirm this finding. A prospective cohort study performed on 102 patients with HCC who underwent TACE showed similar survival and safety profile irrespective of age<sup>[64,65]</sup>. In a large retrospective study from Korea, the authors found that TACE was associated with even better results in elderly than in younger patients, with respect to median OS and disease-specific survival (15.2 mo vs 8.7 mo,  $P < 0.001$ ) without significant differences in terms of TACE-related mortality<sup>[43]</sup>. In an "in field" study from Italy, the authors reported similar outcomes in elderly and younger patients treated with TACE<sup>[66]</sup>. These data suggest that in the elderly population, TACE should be part of therapeutic armamentarium for HCC being effective with a satisfactorily safety profile.

## SORAFENIB

Sorafenib (Nexavar, Bayer Healthcare Pharmaceuticals-OnyxPharmaceuticals), is a multikinase inhibitor which exerts a proven anti-angiogenic and anti-proliferative activity on several solid tumors. Since 2008, it has been approved for treatment of HCC thanks to the results of two international randomized controlled trials<sup>[67,68]</sup>, which were however conducted in well-selected patients with a mean age of about 60 years and without relevant comorbidities.

The efficacy of sorafenib in elderly patients is supported by a number of studies<sup>[69-72]</sup>, which showed similar, or even a trend to longer, overall survival and time to progression in elderly patients compared with younger subjects. Overall, evidence collected to date shows that the efficacy and safety profile of sorafenib is not influenced by age<sup>[73,74]</sup>. A more strict monitoring might be considered in the elderly because of increased risk in developing comorbidities<sup>[73]</sup>.

## CONCLUSION

Since the progressive ageing of the population, the number of elderly HCC patients will increase in the next future. Unfortunately, international guidelines do not specifically address this aspect which, on the other hand, is relevant in clinical practice. Importantly, elderly patients often carry comorbidities and, in clinical practice, comorbidities contribute to poor adherence to guidelines recommendations.

Available data seem to indicate that, beside OLT, any other therapeutic option according to HCC stage, liver function and general clinical conditions, should be offered to aged patients since the expected efficacy depend on

HCC stage rather than on the actual age of the patient. Thus a nihilistic attitude of physicians towards under- or no-treatment should be discouraged. It is important to note however, that these recommendations are based on data mostly obtained in carefully selected patients. The decision whether or not to start treatment should therefore follow a patient-by patient strategy, discussed within a multidisciplinary team and shared with patient and relatives taking in great consideration the balance between clinical benefit, risks and life expectancy.

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