Original article

Effect of age on survival in patients undergoing resection of hepatocellular carcinoma

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Background: **The benefit of surgical intervention for cancer should be estimated in relation to the life expectancy of the general population. The aim of this study was to provide a measure of relative survival after hepatectomy for hepatocellular carcinoma (HCC).**
Methods: **Consecutive patients with liver cirrhosis and HCC who underwent hepatectomy were divided into age quartiles for analysis. Short- and mid-term survival rates were used to estimate survival until death for all patients, in relation to age and other co-variables. Years of life lost (YLL) were estimated using a reference cohort, derived from the general population matched for sex, age and year of diagnosis.**
Results: **Some 919 patients were included in the study. The following age quartiles were identified: less than 60 years (229 patients), 60–66 years (230), 67–70 years (231) and over 70 years (229). Postoperative mortality rates were similar between age quartiles, as were survival rates up to 3 years ($P = 0{\cdot}404$). A statistically significant reduction in 5–10-year survival rates was observed with ageing ($P = 0{\cdot}001$). Relative survival calculation showed that the youngest age quartile (less than 60 years) experienced the longest entire postoperative lifespan (15·6 years) but also the greatest number of YLL (11·0 years). Patients aged over 70 years had the shortest entire postoperative lifespan (6·4 years) but also the smallest number of YLL (3·7 years).**
Conclusion: **Although survival after liver resection for HCC is shortest in elderly patients, relative survival estimates suggest that hepatectomy can be of benefit in these patients, with a small loss of the entire individual lifespan.**

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Introduction

Increased life expectancy over recent decades[1] has paralleled the rising incidence of hepatocellular carcinoma (HCC), and the prevalence of elderly patients with HCC is expected to increase[2]. An explanation for the observed trends could be improved socioeconomic conditions and the development of more effective treatments for chronic liver disease, a common cause of HCC[3–5].

Liver transplantation is the treatment of choice for HCC and liver cirrhosis, but most elderly patients are referred for hepatic resection or alternative treatments owing to a shortage of organ donors. Hepatectomy in elderly patients with HCC is associated with significant morbidity and mortality. Studies[6,7] comparing the outcome of surgery for HCC in old and young patients have shown similar operative mortality (ranging from 0 to 3·2 per cent) and postoperative morbidity, and equivalent 5-year overall and disease-free survival rates.

Long-term survival is inevitably affected by age-related life expectancy. This introduces bias when survival is compared between age groups[8,9]. Besides age, survival after surgery is also affected by other clinical and tumour characteristics. Relative survival has been introduced to provide a more objective measure of survival probability from cancer by controlling for differences in mortality from causes other than cancer[9,10]. Relative survival is assessed by comparing the observed survival probability of a group of patients with cancer with the survival of a matched cancer-free cohort from the general population[8–10]. Years of life lost (YLL) is a measure of relative survival. It is defined as the mean number of years a person would have lived if they had not died prematurely[8–10]. This measure is commonly used to quantify social and economic losses owing to premature death, and might be helpful when deciding the allocation of economic and medical resources. This includes the care for patients with cirrhosis and HCC who undergo expensive surgical and medical treatments, including hepatectomy and liver transplantation[11]. The aim of this study was to assess YLL after hepatectomy for HCC in patients with liver cirrhosis among different age groups, with an emphasis on elderly patients.

Methods

Consecutive patients who underwent curative resection with tumour-negative resection margins (R0) for HCC between January 1997 and December 2013 were identified from a prospectively created database of two Italian tertiary referral hospitals. Demographic and clinical data were collected for each patient. Exclusion criteria were: surgical portasystemic shunts, emergency operations, tumour invasion into a major branch of the portal or hepatic vein, direct invasion of adjacent organs, or involved lymph nodes of the hepatic hilum.

The indications for hepatic resection have been already published[12]. Briefly, clinical signs of portal hypertension were not considered an absolute contraindication to surgery. Resectability was determined mainly by the calculated residual liver volume expected to be sufficient after curative resection. Liver functional reserve was assessed, and the decision to operate was based mainly on the preoperative Model for End-stage Liver Disease (MELD) score[12]. Intraoperative ultrasound examination was performed systematically to detect the presence of any additional nodules and for planning the resection with a tumour-free margin of at least 1 cm. The extent of hepatectomy was defined according to the International Hepato-Pancreato-Biliary Association nomenclature[13].

All patients were followed up periodically to exclude recurrence of HCC. Biochemical liver function tests, measurement of serum α-fetoprotein levels, and ultrasonography or CT were performed 3 and 6 months after discharge, and then according to an annual or half-yearly surveillance programme in more recent years[14]. None of the patients in this study received adjuvant chemotherapy. Patients with tumour recurrence were managed with various therapeutic modalities, including further resection and salvage liver transplantation in selected patients.

Statistical analysis

Patients were grouped into age quartiles for analysis. Continuous data are reported as mean(s.d.) unless indicated otherwise. Differences in means were investigated by ANOVA, and differences in percentages using the χ^2 test. Patient survival was calculated by means of the Kaplan–Meier method from the date of hepatic resection until death or the date of last follow-up; patients who subsequently underwent liver transplantation were censored the day before this procedure (16 patients; 1·7 per cent). Follow-up ended on 30 June 2015. Mean survival estimates were obtained by measuring the area under the Kaplan–Meier survival curve (observed survival).

Table 1 Characteristics of patients and tumours, and surgical procedure

	No. of patients (*n* = 919)
Age (years)	
< 60	229 (24·9)
60–66	230 (25·0)
67–70	231 (25·1)
> 70	229 (24·9)
Sex ratio (M : F)	715 : 204
Aetiology	
HCV	576 (62·7)
HBV	212 (23·1)
Alcohol/other	129 (14·0)
Bilirubin (mg/dl)*	1·01(0·52)
Albumin (g/dl)*	4·0(0·5)
International normalized ratio*	1·16(0·13)
Platelet count (× 10^3/ml)*	149(74)
Oesophageal varices	252 (27·4)
Child–Pugh grade	
A5	663 (72·1)
A6	201 (21·9)
B7–8	55 (6·0)
Tumour size (cm)*†	4·0(2·4)
Single nodule†	717 (78·0)
Very early stage†	87 (9·5)
Within Milan criteria†	655 (71·3)
Extent of hepatectomy	
Wedge/segmentectomy	669 (72·8)
Bisegmentectomy	153 (16·6)
≥ 3 segments	97 (10·6)
Microvascular invasion	483 (52·6)

Values in parentheses are percentages unless indicated otherwise; *values are mean(s.d.). †Based on radiological imaging. HCV, hepatitis C virus; HBV, hepatitis B virus.

Extrapolation of long-term survival

After surgery, patients with liver cirrhosis die from causes directly related to their liver disease (excess hazard rate), in addition to the common causes experienced by the age- and sex-matched general population. Extrapolation to estimate long-term survival is based on the assumption that such an excess hazard rate would become stable several years after follow-up for cancer[15,16]. With knowledge of the mortality excess, the postoperative lifetime survival function was derived from general population life-tables

Table 2 Clinical and tumour features, early postoperative outcome and survival in relation to age

	Age (years)				
	< 60 (*n* = 229)	60–66 (*n* = 230)	67–70 (*n* = 231)	> 70 (*n* = 229)	*P*†
Clinical characteristics					
Male sex	211 (92·1)	183 (79·6)	165 (71·4)	156 (68·1)	0·001
Hepatitis C virus infection	133 (58·1)	134 (58·3)	152 (65·8)	157 (68·6)	0·006
Bilirubin > 1 mg/dl	84 (36·7)	98 (42·6)	82 (35·5)	86 (37·6)	0·752
Albumin ≤ 3·5 g/l	51 (22·3)	37 (16·1)	44 (19·0)	50 (21·8)	0·888
Platelet count < 100 000/ml	77 (33·6)	62 (27·0)	53 (22·9)	41 (17·9)	0·001
Oesophageal varices	70 (30·6)	65 (28·3)	63 (27·3)	54 (23·6)	0·096
Within Milan criteria	162 (70·7)	168 (73·0)	176 (76·2)	149 (65·1)	0·301
Microvascular invasion	129 (56·3)	116 (50·4)	121 (52·4)	117 (51·1)	0·351
Mortality					
30 days	2 (0·9)	3 (1·3)	4 (1·7)	2 (0·9)	0·893
90 days	9 (3·9)	5 (2·2)	7 (3·0)	6 (2·7)	0·539
Survival (%)*					
1 year	86·5(0·3)	92·9(0·3)	90·2(0·3)	89·5(0·3)	–
3 years	67·6(0·4)	68·9(0·4)	69·8(0·4)	68·9(0·4)	0·404‡§
5 years	57·8(0·4)	56·6(0·4)	54·7(0·5)	44·8(0·3)	–
10 years	42·9(0·5)	34·4(0·5)	32·7(0·6)	22·0(0·6)	0·001‡¶
Salvage liver transplantation	11 (4·8)	3 (1·3)	2 (0·9)	0 (0)	0·001

Values in parentheses are percentages unless indicated otherwise; *values are mean(s.d.). Continuous variables were dichotomized on the basis of clinically accepted thresholds. †χ^2 unless indicated otherwise; ‡log rank test, for §comparison of rates up to 3 years and ¶comparison from 4 to 10 years.

as follows: for every patient in the present study an age-, sex- and year (of surgery)-matched reference cohort was generated from population survival tables obtained from the Italian National Institute of Statistics, using the Monte Carlo method described by Hwang and Wang[16,17]; a linear regression was fitted between the logit of the ratio of survival functions between the study population and the reference cohort to the end of follow-up; and the regression line obtained and the survival curve of the reference cohort were used to predict the long-term survival curve beyond the follow-up of the present study population. The long-term survival curve was extrapolated up to 40 years after surgery, to account for the usual life expectancy of the general population with a median age similar to that of the youngest age quartile (life expectancy from birth of the general Italian population is 83·0 years, 80·4 years for men and 85·6 years for women)[18]. One hundred bootstrap samples were adopted to obtain the standard errors of the means.

Estimation of years of life lost

Once the entire postoperative life expectancy had been obtained, YLL after hepatic surgery was estimated as the difference in the area between the mean survival curves of the present cohort and that of the reference population. The ISQoL (integration of survival and quality of life) package of R (R Project for Statistical Computing, Vienna, Austria) was used for all calculations (http://www.stat.sinica.edu.tw/jshwang/isqol/). Mathematical details have been described elsewhere[15–19].

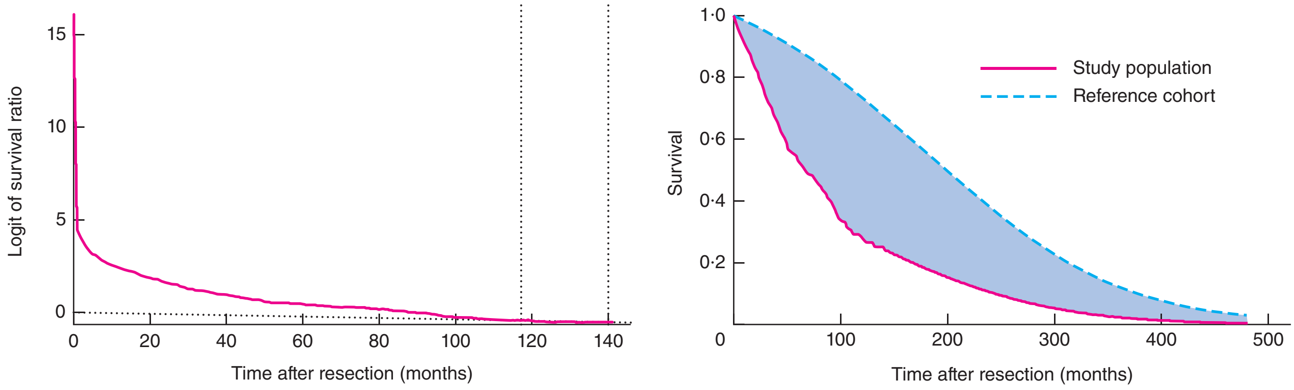
Results

Some 919 patients were included in the study. Baseline characteristics are shown in *Table 1*. The mean age was 65·7(9·1) years. The following age quartiles were identified: less than 60 years (229 patients), 60–66 years (230), 67–70 years (231) and over 70 years (229). Clinical characteristics according to age group are presented in *Table 2*. Male sex and low platelet count were more prevalent (both *P* = 0·001), and hepatitis C virus (HCV) infection less prevalent (*P* = 0·006), in the younger age group. These differences were accounted for in the extrapolation of long-term survival.

After a median follow-up of 5·5 (range 0–13) years, 512 patients (55·7 per cent) had tumour recurrence and 387 (42·1 per cent) had died. The 30- and 90-day mortality rates were 1·2 and 2·9 per cent respectively, and did not differ significantly between age groups (*P* = 0·893 and *P* = 0·539 respectively). Overall 1-, 3-, 5- and 10-year survival rates were 89·2, 70·7, 54·1 and 28·6 per cent respectively. Survival according to age group is shown in *Table 2*. From year 4 onwards, there was a statistically significant difference in survival between the age groups (*P* = 0·001).

Relative survival after surgery

Calibration of the long-term survival model is shown in *Fig. 1a*. The logit transformation slope of the survival ratio between the study population and the reference cohort matched for age, sex and year of surgery was estimable, providing evidence for the constant excess hazard assumption



a Logit transformation of survival ratio **b** Mean survival difference

Fig. 1 **a** Logit transformation of the ratio between the survival function of patients who underwent resection and that of the age-, year- and sex-matched reference population. The vertical dotted lines mark the interval when the data were used for extrapolation (10–12 years); the horizontal dotted line indicates the slope of the logit survival ratio. **b** Mean survival difference between patients who underwent resection and the age-, year- and sex-matched reference population after 40 years of extrapolation. The shaded area represents the mean number of years for life lost after surgery for the entire study population

Table 3 Observed survival after surgery, estimated long-term survival and years of life lost in comparison with the reference cohort

	Age (years)	Observed survival (years)	*P**	Long-term survival estimate (years)	Years of life lost	*P**
Age (years)			0·012			0·001
< 60 (*n* = 229)	53·6(6·1)	7·1(6·1)		15·6(13·7)	11·0(9·7)	
60–66 (*n* = 230)	63·7(1·5)	6·7(6·0)		9·1(7·6)	9·5(7·6)	
67–70 (*n* = 231)	69·3(1·5)	6·6(6·1)		7·4(6·7)	7·2(6·2)	
> 70 (*n* = 229)	76·1(3·0)	5·4(4·5)		6·4(3·1)	3·7(1·6)	
Sex			0·026			0·717
M (*n* = 715)	64·6(8·0)	6·9(5·3)		8·7(7·4)	8·9(7·3)	
F (*n* = 204)	69·3(7·1)	5·6(4·7)		7·5(6·9)	9·6(6·8)	
HCV infection			0·565			0·248
Yes (*n* = 576)	66·2(9·6)	6·6(5·2)		9·9(8·7)	7·4(6·4)	
No (*n* = 373)	64·8(9·7)	6·4(3·9)		8·2(4·9)	8·6(7·4)	
Bilirubin (mg/dl)			0·010			0·001
≤ 1 (*n* = 569)	65·8(9·5)	6·9(5·2)		10·2(9·5)	5·5(4·7)	
> 1 (*n* = 350)	65·4(9·5)	5·8(4·7)		6·7(5·6)	11·1(9·4)	
Albumin (g/l)			0·001			0·014
≤ 3·5 (*n* = 182)	65·3(9·4)	6·9(2·0)		5·3(4·5)	12·9(9·2)	
> 3·5 (*n* = 737)	65·8(8·1)	4·9(3·5)		9·1(5·7)	8·2(7·9)	
Platelet count (/ml)			0·003			0·031
< 100 000 (*n* = 233)	63·4(9·2)	5·3(3·8)		7·4(6·7)	12·0(9·9)	
≥ 100 000 (*n* = 686)	66·4(7·9)	6·9(6·5)		9·2(8·1)	7·7(6·5)	
Oesophageal varices			0·001			0·038
No (*n* = 667)	66·0(7·7)	6·9(5·7)		9·9(8·5)	7·1(6·0)	
Yes (*n* = 252)	64·7(9·5)	5·3(4·3)		8·1(7·1)	10·4(9·1)	
Milan criteria			0·002			0·048
Within (*n* = 655)	65·5(9·9)	7·0(6·4)		11·4(9·1)	6·3(5·3)	
Beyond (*n* = 264)	66·2(9·7)	5·5(4·7)		8·8(6·2)	8·3(4·6)	
Microvascular invasion			0·001			0·002
No (*n* = 436)	66·1(8·4)	7·2(5·2)		11·0(9·7)	6·1(5·6)	
Yes (*n* = 483)	65·3(8·8)	5·7(4·7)		7·6(7·1)	10·2(7·1)	

Values are mean(s.d.). HCV, hepatitis C virus. *ANOVA.

for the surgical population. For the whole study group (*Fig. 1b*) the mean entire postoperative lifespan was estimated to be 8·7 (95 per cent c.i. 5·9 to 11·5) years. The matched reference cohort had a mean life expectancy of 17·4 years, giving 8·6 (5·8 to 11·4) YLL after surgery.

Older patients had shorter long-term survival, but YLL was significantly lower compared with the value for younger patients (*Table 3*) ($P = 0{\cdot}001$). For example, patients aged less than 60 years had the longest postoperative lifespan (15·6 years) but also the greatest number of YLL (11·0 years). In contrast, patients older than 70 years had the lowest postoperative lifespan (6·4 years) but also the fewest YLL (3·7 years). Patient sex lost its significance in determining YLL ($P = 0{\cdot}717$); HCV infection was not related to survival ($P = 0{\cdot}565$) or YLL ($P = 0{\cdot}248$). The other clinical and tumour-related factors that affected observed survival also had an impact in the long-term model.

Subgroup analyses showed that, among 441 patients aged less than 70 years who fulfilled the Milan criteria (mean age 61 years), the mean life expectancy after surgery was 11·0(8·7) years, with mean of 9·9(8·7) YLL. For 320 patients aged less than 67 years with a normal platelet count, the life expectancy after surgery was 12·2(9·7) years with 10·0(9·7) YLL, whereas for 366 patients aged 67 years or more the life expectancy after surgery was 7·9(6·5) years with 4·2(6·0) YLL ($P = 0{\cdot}001$). Results for other substratifications were considered unreliable as the confidence intervals were too large.

Discussion

In the present study, the survival time after surgery decreased with ageing, being about 1·3 times lower in the oldest patients (aged more than 70 years) than in the youngest ones (less than 60 years old). However, for a comprehensive interpretation of the true potential benefit obtained from the therapeutic intervention, survival after surgery should be interpreted within the frame of the life expectancy of individuals who did not develop the disease. In this study, elderly patients (aged over 70 years) achieved the lowest number of YLL, and this supports the practice of surgery in the elderly. Hepatic resection for HCC yielded a lifespan from birth very near to that of the reference population, with the loss of only 3·7 years over the entire lifespan of 83 years (as derived from population life-tables), surgery in elderly patients can achieve their greatest benefit in tems of lifespan from birth.

The present findings may have implications for clinical practice. Clinicians are worried about referring elderly patients with liver cirrhosis and HCC for surgical treatment given the perceived small benefit from resection in the setting of advanced age[20,21]. Therefore, other less invasive, but also less effective, therapeutic modalities are often considered. This argument is supported by the lower survival rate in elderly patients compared with the youngest age quartile over a time span of about 10 years. Considering the entire lifespan from birth onwards, surgery may be of benefit in these older patients. This is important to take into consideration when deciding on the most appropriate treatment strategies[20,21]. Hepatic resection in the elderly can provide a survival benefit at reasonable costs. Costs of alternative treatments may be lower, but are unlikely to be counterbalanced by a similar chance of long-term survival. These considerations are valid only if elderly candidates for surgery are selected carefully, as in the present study where postoperative mortality was consistently low across all age groups. More studies on the cost-effectiveness of surgical and non-surgical therapies in the elderly, considering the entire lifespan from birth, are required to gain more insight into the most effective treatment.

Another practical aspect concerns patients whose age is within the limits generally accepted for transplantation (less than 70 years). Patients within the Milan criteria and aged less than 70 years (with a mean age at surgery of 61 years) had approximately 10 YLL after liver resection. The number of YLL after liver transplantation for patients of similar age ranges from 4·0 to 8·6 years, mainly depending on the quality of the donor liver[22]. Thus, for younger patients, liver transplantation would provide fewer YLL and should be considered the preferred therapeutic strategy. In parallel, resection for patients aged over 70 years can provide very few YLL and this indirect comparison supports the hypothesis of the philosopher Norman Daniels[23] that ‘unequal benefit treatments in different stages of life can be aimed at obtaining a fair distribution of lifespan from birth-cohorts’. It should also be noted that the proportion of patients who underwent liver transplantation (for recurrence or worsening of liver failure) decreased with ageing in the present study (*Table 2*). This finding confirms previous analyses suggesting that resection, as a bridge therapy for patients near the age limit accepted for transplantation, can preclude subsequent liver transplant because of the risk of becoming too old[24–26]. However, the harm caused by the ‘lifespan from birth’ point of view would be negligible.

Elderly patients may have been selected for liver resection because they were healthier than the average patient of a similar age with HCC. Alternatively, surgeons may have been more prone to operate on younger patients even if they were in worse condition[6,7]. This may have led to a study group that was not fully representative of the population of patients with liver cirrhosis and HCC. Hence, the YLL values may have been underestimated for the elderly and overestimated for the younger patients. Moreover, only patients who underwent R0 resection were included in the present study, and there was no comparison between different treatments for HCC. Two conclusions can be drawn from these observations. First, the reference cohort would probably be best represented by a sex- and age-matched cohort of individuals with similar general conditions, but this is not possible when relative survival is used as an outcome measure as such a reference cohort is not available from population-based statistics[18]. Second, future research should focus on comparing YLL estimates between surgical and non-surgical patients, and inclusion criteria should be more representative of the entire population with HCC.

The present analysis has other limitations. Some confounders known to affect survival after liver resection were also related to YLL (*Table 3*). These factors could have masked the prognostic role of age. It was not possible to investigate their competitive role in determining the entire postoperative lifespan and calculation of YLL in the present analysis, but the subanalyses performed may have reduced the possible inter-relations between variables. Three variables were found to vary between the age groups: male sex, HCV infection and platelet count. Sex was adjusted for within the reference population. HCV infection did not appear to affect survival, reflecting an epidemiological feature of older patients rather than a prognostic factor. Patients with a normal platelet count showed a progressive decline in YLL through the age groups, as observed in the whole study population, confirming the overall results of the study. Further subgroup analyses showed a loss of goodness-of-fit of the long-term model, with very wide confidence intervals, suggesting loss of robustness of estimates. To overcome this, a larger patient cohort would be needed. Despite these limitations, a different point of view is provided here to support the choice of hepatic resection for HCC in elderly patients with cirrhosis.

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Old Woman Dozing. Nicolaes Maes. 1634–1693. From Web Gallery of Art.