Long-term Outcome after Liver Resection for Hepatocellular Carcinoma Larger than 10 cm

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Abstract

Background   The purpose of the present study was to analyze long-term survival and disease-free survival after liver resection for giant hepatocellular carcinoma (HCC) $\geq$ 10 cm compared to HCC < 10 cm in diameter. The surgical approach in the treatment of giant HCC may achieve long-term survival and disease-free survival comparable to treatment of smaller lesions.

Methods   This retrospective analysis was a monocentric study conducted in a tertiary university center. It included 101 patients from 114 consecutive liver resections for HCC, separated into two groups: those with tumors less than 10 cm in diameter (small HCC; $n = 79$) and those with tumors larger than 10 cm (giant HCC; $n = 22$). The main outcome measures were overall five-year survival, five-year disease-free survival, recurrence rate, perioperative mortality at 30 days, surgical complication rate, and re-intervention rate.

Results   The two groups were homogeneously distributed, apart from cirrhosis, which was found more frequently in the group with small HCC (77 vs. 41 %; $p = 0.0013$). Both median survival (24 vs. 27 months; $p = 0.0085$) and overall 5-year survival (21 vs. 45; $p = 0.04$) were significantly poorer in the small HCC group compared to the giant HCC group. There were no differences en terms of recurrence rate, pattern, and timing.

Conclusions   Liver resection for HCC larger than 10 cm is a valuable option in selected patients, one that provides overall survival and disease-free survival comparable to smaller lesions. Functional reserves of the liver, more than the size of the lesion, may be important in patient selection for surgical resection.

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Introduction

Among various factors, management guidelines for hepatocellular carcinoma (HCC) rely on the size of the lesion as a factor in selection of the most appropriate treatment. This approach is anchored in the Milan criteria [1] for liver transplantation and is also applied in other guidelines [2], to determine whether liver resection (LR), radiofrequency ablation (RFA), or transcatheter arterial chemoembolization (TACE) should be proposed for the treatment of individual HCC patients. The widespread use of size criteria to guide HCC treatment is based, among other factors, on the observation that both survival and risk for recurrence may be related to the size of the lesion [3–7], even if this approach has not been observed in some series [8, 9].

Although the management of HCC lesions larger than 5 cm continues to be debated, few data are available regarding giant HCC ($\geq$10 cm) [4–26], and are in most cases retrospective. Some investigators suggest that giant lesions represent more aggressive tumors [25] and are associated with higher rates of vascular invasion [7], which brings into question the value of surgery as a therapeutic option. However, adverse outcomes have not been observed in all studies [6, 20, 24]. Still, the lack of significant data may lead to confusion in the choice of

therapeutic options. For example, RFA technology and results continue to improve, but experience with large tumors remains limited and the few available reports are confined to small series [25, 27–29]. Moreover, complete ablation of large lesion remains exceptional, due to the limitations of thermal diffusion volume and the frequent proximity of large blood vessels, factors that inhibit the effectiveness of RFA in these cases [30]. As consequence, RFA is currently proposed as palliative treatment [27–29], or is used in combination with resection [25]. Transcatheter arterial chemoembolization has been reported to be feasible in the treatment of giant HCC [31–34], but there are no published reports of complete cure, thus TACE is not validated as therapeutic approach in giant HCC. Finally, liver resection may be the only chance of cure in these patients [3–26], despite surgical limitations like liver size, functional reserve, and anatomical restrictions. In fact, radical surgery for giant HCC has been reported in some case series, but this approach remains controversial due to concerns regarding the potential aggressiveness of such tumors [7, 25] the high morbidity associated with major liver interventions—25 % to more than 50 % in recent series [4, 16–19, 23, 26]—and a mortality rate ranging from 0 to 8 % [4, 7, 16–19, 21–26]. These concerns are reflected in numerous international guidelines, which limit recommendations for liver resection to small tumors [2]. In contrast, recent Japanese guidelines used physiological criteria and liver remnant size, rather than tumor size, to determine the indications for liver resection in HCC [35–37]. This difference in recommendations stems from the lack of data and reflects concerns regarding the long-term results of such aggressive management.

The goal of the present study was to analyze long-term survival and disease-free survival after liver resection for giant HCC ≥ 10 cm compared to HCC < 10 cm in diameter. Our hypothesis was that tumor size may not be the determinant for survival, thus allowing treatment of giant HCC by firstline surgery in selected patients.

Patients and methods

From 1 January 1997 to 31 December 2009, 311 consecutive patients with HCC were admitted to the Department of Digestive Surgery at the University Hospital of Lausanne, Switzerland. Of these 311 patients, 114 underwent liver resection with curative intent and constituted the study population (Fig. 1). All patients had a confirmed histological diagnosis of HCC, none of the fibrolamellar subtype. Thirteen patients were excluded from the analysis (2 had mixed tumor HCC–cholangiocarcinoma and 11 had incomplete data). The remaining 101 patients were categorized into two groups: patients with tumors less than

10 cm in diameter (small HCC; $n = 79$) and patients with tumors larger than 10 cm (giant HCC; $n = 22$). For the giant HCC group, all histological findings were reviewed by an independent senior pathologist.

The preoperative work-up included blood tests, including alpha-fetoprotein and determination of values needed to calculate the CHILD score and the MELD score, dual radiology modalities (thoracoabdominal computed tomography [CT] and liver magnetic resonance imaging [MRI]) with liver volumetry. In addition, the indocyanine green retention (ICGR) test at 15 min and invasive portal pressure measurement were performed. Percutaneous biopsy was only considered in lesions with non-HCC-typical imaging. The management strategy for all patients was discussed during the weekly multidisciplinary hepatobiliary conferences, which included surgeons, radiologists, gastroenterologists, and pathologists.

Liver resection was the treatment proposed to all patients with a CHILD score of A or B, a MELD score less than 9 points, a remnant liver volume of at least 40 %, an ICGR test of less than 15 % at 15 min, and an invasive portal pressure of less than 10 mmHg.

After IRB approval from the Ethics Committee (University of Lausanne, Switzerland), an anonymized Excel database was constructed with patient demographic, operative data, pathological findings, and early follow-up data. A retrospective analysis of data was performed. The long-term outcomes were determined by telephone interviews with the attending physicians.

The primary endpoint was overall five-year survival, and the secondary endpoints were five-year disease-free survival, recurrence rate, perioperative mortality at 30 days, surgical complication rate, and reintervention rate.

Statistical analyses were performed with STATA software (Statacorp LP, College Station, TX) using Student's t test for categorical data, the Mann–Whitney U test for continuous data, and the Kaplan–Meier or log-rank test for survival analysis. The results were expressed as median and range. The cut-off for statistically significant outcome was a p value less than 0.05.

Results

Population characteristics and perioperative data

The demographic, histological, and operative data of the two groups are presented in Table 1. The two groups were homogeneously distributed in terms of age and preoperative American Society of Anesthesiologists (ASA) scores. There were significantly more patients with cirrhosis in the group with small HCC (77 vs. 41 %; $p = 0.0013$). In this group, four patients presented with Child–Pugh class B

Fig. 1 Study flowchart
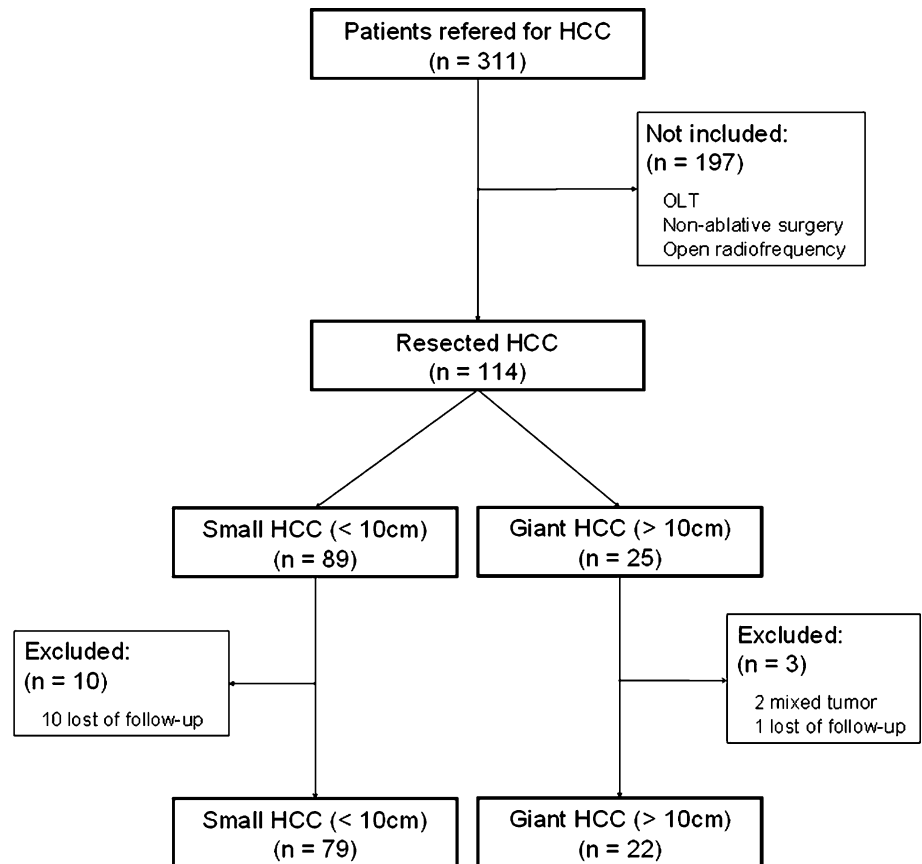
cirrhosis compared to none in the giant HCC group, where all patients presenting with cirrhosis were Child–Pugh class A. The cirrhosis etiologies were not different between the two groups apart from non-alcoholic non-viral causes (primary biliary cirrhosis and hemochromatosis), which were found more frequently in the small HCC group. The incidence of non-cirrhotic fibrotic liver disease did not differ statistically between the two populations.

The median number of liver segments resected per patient was statistically lower in the group with small HCC (3 vs. 4; $p = 0.005$), as was the rate of major hepatectomy, defined as more than three segments (51 vs. 76 %; $p = 0.03$). Despite the differences in this feature of the operations, the operative time and the time of the Pringle maneuver were similar. After histological examination, the rate of R0 resection—defined as the absence of tumor in contact with the resection plane—was comparable in the two groups. In terms of staging, no differences were found between the small and giant HCC groups when comparing the grade of differentiation, the positive lymph node rate, and the rate of vascular invasion (microscopic or macroscopic). The median follow-up time was also similar in the two populations (24 vs. 25 months; $p = 0.16$).

The follow-up data, and the immediate and long term postoperative data are presented in Table 2.

Immediate postoperative data

The 30-day mortality was not significantly different between the small and giant HCC groups (7 vs. 0 %; $p = 0.14$), but there was higher postoperative morbidity in the small HCC group (50 vs. 23 %; $p = 0.02$). Liver-related complications accounted for 57 % in the small HCC group and 40 % in the giant HCC group.

Survival

Results of the Kaplan–Meier analysis for overall survival are presented in Fig. 2. Both median survival (24 vs. 27 months; $p = 0.0085$) and overall 5-year survival (21 vs. 45 %; $p = 0.04$) were significantly poorer in the small HCC group than in the giant HCC group.

Recurrence

Results of the Kaplan–Meier analysis for disease-free survival are presented in Fig. 3. The median disease-free survival for the two groups was not significantly different (10 vs. 15 months; $p = 0.47$); as was the 5-year disease-free survival (14 vs. 27 %; $p = 0.06$). The recurrence rate was identical in the two groups (47 % for the small HCC

Table 1 Demographic, histological, and operative data for patients with small hepatocellular carcinoma and giant HCC

	Small HCC ($n = 79$)	Giant HCC ($n = 22$)	p Value
Age, years (range)	67 (21–85)	72 (36–88)	0.14
ASA score	3	3	0.85
Cirrhosis, n (%)	61 (77)	9 (41)	0.0013*
Fibrosis, n (%)	6 (7)	3 (14)	0.46
Child-Pugh class, n (%)			
A	75 (95)	22 (100)	0.08
B	4 (5)	0 (0)	0.04*
C	0 (0)	0 (0)	–
Etiology of cirrhosis, proportion (%)			
Alcoholic	33/61 (54)	3/9 (33)	0.29
Hepatitis C virus	13/61 (21)	2/9 (22)	0.78
Hepatitis B virus	10/61 (16)	4/9 (45)	0.16
Other	5/61 (9)	0/9 (0)	0.02*
Alpha fetoprotein (U/l)	1921 (5–50′500)	2040 (2–17′000)	0.30
Segments resected, n (range)	3 (1–5)	4 (1–6)	0.005*
Major hepatectomy, n (%)	40 (51)	17 (76)	0.03*
Operative time (min)	199	215	0.31
Pringle maneuver, cumulative min	30	31	0.71
R0 resection, n (%)	77 (97)	21 (95)	0.08
Tumor size, cm (%)	4.9 (1–9)	13.5 (10–21)	–
Tumor differentiation, n (%)			
Well	38 (48)	7 (33)	0.40
Moderate	29 (37)	9 (40)	0.42
Poor	12 (15)	6 (27)	0.19
Positive lymph nodes, n (%)	1 (1)	0 (0)	0.72
Vascular invasion by histology, n (%)	13 (16)	2 (9)	0.33

ASA American Society of Anesthesiologists

* Statistically significant $p < 0.05$

Table 2 Patient outcomes

Outcome	Small HCC ($n = 79$)	Giant HCC ($n = 22$)	p Value
Follow-up, months (range)	24 (1–186)	25 (2–164)	0.16
Median survival, months (range)	24 (2–186)	27 (6–164)	0.0085*
5-Year survival (%)	21	45	0.04*
5-Year disease-free survival (%)	14	27	0.06
Recurrence, n (%)	37 (47)	10 (45)	0.82
Median recurrence time, months (range)	15 (3–60)	10 (5–34)	0.47
30-Day mortality, n (%)	6 (7)	0 (0)	0.14
Complication rate, n (%)	40 (50)	5 (23)	0.02*

* $p < 0.05$

Fig. 2 Overall survival for giant hepatocellular carcinoma (HCC) versus small HCC (Kaplan–Meier analysis)

and 45 % for the giant HCC group; $p = 0.82$). In the group with small HCC, 10 % of recurrences were local, 41 % were hepatic recurrence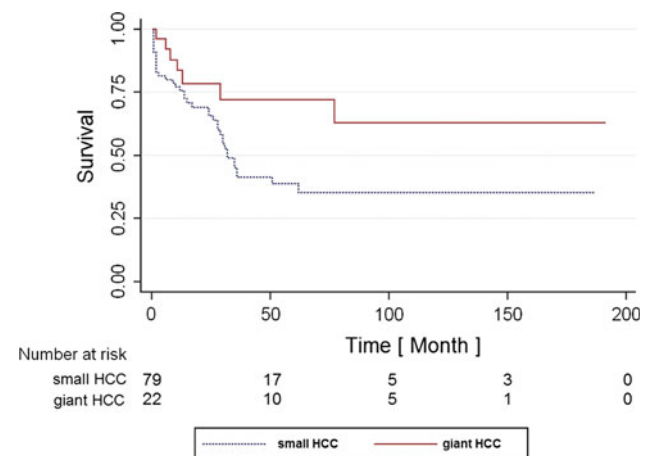s at other locations, and 49 % were systemic recurrences (distant lymph nodes, lung, bone, and brain). In the group with giant HCC, 10 % of recurrences were local, 10 % were hepatic, and 80 % were systemic
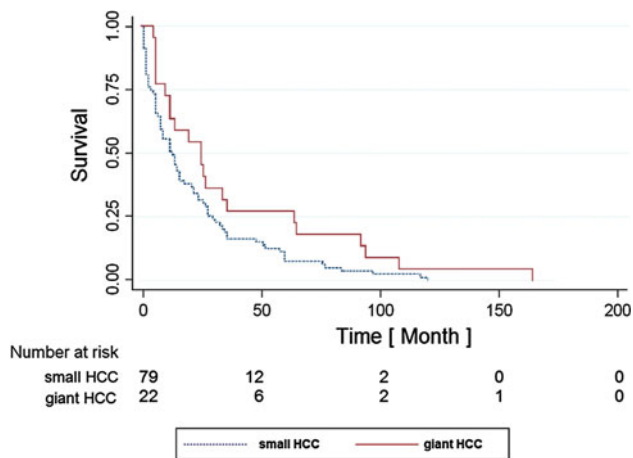
Fig. 3 Disease-free survival for giant HCC versus small HCC (Kaplan–Meier analysis)

recurrences (distant lymph nodes, lung). In patients with small HCC, 62 % of the recurrences were treated with interventional radiology (RFA or TACE), and 22 % underwent reoperation. In the group with giant HCC, the corresponding figures were 20 and 20 % for these interventions, respectively.

Discussion

Our results suggest that there is no outcome difference in surgery for giant HCC compared to smaller HCC, even if more complex surgery was performed in giant HCC.

In the present comparative retrospective study, we observed that overall survival, disease-free survival, and recurrence rates were similar after resection of giant HCC and resection of smaller lesions. This result strongly suggests that liver resection is an appropriate option for treating even very large lesions, as observed in other surgical series [4–26]. In giant HCC, surgery should probably be considered as firstline therapy, provided sufficient physiological liver reserves are available. Our results were concordant with those of Shah et al. [18] and Wang et al. [19], with 5-year survival rates reported to be as high as 50 %. However, it must be emphasized that the literature on this topic is somewhat confusing, with contradictory reports and some 5-year survival rates lower than 25 % [16, 20, 25].

In our own comparison, we observed that survival was significantly better in the giant HCC group. This is probably because our patient population in the giant HCC group included fewer patients with cirrhosis and no patients with CHILD B disease. Because of the limited sample size, we did not specifically analyze prognostic factors after resection of giant lesions, but, as observed in many other series

[4, 19, 20, 22], the presence of cirrhosis seems to influence negatively overall survival, regardless of the lesion size.

Having said that, this study was limited by the small sample size and the retrospective design, but this has been the case for the majority of other reports on giant HCC, and these limitations seem difficult to overcome, especially today, as primary liver resection is used less frequently in the management of HCC. However, with OLT and interventional radiology for small lesions, it seems that the number of patients with giant HCC referred for surgical consultation may be increasing, making understanding of such tumors more and more critical.

Another potential bias is the surgical nature of the present series, including good patient selection. Considering the small liver remnant, surgeons could have been negatively influenced, proposing interventions in patients who had a better functional reserve. Bearing in mind that the management strategy was proposed by a multidisciplinary board, it can be considered that this bias was minimized and that patient selection was adequate. Finally, patients with giant HCC may have had less aggressive tumors, as patients with advanced disease (bilateral involvement, extrahepatic disease, etc.) are less likely to be referred for surgical treatment. In addition, it is obvious that we did not compare our results to other treatment modalities like RFA or TACE, because of a lack of data and because these approaches have not been used to treat tumors larger than 10 cm in our center.

As in other studies [35–37], our results suggest that functional reserve of the remnant liver parenchyma, more than size of the lesion, may be important in patient selection for surgical resection. To assess and improve selection criteria, our patients underwent an extensive preoperative work-up that included indocyanine green retention time, invasive portal vein pressure, and liver volumetric evaluation.

To further improve the management of giant HCC, more information about tumor biology and histology should be obtained. Key points like differentiation grade and the presence of vascular invasion have been reported to be associated with poor prognosis [3–5, 7, 15–18, 20–23, 26]. Interestingly however, we did not observe any differences between our two populations. This point is of importance, because the assumed aggressiveness of large HCC tumors represents for some investigators a clear limitation to surgery [38], which was not confirmed by our observations.

In conclusion, our results suggest that liver resection in the treatment of HCC larger than 10 cm is the best available therapeutic option in selected patients. A radical surgical approach may achieve good long-term survival and acceptable disease-free survival comparable to treatment of smaller lesions.

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