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ORIGINAL ARTICLE

Dissecting the multinodular hepatocellular carcinoma subset: is there a survival benefit after hepatectomy?

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Abstract
Whether hepatic resection for multinodular hepatocellular carcinoma (HCC) is indicated remains to be demonstrated. We investigated the prognostic factors in a large series of patients treated with hepatic resection at a reference cancer center. All consecutive patients resected for multinodular HCC from January 2004 to April 2015 were reviewed. The study endpoints were the survival analysis and the definition of resection criteria. Among 380 patients resected for HCC, 116 (31%) were affected by multinodular HCC without macrovascular invasion. The median tumor number was 2 (range 2–30), while the median tumor size was 3.5 cm (range 1.1–28). The 90-day mortality was 2.6%. Morbidity was 31%. After a median follow-up of 31 months (range 3.1–149.7), the 1-, 3-, and 5-year overall survival rates were 85, 52, and 35%, respectively. At the multivariate analysis, tumor number more than 4 (HR = 2.15; 95% CI 1.8–4.18; $P = 0.001$), tumor size more than 6 cm (HR = 2.78; 95% CI 2.08–4.91; $P = 0.001$), esophageal varices (HR = 3.01; 95% CI 1.98–5.61; $P = 0.002$), and major hepatectomy (HR = 2.91; 95% CI 1.97–4.54; $P = 0.001$) were independently significant for survival. Median survival shifted from 20 to 52 months based on these factors. Hepatic resection for multinodular HCC may result in survival benefit for patients up to four tumors, none more than 6 cm, without varices, and eventually treated by conservative surgery.

Keywords Multinodular hepatocellular carcinoma · Multiple hepatocellular carcinoma · Hepatectomy · Survival for multiple hepatocellular carcinoma

Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver tumor. It is the fifth most common cancer and the third most common cause of cancer-related death worldwide and it is increasing in incidence [1]. The treatment of HCC is a major health issue because of its increasing incidence and because of the complexity of its management. In addition to liver transplantation, which is considered the standard of care for patients who satisfy specific inclusion criteria, local therapies (e.g., hepatectomy, percutaneous ablations, and transarterial therapies) are generally prescribed with disparate inclusion criteria due to the lack of common protocols [2]. Indeed, the lack of widely accepted treatments guidelines is still a major problem in managing HCC. This is particularly true in the case of multinodular HCC, for which the current recommended treatment is transarterial chemoembolization (TACE), expecting approximately 20 months of median survival [3]. However, the "multinodular area" includes a large variety of tumor presentations for which a single therapeutic option appears to be too restrictive. Indeed, recent studies from different authors reported significant long-term survival after surgery for at least a portion of these patients [4–7].

In this perspective, we herein analyzed our series of patients resected for multinodular HCC with the aim to find out the prognostic factors for survival and, consequently, define the tumor limits for which hepatic resection may be considered indicated. Furthermore, we added a literature review to offer an overview of TACE versus liver resection in the multinodular HCC treatment, according to the most recent published series worldwide.

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Methods

Study design and data collection

This is a retrospective study based on a prospectively enrolled cohort of patients undergoing curative hepatic resection for HCC at our department. Each patient gave the informed consent for operation and clincial data acquisition. Inclusion criteria were: only patients with a primary untreated HCC; patients with any types of underlying liver diseases; complete follow-up (minimum 12 months). Exclusion criteria were: patients treated with ablation alone or in combination with surgery; patients treated with non-radical surgery. The study protocol was submitted to the clinicaltrials.gov registry (ID-NCT01387061).

Study endpoints

The primary study endpoint was a survival analysis based on the tumor features of patients with multinodular HCC. The secondary study endpoint was the definition of the tumor limits for which hepatic resection is indicated. For these endpoints, the overall and disease-free survival were calculated and univariate and multivariate analyses of prognostic factors were performed.

Study definitions

The nomenclature and extent of hepatic resection were recorded according with the Brisbane classification [8]. Hepatic resection was considered major when at least three adjacent segments were removed. Postoperative morbidity was graded based on the Dindo–Clavien classification [9]. Postoperative mortality was recorded 90-day after surgery.

Literature search

The literature search was performed using the PubMed database. For the search, the following keywords were used: hepatic resection, transcatheter arterial chemoembolization/embolization, hepatocellular carcinoma, multinodular hepatocellular carcinoma, and overall survival. A manual search was also performed using the references in reviews and articles. The selection was limited to articles published in English.

Diagnosis and preoperative workup

All the patients were discussed at our weekly multidisciplinary team meeting to tailor the treatment from the oncological and technical standpoints. The preoperative workup consisted of computed tomography (CT) and/or magnetic resonance imaging (MRI) in all patients. The patients were selected for surgery on the basis of the hepatic functional reserve estimation, as previously described and essentially based on serum total bilirubin and cholinesterases [10]. All patients belonged to class A of the Child–Pugh–Turcotte (CPT) classification [11]. For the purpose of the present study, the patients with macrovascular tumoral invasion were excluded with. The extent of the acceptable liver volume was estimated using the standard volumetric analysis on CT or MRI images. In cases of major or extended hepatectomy, the value of the minimal acceptable remnant liver was set at 50% [12]. In case of insufficient remnant liver, portal vein embolization was considered [13]. However, we systematically adopted parenchymal-sparing techniques to minimize the need for major hepatectomy [14].

Surgical technique

A J-shaped laparotomy was performed. In cases with tumors in segments 1, 4-superior, 7, and 8 and in cases of narrow thoracic cage or obese patients, a J-shaped thoracoabdominal approach was considered. Intraoperative ultrasound (IOUS) was always used for staging and for resection guidance. In general, anatomical resections were selected for those patients with preserved liver function and performed using the IOUS-guided compression technique [15]. Instead, non-anatomical resections were chosen in case of impaired liver function. However, non-anatomical resections were always performed using IOUS-guidance with the division of afferent the sub-segmental glissonian pedicle. [16]. Parenchymal transection was performed using the crush-clamping technique and thin ligatures with the intermittent Pringle maneuver. Each patient was systematically drained after surgery with standard closed suction systems. Such drains were placed on the cut surface of the liver with the rule of one drain per area of resection and they were removed not before postoperative day 7 based on the reported protocol [17].

Postoperative follow-up

The postoperative follow-up was conducted by the authors in the outpatient clinic every 3 months after surgery. It was based on physical examination, liver function tests, alpha-fetoprotein, ultrasound, and CT or MRI.

Postoperative treatments

The postoperative treatments, including TACE, percutanous ablations and Sorafenib, were selected only in case of disease recurrence. None of the patients included in this study received any of this treatment as postoperative adjuvant therapy.

Statistical analyses

Continuous variables are presented as median and range, while discrete variables are presented as number and percentage. Kaplan–Meier curves were used to analyze differences in overall and disease-free survival and were compared using the log-rank test. The Cox-proportional hazard model was used to identify independent prognostic factors for survival, and the effect size was also calculated for each covariate [18–20]. The proportional hazards assumption was verified by testing time correlations and examining residual plots. An internal validation was performed using bootstrap resampling to detect model overfitting [19]. Although no formal sample-size calculation was requested, the high number of events (deaths) compared with the number of Cox model variables implied that the "ten events per variable" rule was largely exceeded, thus implying sufficient accuracy and precision of regression estimates [20]. All analyses were performed using the software SPSS (Chicago, IL, USA).

Results

Patients

Among 380 consecutive patients resected for HCC at our department between January 2004 and April 2015, 116 (31%) had multinodular HCC. All patients were N0 and M0. Table 1 details the baseline characteristics of these patients. Twenty-three (20%) patients had esophageal varices as shown during the preoperative upper gastrointestinal endoscopy; they underwent endoscopic binding before hepatectomy. The value of the Model for End-Stage Liver Disease (MELD) score was 8 points as the median, range 6–16 [21].

Surgical procedures

Table 1 details the surgical procedures. As shown, the median tumor number was 2, range 2–30, and the median tumor size was 3.5 cm, range 1.1–28 cm. In 36 (31%) of the patients the thoraco-abdominal approach was selected, but only in 17 (15%) major hepatectomy was performed. In 34 (29%) patients, an anatomical resection was carried out.

Short-term outcome

In total, postoperative morbidity was recorded in 36 (31%) patients. Of these patients, 29 (25%) experienced minor morbidity (Clavien–Dindo 1–2) and 7 (6%) experienced

Table 1 Patients characteristics

Baseline characteristics	*N* (%)
Patients number	116
Age	
Median; range	70; 34–82
> 65 years	85 (73)
Sex	
M/F	94/22
Etiology	
HCV	58 (50)
HBV	23 (20)
Alcohol	22 (19)
Unknown	13 (11)
Underlying liver	
Chronic hepatitis or cirrhosis	93 (80)
Normal liver	23 (20)
Barcelona clinic liver cancer stage	
0-A	64 (55)
B	52 (45)
C	–
Alpha-Fetoprotein	
Median; range	13.4; 1.50,614
Elevated*	17 (15)
Bilirubin	
> 1 mg/dl	43 (37)
Platelet count	
≤ 100,000 μL/mm^3	21 (18)
Albumin (g/dL)	
Median; range	3.1; 2.8–4.9
Esophageal varices	23 (20)
Child–Pugh–Turcotte score A	116 (100)
Model for end-stage liver disease	
Median; range	8; 6–16
Tumor and surgical characteristics	
Tumor size (cm)	
Median; range	3.5; 1.1–28
Tumor number	
Median; range	2; 2–30
Vascular invasion	
Micro	48 (41)
Macro	–
Grading	
1–2	49 (42)
3–4	58 (50)
Unknown	9 (8)
Extent of hepatectomy	
Major (> 3 segments)	17 (15)
Minor	99 (85)
Type of hepatectomy	
Anatomical	34 (29)
Non-anatomical	82 (71)
Thoraco-abdominal approach	36 (31)

Table 1 (continued)

Length of operations (minutes)	
Median; range	419; 159–803
Intermittent Pringle maneuver	116 (100)
Length of intermittent Pringle maneuver	
Median; range	82; 18–223
Blood loss > 500 ml	39 (33)
Red packed cells transfusion	57 (49)
Postoperative complications	
Overall	36 (31)
Clavien–Dindo 1–2	29 (25)
Clavien–Dindo 3–4	7 (6)
Length of stay (day)	
Median; range	9; 6–45
90-day mortality	3 (2.6)

* > 7 ng/ml (upper limit of the normal range)

major morbidity (Clavien–Dindo 3–4). Unfortunately, 3 (2.6%) patients died within 90 days after surgery. The causes of death were sepsis and liver failure.

Long-term outcome

After a median follow-up of 31 months (range 3.1–149.7 months), the median overall survival was 42.1 months. The 1-, 3-, and 5-year overall survival rates were 85, 52, and 35%, respectively (Fig. 1a). In that period of time, 83 (71.5%) patients developed disease recurrence, giving a median disease-free survival of 15 months. The 1-, 3-, and 5-year disease-free survival were 56, 26, and 19%, respectively (Fig. 1b).

Postoperative therapy

Among the 83 patients that developed disease recurrence, 7 (8%) did not receive treatments, 49 (59%) underwent TACE, 16 (19%) had radiofrequency ablations, and 11 (14%) received systemic therapy with Sorafenib during the courses of their diseases. Of note, these types of therapies have been tested in the multivariate model as variables that potentially may influence the survival (Table 2).

Analyses of prognostic factors for overall survival

Table 2 details the analyses of prognostic factors for overall survival. Of note, the Child–Pugh–Turcotte score was not tested being all the patients in score A. Similarly, the values of serum albumin and of MELD score were not tested because they were in the normal range. At the multivariate analysis, the number of tumors more than 4 (HR = 2.15; 95% CI 1.8–4.18; $P = 0.001$), the size of tumors more than 6 cm (HR = 2.78; 95% CI 2.08–4.91; $P = 0.001$), the performance of major resection (HR = 3.01; 95% CI 1.98–5.61; $P = 0.002$), and the presence of esophageal varices (HR = 2.91; 95% CI 1.97–4.54; $P = 0.001$) were found to be statistically independently significant for survival. Interestingly, the underlying liver (chronic hepatitis or cirrhosis versus normal liver), the grading

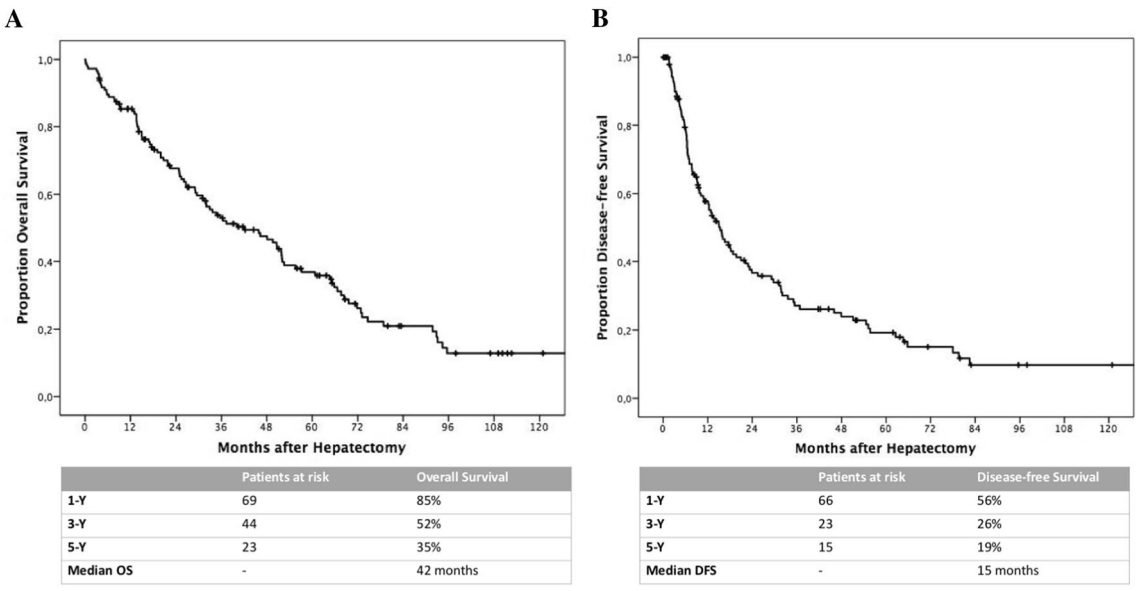

Fig. 1 **a** Overall survival of 116 patients resected for multinodular HCC. The 1-, 3-, and 5-year overall survival rates were 85, 52, and 35%, respectively. **b** Disease-free survival of 116 patients resected for multinodular HCC. The 1-, 3-, and 5-year disease-free survival was 56, 26, and 19%, respectively

Table 2 Analyses of prognostic factors for overall survival

Variable	*N* (%)	5-Y OS	Univariate *P*	HR (95% CI)	Multivariate *P*
Age					
≤ 65 years	43 (37)	48%	0.261	–	–
> 65 years	73 (73)	33%			
Sex					
Male	94 (81)	38%	0.434	–	–
Female	22 (19)	22%			
Number of tumors					
≤ 2	47 (41)	32.5%	0.122	–	–
> 2	69 (59)	37			
Number of tumors					
≤ 3	97 (84)	34%	0.278	–	–
> 3	19 (16)	43%			
Number of tumors					
≤ 4	104 (90)	49%	**0.002**	**2.15 (1.18–4.18)**	**0.001**
> 4	12 (10)	18%			
Size of tumors (cm)					
≤ 3	49 (42)	43%	0.457	–	–
> 3	67 (58)	30%			
Size of tumors (cm)					
≤ 4	70 (60)	39%	0.277	–	–
> 4	46 (40)	30%			
Size of tumors (cm)					
≤ 5	79 (68)	38%	0.253	–	–
> 5	37 (32)	31%			
Size of tumors (cm)					
≤ 6	85 (73)	40%	**0.013**	**2.78 (2.08–4.91)**	**0.001**
> 6	31 (27)	24%			
Serum bilirubin level (mg/dl)					
≤ 1	73 (63)	33%	0.849	–	–
> 1	43 (37)	39%			
Serum alpha-fetoprotein (UI/l)					
≤ 200	99 (85)	37%	0.534	–	–
> 200	17 (15)	29%			
Serum platelet count (μl/mm^3)					
≤ 100	21 (18)	29%	0.566	–	–
> 100	95 (82)	37%			
Esophageal varices					
Yes	23 (20)	22%	**0.003**	**3.01 (1.98–5.61)**	**0.002**
No	93 (80)	45%			
Etiology					
HCV	58 (50)	23%	0.689	**–**	**–**
HBV	23 (20)	19%			
Underlying liver					
Chronic/cirrhosis	93 (80)	31%	0.061	**–**	**–**
Normal	23 (20)	41%			
Grading					
1–2	49 (42)	27%	0.071	**–**	**–**
3–4	58 (50)	19%			
Microvascular invasion					
Yes	48 (41)	29%	–	**–**	**–**
No	68 (59)	37%			

Table 2 (continued)

Variable	*N* (%)	5-Y OS	Univariate *P*	HR (95% CI)	Multivariate *P*
Extent of hepatectomy					
Major	17 (15)	18%	**0.021**	**2.91 (1.97–4.54)**	**0.001**
Minor	99 (85)	38%			
Type of hepatectomy					
Non-anatomical	82 (30)	38%	0.730	–	–
Anatomical	34 (70)	34%			
Postoperative therapy*					
No treatment	7 (8)	10%	0.654	–	–
Ablation	16 (19)	9%			
TACE	49 (59)	8%			
Sorafenib	11 (11)	–			

Bold values indicate statistically significant factors

5-Y OS 5-year overall survival, *HR* hazard ration, *95% CI* 95% confidential interval

*In case of disease recurrence

(G1–2 versus G3–4), and the etiology (HCV versus HBV) were not significant. Similarly, there was no difference among the postoperative treatments of patients (no treatment versus TACE versus radiofrequency ablation versus Sorafenib) meaning that these types of treatments, at least in the present cohort, did not significantly influence the survival of patients with HCC recurrence after hepatectomy. With the aim to define the limits in terms of number and size of tumors for which hepatic resection for multinodular HCC may be considered indicated, we searched for the combinations of two of the four factors that were found to be independently significant for survival: number of tumors more than 4, and size of tumors more than 6 cm.

The up to 4 and 6 rule

Combining the number of tumors (=4) and the size of tumors (=6 cm), we found that an adequate overall survival was achieved only grouping the patients with up to 4 tumors, none more than 6 cm in size (*N.* = 71). They had a 5-year overall survival rate of 42%. None of the patients in the other combinations experienced such long-term survival (*N.* = 45) (Fig. 2a). Thus, the up to 4 and 6 rule was introduced. The 1-, 3-, and 5-year overall survival was 94, 63, and 42% for patients within the rule and 66, 32 and 23% for patients beyond the rule (*P* = 0.001), with a corresponding median survival of 52 months and 20 months, respectively (Fig. 2b).

The effect of varices on survival within each of these categories was also analyzed. The presence of varices, i.e.,

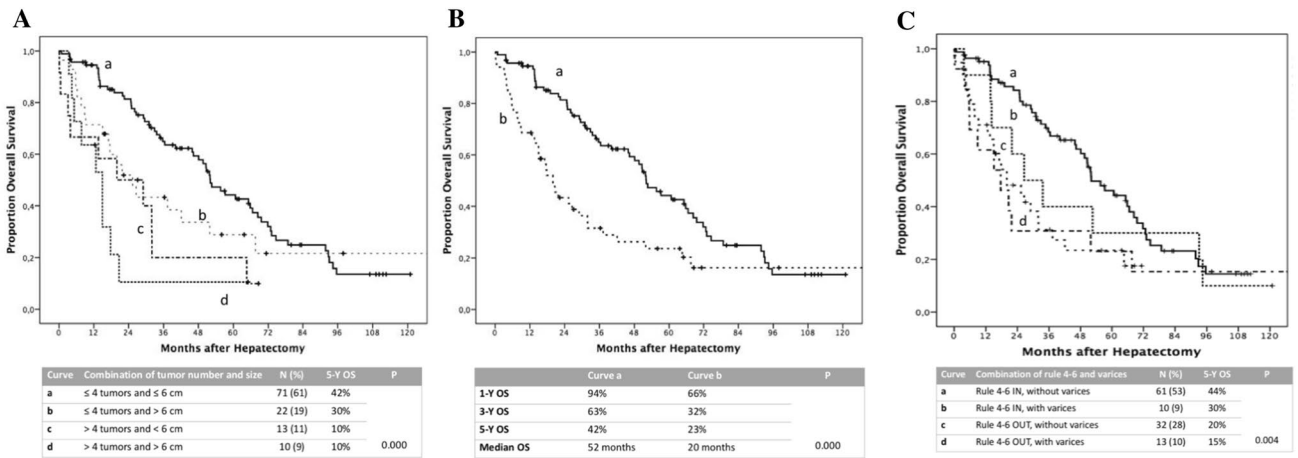

Fig. 2 **a** Overall survival of 116 patients resected for multinodular HCC stratified in four groups according with the up to 4 and 6 rule. **b** Overall survival of 116 patients resected for multinodular HCC stratified in two groups: curve a, within the up to 4 and 6 rule; b, beyond the up to 4 and 6 rule. **c** Overall survival of 116 patients resected for multinodular HCC stratified in four groups according with the up to 4 and 6 rule and the presence of varices

of portal hypertension, significantly reduced the overall survival as detailed in Fig. 2c. Five-year survival rates for patients within and beyond the rule without and with varices were as follows: 44% for patients within the rule but without varices; 30% for patients within the rule but with varices; 20% for patients beyond the rule but without varices; and 15% for patients beyond the rule but with varices. Adding the presence of varices means a significant detriment in survival in each category. However, the survival rates for patient within the up to 4 and 6 rule are still worthy to be considered, being those rates superior to those expected after TACE.

Literature search results

Table 3 details the summary of the literature review. Of the ten included studies, seven are retrospective, two are meta-analysis, and one is a randomized controlled trial (RCT) [6, 22–30]. Overall, all these studies reported statistically significant differences in survival advantage for surgery over TACE in cases of multinodular HCC. Most studies reported some prognostic factors that can be used to refine the selection criteria when deciding whether hepatic resection may be indicated or not (Table 3). Interestingly, the only RCT available showed a net survival benefit for surgery over TACE in cases of multinodular HCC, specifically for HCC beyond the Milan criteria. Yin et al. in fact, reported a 5-year overall survival rate of 51% and of 18%, respectively, for surgery and TACE [22].

Discussion

The current international guidelines, which rely on the BCLC classification, recommend TACE in cases of multinodular HCC, expecting a median survival of 20 months [3].

The rationale of the recommendation of TACE originates from two RCTs and three meta-analyses, which with a high

Table 3 Review of the literature

References	Year	Study type	Patients	Survival benefit	Prognostic factors	Included patients
Ciria [6]	2015	Retrospective	LR: 36 TACE: 44	5-Y OS LR = 44% 5-Y OS TACE = 38%	Bilirubin level; B1 stage; G1–2 HCC; no microvascular invasion	Single, large and multinodular HCC
Yin [22]	2014	Randomized	LR: 88 TACE: 85	5-Y OS LR = 51% 5-Y OS TACE = 18%	TACE; tumors number > 2	–
Zhong [23]	2013	Retrospective	LR: 58 TACE: 31	5-Y OS LR = 24% 5-Y OS TACE = 4%	TACE; AFP > 400 ng/ml; macro-vascular invasion; serum ALT level	BCLC B multinodular
Choi [24]	2013	Retrospective	LR: 36 TACE: 107 LT: 17	5-Y OS LR = 48% 5-Y OS TACE = 29% 5-Y OS LT = 80%	TACE; cirrhosis	–
Farinati [25]	2015	Retrospective	LR: 52 TACE: 185 BSC: 103	LR = 37 MMS TACE = 27 MMS BSC = 14 MMS $P < 0.001$	AFP > 200 ng/dl, esophageal varices, Child–Pugh B	20% single HCC; 80% multinodular HCC
Yang [26]	2015	Retrospective	LR: 9580 TACE: 1594	5-Y OS LR = 37% 5-Y OS TACE = 17%	N.A.	Single, large and multinodular HCC
Qi [27]	2015	Meta-analysis	LR: 1864 TACE: 2379	Favorable outcome for LR HR = 0.60, P < 0.001	N.A.	Any HCC beyond BCLC A
Kapitanov [28]	2015	Meta-analysis	LR: 5394 TACE: 3722	Favorable outcome for LR HR = 0.70, P < 0.001	N.A.	BCLC A and B patients
Vitale [29]	2014	Retrospective	LR: 171 LRT: 327 BSC: 198	Net survival difference LR vs. LRT or BSC = 71%	MELD≥9; PF≥2; Child–Pugh B-C	BCLC B
Jianyong [30]	2014	Retrospective	2-3 nodules: LR: 186 TACE: 161 >3 nodules: LR: 76 TACE: 139	2-3 nodules: 5-Y OS LR = 65% 5-Y OS TACE = 50% 3 nodules: 5-Y OS LR = 40% 5-Y OS TACE = 21%	TACE; tumors number > 3; AFP > 400 ng/ml; portal hypertension; neutrophil-to-lymphocyte ratio	BCLC B multinodular

LR liver resection, *TACE* transcatheter arterial chemoembolization, *5-Y OS* 5-year overall survival, *N.A.* not available, *HR* hazard ratio, *BCLC* barcelona clinic liver cancer classification, *BSC* best supportive care, *LRT* loco-regional therapy, *MELD* model for end-stage liver disease, *PF* performance status, *LT* liver transplantation

degree of heterogeneity reported a survival benefit for TACE over best supportive care (BSC) [31–35]. Of note, these studies compared TACE over BSC based on unresectable HCC patients. Despite that, the guidelines drew these results recommending TACE, thus excluding the patients with resectable multinodular HCC. It deserves to be mentioned that at the time of the referred article there were extensive reports sustaining the efficacy and safety of surgery in HCC patients [36].

On the other hand, the role of surgery in these patients has been recently reaffirmed in a recent large multicenter study based on 2046 patients from ten different worldwide hepatobiliary centers showing adequate mortality and morbidity rates and surprising survival for patients in the intermediate and advanced stages [4]. In addition to that there are other reports by single or multiple institutions sustaining the role of surgery in such patients [5–7, 37].

The recommendation of TACE for multinodular HCC has been recently challenged by Farinati et al. that in a multicenter Italian study of 405 patients reported that TACE cannot be considered the best therapy for BCLC B patients since this group includes a heterogeneous population [25]. Notably, this message comes from hepatologists and not from surgeons. Consistently with the conclusions of Farinati et al., our literature search depicts that surgery is associated with increased survival over TACE for multinodular HCC (Table 3) which is the same even compared to the most promising advancement in transarterial therapy, such as the transarterial radio-embolization (TARE). Indeed, Sangro et al. and Mazzaferro et al. reported a median survival of 16.9 months and 18 months, respectively, for multinodular HCC patients, in which survivals are even inferior to the 20 months expected by the guidelines [38, 39].

The recommendation for TACE is also in contrast with other studies from different surgeons that reported that the surgical community does not follow the guidelines and that surgery, rather than TACE, may be associated with long-term survival [4–7]. In addition, Cucchetti et al. [40] showed that when comparing the so-called average treatment effect between TACE and liver resection for HCC, this last option returned to be associated with increased survival. In particular, the option of operating on HCC patients who had TACE instead of surgery returned an average treatment effect of more than 27 months [40]. Nevertheless, the BCLC community seems to ignore such evidence, probably supposing the presence of selection biases in those studies.

Even if it is a matter of patient selection, the a priori exclusion of surgery from the therapeutic algorithm of the international guidelines does not seem justified, especially considering that any paper arguing on this population is limited by the heterogeneity of this class of patients, and the lack of a commonly shared criteria of resectability. This is particularly important if we consider that unresectability has been repeatedly recalled in all the papers on which the recommendations are based.

In the present study, we found after a median follow-up of 31 months (range 3.1–149.7 months) 1-, 3-, and 5-year overall survival rates of 85, 52, and 35%, respectively (Fig. 1a).

The median survival was 42.1 months, which is twofold longer than the median survival expected by the BCLC algorithm [3]. Of note, the disease-free survival was not equally good since the 1-, 3-, and 5-year disease-free survival rates were 56, 26, and 19%, respectively (Fig. 1b). However, the present series includes patients with multinodular HCC (100%) with a significant tumor burden added to the underlying cirrhosis or chronic hepatitis; this explains the low disease-free survival rates. Interestingly, all the patients were CPT score A, and the MELD score was relatively low with a median of eight points, range 6–16. In our experience, only patients with normal liver function should be considered for surgery to minimize not only the postoperative complications, but also to reach significant survival. Multinodular HCC patients defined as CPT B, and of course CPT C, and with high values of the MELD score should be considered only for TACE.

These long-term results have been achieved with an overall postoperative morbidity of 31% and a 90-day mortality of 2.6%. This mortality rate should be considered adequate since it was calculated at 90-day. More interestingly, our analysis was focused on those prognostic factors that can define if hepatic resection for multinodular HCC is indicated. As said, only the number of tumors more than 4, the size of tumors more than 6 cm, the performance of major resection, and the presence of esophageal varices were independently significant for survival. Combining the number of tumors (=4) and the size of tumors (=6 cm), we were able to introduce the "up to 4 and 6 rule" that allowed us to extract two populations with different survival rates: the 1-, 3-, and 5-year overall survival rates were 94, 63, and 42% for patients within the rule and 66, 32, and 23% for patients beyond the rule ($P=0.001$) with the corresponding median survival of 52 months and 20 months, respectively (Fig. 2b). Intriguingly, the patients beyond the up to 4 and 6 rule had the same median survival, 20 months, expected by the BCLC algorithm [3]. As a consequence, the expansion of the indications for surgery should not lead to offering surgery indiscriminately to any patient with multinodular HCC. The patients beyond the up to 4 and 6 rule should be considered for TACE rather than for surgery. Conversely, patients within the up to 4 and 6 rule should be considered for surgery and not for TACE. As showed, adding the presence of varices means a significant detriment in survival in each category, even if the survival rates for patient within the up to 4 and 6 rule are still worthy to be considered, being those rates superior to those expected after TACE. Then, we propose to initially stage the patients according to the number and size

of tumors and later considering the presence of varices to further stratify patients. Of note, our results are in line with those reported by Giuliante et al. [41], who on a large multicenter Italian series have shown a median overall survival of 51 months for 134 patients resected for multinodular HCC.

Regarding the postoperative treatments, none of the included patients receive any treatment as adjuvant therapy after hepatic resection. Indeed, there is no evidence that any therapy, such as systemic therapy, may impact the survival after hepatectomy [42]. However, 71.5% of the patients developed recurrence after surgery. TACE, Sorafenib and radiofrequency ablation, which were used to treat HCC recurrence, were analyzed as potentially confounding variables in the survival analysis herein presented. None of them significantly influenced the survival meaning that, at least in the present cohort, hepatectomy represented the main therapy able to impact the survival.

Given the heterogeneity of patients with multinodular HCC, our present work supports attempts, already made by other authors, to identify sub-groups of patients with intermediate HCC for which different treatments might be considered. As shown by Bolondi et al. [43], Weinmann et al. [44] and more recently Ciria et al. [6], several subclassifications have been proposed without broad consensus. In contrast to these authors, we did not focus our attention on stage B HCC patients, but rather on the fact that using our simple up to 4 and 6 rule, the median survival after hepatic resection for multinodular HCC might approach 52 months.

This study has several limitations. Being a retrospective study, we may not rule out selection and confounding biases. A cautious approach is required before generalization. It is difficult to calculate the proportion of patients in the whole population of multinodular HCC patients that may benefit from surgery. In this sense, our sample size might be considered too small to be representative. However, it should be noted that this is a single-center study while most of the previously published reports on the same topic were multicenter studies, in which anyway the number of patients with multinodular HCC were similar to the herein present study [4, 7, 29]. Nevertheless, a consistent body of the literature together with the results of the present study enhances the evidence that clinicians should work to refine the selection criteria for surgery rather than deny surgery a priori.

In summary, this study indicates that some patients with multinodular HCC may benefit from surgery even if they should be considered only for TACE based on the current international guidelines. Hepatic resection is not offered routinely for patients with multinodular HCC. However, it appears that the subgroup of patients within the up to 4 and 6 rule may achieve more than adequate long-term survival. Further multicenter prospective trials are recommended to validate our single-center experience.

Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest.

Research involving human participants and/or animals The study was conducted according with the Helsinki declaration about ethical standards. Moreover, it was approved by the local ethical committee of our institution.

Informed consent Informed consent was obtained by each patient included in the study.

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