Combined liver resection and transarterial chemoembolization versus liver resection alone for the management of solitary large exophytic hepatocellular carcinoma with extrahepatic arterial supply: is two always better than one?

Ahmed M. El-Gendi[a], Mohamed El-Shafei[b], Essam Bedewy[c]

Departments of [a]Surgery, [b]Diagnostic and Interventional Radiology, [c]Hepatology and Tropical Medicine, Faculty of Medicine, Alexandria University, Alexandria, Egypt

Correspondence to Ahmed M. El-Gendi, MD, MRCS, PhD, Department of Surgery, Faculty of Medicine, University of Alexandria, Alexandria 21131, Egypt. Tel: +20 3484 7426/ +20 122 240 8223; fax: +20 3542 6676; e-mails: draelgendi@gmail.com, ahmed.elgendi@alexmed.edu.eg

Received 15 October 2017
Accepted 10 January 2018

The Egyptian Journal of Surgery
2018, 37:78–88

Purpose
Does the control of extrahepatic arterial feeders with preoperative transarterial chemoembolization (TACE) in large exophytic hepatocellular carcinoma improve surgical and oncological outcomes compared with surgery alone?
Patients and methods
A total of 545 patients were assessed for eligibility, and 108 patients fulfilled the inclusion criteria and were assigned to either upfront surgery (group I) or surgery after TACE (group II).
Results
Patients in both groups had no significant difference with respect to age (P=0.573), sex (P=0.464), α-fetoprotein (P=0.313), American Society of Anesthesiologists score (P=0.820), and Child–Pugh score (P=0.577). The mean tumor size was comparable (9.8±2.2 cm in group I vs. 10.3±2.3 cm in group II, P=0.265). In group I, four patients underwent major hepatectomy, whereas 48 patients underwent minor hepatectomy. In group II, 54 patients underwent 121 TACE sessions with a mean of number of 2±0.8 session (range: 1–4 sessions). The mean interval between first TACE and surgery was 45±10.7 days (range: 12–72 days). Surgery after TACE had significantly higher rate of perihepatic adhesions (P=0.006), longer operative time ($P<0.0001$), increased blood loss (P=0.035), and longer hospital stay (P=0.020) compared with upfront surgery but with comparable outcomes regarding in-hospital and 30-day morbidity (P=0.819). After a mean follow-up of 14.3±5.9 months, both groups had similar disease-free survival, with none of the tumors in both groups showed local recurrence. There was no significant difference in the type, time of recurrence following resection, or the mean numbers of new (de-novo) tumors detected in both groups (2.22±1.60 and 2.54±1.69 in groups I and II, respectively).
Conclusion
In patients with solitary large exophytic hepatocellular carcinoma, combined hepatic resection plus TACE is associated with increased perihepatic adhesions, increased operative time, blood loss, and postoperative hospital stay compared with liver resection alone. Preoperative TACE has no additional oncological benefit, with no reduction in recurrence rate or improvement in disease-free survival.

Keywords:
exophytic hepatocellular carcinoma, extrahepatic feeders, large solitary hepatocellular carcinoma, neoadjuvant transarterial chemoembolization

Egyptian J Surgery 37:78–88

1110-1121

Introduction

Hepatic resection is currently recommended for solitary hepatocellular carcinoma (HCC) less than 5 cm in size in patients with well-preserved liver function without significant portal hypertension and major vascular or lymphatic invasion [1]. Published literature has reported outcomes of surgical resection for solitary large HCC (beyond 5 cm) to be similar to those of solitary small HCCs less than 5 cm [2]. Most HCC arises on top of liver cirrhosis with a poor hepatic functional reserve, and it is frequently multicentric; therefore, transarterial chemoembolization (TACE) has an established role mounting to first-line treatment of unresectable HCC, aiming at either palliation or improving survival [3–5]. Its role in management of resectable HCC is still controversial. The main rationale behind using TACE preoperatively as a neoadjuvant therapy in patients with resectable HCC is to decrease incidence of recurrence and improve disease-free survival. However, published literature contains numerous studies reporting conflicting data, with some studies demonstrating improved survival with reduced recurrence rate [6–8], whereas others have failed to show any significant survival benefit [9–12] to the extent of reporting a reduction in long-term survival rates [12,13]. Therefore, it remains uncertain whether preoperative TACE has positive or negative effect on patients with resectable HCC, taking in consideration the wide spectrum of patients included under the term 'resectable HCC' regarding to size, number, location, growth pattern, multiplicity, Child score, and liver reserve.

An extrahepatic collateral pathway to the liver is established in various conditions [14–16]. It mainly develops after interruption of the hepatic artery by surgical ligation, arterial injury induced by repeat TACE, or placement of a catheter. Not infrequently, an extrahepatic blood supply to HCC also develops in the anatomic location of HCC, even when the hepatic artery is patent [15,17–21]. This is very commonly encountered in exophytic HCC [21,22]. Adhesion between the liver and other organs exaggerates the degree of extrahepatic collaterals [14–16,23]. Besides the surface location of the tumor as a prerequisite for the formation of the parasitic feeders, the size of the tumor when above 6 cm in maximum diameter has a high prevalence for such condition [21,22,24]. The presence of extrahepatic feeders may be of an oncological concern because of a chance of tumor spread to surrounding neighbor structures. Manipulation of the tumor during surgery before the control of those collaterals may increase the chance of tumor spread. Preoperative control of these collaterals through TACE may obviate this risk. For transcatheter management of HCC to be effective, these collaterals should be adequately embolized [15,17–20,25–30].

The aim of this study was to compare prospectively the surgical and oncological outcomes of combined hepatic resection and TACE versus surgical resection alone in the management of solitary large exophytic HCC with extrahepatic collateral arterial supply in Child A cirrhotic patients.

Patients and methods

The study was conducted at the Surgery Department, Main University Hospital, which is a 1000-bed teaching hospital and a tertiary referral center serving a community of four million people. The Ethics Committee and review board in our institute approved the study and treatment protocol. An informed consent was obtained from all patients who agreed to participate in the study.

Between January 2015 and July 2017, all patients with solitary HCC were assessed for eligibility. Inclusion criteria were patients with Child A cirrhosis presenting with solitary HCC equal or more than 7 cm, exhibiting an exophytic growth pattern with at least one extrahepatic collateral artery detected on initial dynamic abdominal computed tomography (CT) scan. Exclusion criteria were patients with an American Society of Anesthesiologists (ASA) score exceeding 3, a decompensated liver cirrhosis (Child B or C), esophageal varices grade greater than 2, a platelet count less than $80\times10^9/l$, previous upper abdominal surgeries, previous treatment for HCC with TACE or other intervention, occlusion of hepatic artery or celiac trunk, presence of portal vein thrombosis, macroscopic vascular invasion, and distant metastases.

A total of 545 consecutive patients were assessed for eligibility. Of them, 101 patients refused to participate in the study, whereas 336 patients did not fit to the inclusion criteria or had an exclusion criterion. Therefore, 108 patients were enrolled in the study. The diagnosis of HCC was based on the characteristic dynamic abdominal CT or MRI findings and elevation of the α-fetoprotein (AFP) level (>400 ng/ml). Biopsy was not performed to confirm the diagnosis of HCC. All patients with HCC were discussed at a weekly multidisciplinary team conference consisting of hepatopancreaticobiliary surgeons, hepatologists, interventional radiologists, and medical and radiation oncologists. After consent from each patient, 54 patients were assigned to group I (upfront surgery), and 54 patients to group II (surgery after TACE) using closed sealed envelopes that were opened in order when assignments were made. An independent observer managed patients' allocation in either group. The allocated treatment was performed within 96 h. The same experienced team of hepatobiliary surgeons and intervention radiologists performed all procedures in both groups.

The following clinical data and treatment outcome in the two groups was recorded and compared: clinicopathological factors including age, sex, BMI, ASA grade, hepatitis serology, and esophageal varices and preintervention laboratory data including AFP level, tumor size (recorded as the maximum diameter in at least one dimension), location, surgical margin status, microscopic vascular invasion, and histological grade as defined by Edmondson and Steiner [31].

All patients had dedicated dynamic abdominal CT study for assessment of number, extent, and size of the tumor with proper delineation of the hepatic and extrahepatic arterial collateral feeder to the tumor and exclusion of any macrovascular tumor invasion. The scans were read thoroughly as source two-dimensional images, maximum intensity projection images, and three-dimensional images. The origin and course of the main hepatic artery was identified, whether classical or replaced, as well as any accessory hepatic arteries. A thorough search for possible extrahepatic arterial feeders was performed, taking in consideration the hepatic segment involvement by the exophytic large HCC. The following arteries were well traced to identify possible feeder collateral arteries:

(1) The right inferior phrenic artery in exophytic HCC within segment VII/VIII, which would appear on CT as passing nearby or toward the lesion and could be rather prominent and dilated compared with the other side.
(2) The left gastric artery in exohytic HCC of segments II/III of the left lobe.
(3) The right renal or adrenal arteries in exophytic tumors of segments VI/VII.
(4) Near totally exophytic and contacting the omental fat, feeders from the gastroduodenal and superior mesenteric arcades are usually encountered and also from the gastroepiploic arteries.
(5) Intercostal and internal mammary parasitic feeders are less commonly found when the tumor is at the most anterosuperior portion of segments IVa/VIII or in contact with the right lateral thoracic/ abdominal wall, respectively.
(6) Moreover, much more rare are the lumbar arteries and usually are seen giving feeding twigs in advanced cases.

Transarterial chemoembolization

TACE was done for all group II patients using the super selective technique. According to the findings, dynamic CT done before the procedure, and a selective angiogram of the celiac trunk was performed with subsequent cannulation of the hepatic artery after the subtraction angiogram of the main hepatic artery (to be sure that there is no double right and left hepatic supply to the mass). A super selective angiogram of the segmental hepatic artery giving the feeder to the HCC mass lesion was performed and looking for the blush of contrast staining the mass whether it is completely covering its volume or there is a defect of staining of the contrast blush within the mass. If this defect is evident, then we put in consideration that there will be more work to be done after managing the main hepatic feeder supplying the mass as there will be definitely another extrahepatic arterial feeder to manage. In some cases, the digital subtraction angiogram was supplemented with a contrast-enhanced cone-beam CT acquisition to verify all arterial feeding vessels in rotatory maximum intensity projection and three-dimensional pattern, as an option in the angiography device. We start first cannulating the subsegmental main arterial hepatic feeder in a super selective approach using hydrophilic microcatheter (Progreat; Terumo Medical Corportaion, Tokyo, Japan), and when satisfied by our location after testing with contrast, we inject the drug mixture of iodized oil (Lipiodol; Andret Gurbet, Paris, France) and 50 ml of doxorubicin hydrochloride emulsion. We inject first a diluted amount followed by a concentrated amount until evident arterial flow stasis occurs, then we inject absorbable gelatin sponge particles (0.5–1 mm; gelfoam) soaked in 2–3 ml of the contrast to block the artery. Thereafter, we perform another digital subtraction angiography to identify the site of the residual part of the lesion not having the radiopaque particle of the lipiodol mixture and that will be corresponding to the staining defect of contrast seen in the first subtraction angiogram done before drug mixture injection. According to the anatomical segment of the lesion and the location of the residual active part, the nearby parasitic feeder will be cannulated. A subraction angiogram will be performed till stasis of the drug mixture followed by blockage using gelfoam. We defined technical success as successful catheterization into the tumor-feeding branch of extrahepatic collaterals and delivery of TACE using injected particles. Follow-up dynamic triphasic CT was requested 1 month after the session to assess the efficacy of the treatment and to exclude any residual viable tumor. Another session of embolization was performed if viable tumor was identified. Complications related to collateral TACE were recorded and analyzed by laboratory tests and CT findings, in addition to post-TACE symptoms.

Hepatic resection

The same surgical team with at least 10 years of experience in liver resection performed all the surgical procedures in group I and group II under general anesthesia. CT volumetric assessment of the residual liver volume was ensured to be more than 40% in all patients. Anatomical hepatectomy based on inflowing vessels was used as a general method for the hepatic resection; however, nonanatomical resections were resorted to if anatomical resection would leave the patient with residual liver volume of less than 40%.

All patients were treated with curative intent aiming at achieving R0 resection. The surgical resection margins were planned at least 1–2 cm from the edge of the tumor. Parenchymal transection was performed using either Cavitron Ultrasonic Surgical Aspirator (CUSA) combined with harmonic scalpel or using radiofrequency-assisted technique. When necessary, the liver pedicle was intermittently clamped in cycles of 10–15 min with 3–5 min of reperfusion. Data recorded included operative and postoperative details (operative time, resection time, need for Pringle maneuver, amount of blood loss, transfusion requirement intraoperatively and postoperatively, ICU admission, duration of hospital stay, postoperative complications, and 30-day mortality). Specific complications were those related to the liver resection procedure or the underlying liver disease and included the following: bile leak, operative site hemorrhage, ascites (defined as clinically detectable or as abdominal drainage output, when present, of 500 ml or more per day), hepatic encephalopathy, jaundice, and variceal bleeding. Other complications were recorded as nonspecific complications.

Postintervention morbidity and mortality were defined as events occurring during the same hospital stay or within 3 months of allocated intervention and was graded following the Dindo–Clavien classification [32]. Postprocedure mortality was defined as any death within 30 days after the procedure was performed. Treatment-related death was defined when patients died directly owing to treatment-related complications that developed within 1 week of treatments.

Follow-up, survival, and recurrence

After discharge, patients were regularly scheduled for follow-up outpatient visit and monitored with a standard oncologic protocol, which included liver function tests, AFP, and liver imaging with triple-phasic multi-slice CT and/or MRI at 1 month and then every 3 months during the first 2 years and then every 6 months thereafter for any intrahepatic recurrence together with annual chest radiography, and CT scan, bone scan for distant metastasis.

Local recurrence was defined as recurrence at surgical resection bed after R0 resection was histopathologically proven or at the local site of previously embolized HCC. Intrahepatic distant recurrence was defined when new tumor growth that met the previously mentioned criteria for diagnosing HCC appeared remote from the previously managed HCC. Extrahepatic metastasis refers to any recurrence outside the liver. All recurrences were recorded in the database immediately after confirmation of the diagnosis, and the site, number, and size of recurrent tumors were documented.

Statistical analysis

The raw data were coded and entered into SPSS system files (SPSS package version 18; SPSS Inc., Chicago, Illinois, USA). Analysis and interpretation of data were conducted. The following statistical measures were used: descriptive statistics including frequency, distribution, mean, median, SD, and interquartile range were used to describe different characteristics. Kolmogorov–Smirnov test was used to examine the normality of data distribution. Univariate analyses including *t*-test, analysis of variance test, Mann–Whitney test and Kruskal–Wallis test and Tamhane post-hoc test were used to test the significance of results of quantitative variables. χ^2-test or its correction namely Monte–Carlo test and Fisher's exact test were used to test the significance of results of qualitative variables. The significance of the results was at the 5% level of significance.

Results

A total of 108 patients with exophytic solitary large HCC greater than 7 cm with at least one collateral extrahepatic arterial supply documented in preassessment dynamic abdominal CT scan were included in the study. Of them, 54 patients underwent surgical resection (upfront surgery group), whereas 54 patients underwent TACE (surgery after TACE group). The baseline demographic and clinicopathological characteristics of the two groups of patients are listed and compared in Table 1. There was no statistical significant difference between both groups with respect to age (P=0.573), sex (P=0.464), or preprocedure laboratory tests, including AST (P=0.282), total bilirubin (P=0.262), AFP (P=0.313), ASA score (P=0.820), and Child–Pugh score (P=0.577). TACE group had a significantly higher BMI (29.4±2.6 vs. 28.4±2.5, P=0.029) than surgery upfront group, whereas the latter had a significantly higher alanine aminotransferase levels than TACE group (P=0.007) as illustrated in Table 1. The most common cause of cirrhosis in both groups was hepatitis C virus infection (90 and 94% in surgery upfront and TACE group, respectively, P=0.508). The mean tumor size in surgery upfront group was 9.8±2.2 (range: 7.2–15.6 cm) versus 10.3±2.3 (range: 7.0–15.5 cm) in surgery after TACE group, with no significant difference (P=0.265).

In surgery upfront group, all patients underwent hepatic resection as shown in Table 2. Major hepatectomy was performed in six patients, whereas 48 patients underwent

Table 1 Baseline demographic and clinicopathological characteristics of the patients in the two groups

Personal characteristics	Upfront surgery group (*n*=54) [*n* (%)]	Surgery after TACE group (*n*=54) [*n* (%)]	Significance
Age (years)			
Minimum–maximum	39.0–64.0	28.0–65.0	*t*=0.565
Mean±SD	52.4±6.5	51.7±7.4	*P*=0.573
Sex			
Male	25 (46.3)	21 (38.9)	χ^2=0.536
Female	29 (53.7)	33 (61.1)	*P*=0.464
BMI			
Minimum–maximum	22.0–34.0	23.0–36.0	*t*=2.206
Mean±SD	28.4±2.5	29.4±2.6	*P*=0.029*
ASA score			
II	44 (81.5)	45 (83.4)	χ^2=0.052
III	10 (18.5)	9 (16.6)	*P*=0.820
Cause of cirrhosis			
HCV	48 (88.2)	51 (94.4)	^{FE}P=0.508
Unknown	6 (11.1)	3 (5.6)	
Previous laparotomy			
No	47 (87.1)	50 (92.6)	χ^2=1.299
Yes	7 (12.9)	4 (7.4)	*P*=0.254
Bilirubin			
Minimum–maximum	0.6–1.2	0.7–1.2	*Z*=1.121
Median (Q1–Q3)	0.9 (0.8–1.0)	0.9 (0.8–1.1)	*P*=0.262
AST			
Minimum–maximum	58–178	45–125	*Z*=1.075
Median (Q1–Q3)	0.9 (0.8–0.9)	0.9 (0.7–0.9)	*P*=0.282
ALT			
Minimum–maximum	67–150	64–150	*Z*=2.680
Median (Q1–Q3)	99 (88–115)	88 (76–100)	*P*=0.007*
AFP			
Minimum–maximum	38–3880	38–3400	*Z*=1.009
Median (Q1–Q3)	670 (417–865)	600 (370–780)	*P*=0.313
Child score			
A5	33 (61.1)	36 (66.7)	χ^2=0.312
A6	21 (38.9)	18 (33.3)	*P*=0.577
Tumor size (cm)	7.2–15.6	7.0–15.5	*t*=1.120
Minimum–maximum	9.8±2.2	10.3±2.3	*P*=0.265
Median (Q1–Q3)	7.2–15.6	7.0–15.5	*t*=1.120

ASA, American Society of Anesthesiologists; AFP, α-fetoprotein; ALT, alanine transaminase; AST, aspartate transaminase ; ^{FE}P, Fisher's exact test; HCV, hepatitis C virus; TACE, transarterial chemoembolization. *$P\leq0.05$, significant.

minor hepatectomy. In spite of the large size of HCCs, major hepatectomies constitutes only 11.1% of all hepatetcomies performed. Curative intent of resection was achieved through final histopathological examination of free resection margin (R0) in all patients with a mean of 1.7±0.5 cm (range: 0.7–3 cm). However, microvascular invasion was detected in 64.8% of tumors resected. The operative time ranged from 110 to 340 min (median: 162 min), with mean blood loss of 607.3 ±386.4 ml (range: 100–1600 ml). Overall, 12 (22.2%) patients required blood transfusion, and 21 (38.9%) patients stayed at least 1 day in ICU with median total postoperative hospital stay of 5 days (range: 3–7 days) as shown in Table 3.

In surgery after TACE group, 54 patients underwent 121 TACE sessions with a mean of number of 2±0.8 session (range: 1–4 sessions). After the initial session of TACE, no patients in TACE group achieved the technical success of full control of hepatic and extrahepatic feeders. The mean interval between first TACE and surgery was 45±10.7 days (range: 12–72 days). The most common complications were owing TACE toxicity itself manifested as fever, sense of fatigue, and right hypochondrial pain, with seldom anorexia nausea/vomiting. A number of complications were encountered during control of extrahepatic collaterals as shown in Table 4.

The comparison of surgical parameters and outcomes of surgery upfront group with surgery after TACE groups are illustrated in Table 2. Patients undergoing surgical resection after TACE experienced significantly higher rate of perihepatic adhesions (*P*=0.006) than upfront

Table 2 Operative characteristics of the studied patients subjected to upfront surgery and surgery after transarterial chemoembolization

Operative characteristics	Upfront surgery (*n*=54) [*n* (%)]	Surgery after TACE (*n*=54) [*n* (%)]	Significance
Type of hepatectomy			
Monosegmentectomy	6 (11.1)	5 (9.3)	χ^2=0.747
Nonanatomical	26 (48.2)	28 (51.9)	^{MC}P=0.949
Bisegmentectomy	10 (18.5)	8 (14.8)	
Right/left hepatectomy	6 (11.1)	5 (9.3)	
Left lateral segmentectomy	6 (11.1)	8 (14.8)	
Perihepatic adhesions			
No	37 (68.5)	23 (42.6)	χ^2=7.617
Yes	17 (31.5)	31 (57.4)	*P*=0.006*
Operative time (min)			
Minimum–maximum	110–340	123–350	*Z*=3.788
Median (Q1–Q3)	162.0 (145.8–180.0)	190.0 (170.0–230.0)	*P*<0.0001*
Blood loss (ml)			
Minimum–maximum	100–1600	190–1800	*t*=2.133
Mean±SD	607.3±386.4	763.7±368.5	*P*=0.035*
Intraoperative transfusion			
No	42 (77.8)	35 (64.8)	χ^2=2.570
Yes	12 (22.2)	19 (35.2)	*P*=0.109
Clamping			
No	51 (94.4)	50 (92.6)	^{FE}P=0.679
Yes	3 (5.6)	4 (7.4)	
Associated procedures			
No	48 (88.9)	45 (83.3)	χ^2=1.150
Yes	6 (11.1)	9 (16.7)	*P*=0.284
Cholecystectomy	6 (11.1)	7 (13.0)	
Hernia repair	0 (0.0)	2 (3.7)	
Histological grade			
Well differentiated	24 (44.4)	25 (46.3)	χ^2=0.046
Moderate differentiated	23 (42.6)	23 (42.6)	*P*=1.0
Poor differentiated	7 (13)	6 (11.1)	
Microvascular invasion			
No	19 (35.2)	20 (37.0)	χ^2=0.068
Yes	35 (64.8)	34 (63.0)	*P*=0.795
Resection margin			
Minimum–maximum	0.7–3.0	0.7–3.0	*t*=2.991
Mean±SD	1.7±0.5	2.0±0.6	*P*=0.003*

^{FE}P, Fisher's exact test; ^{MC}P, Monte–Carlo corrected *P* value; TACE, transarterial chemoembolization; *Z*, Mann–Whitney test. *$P\leq0.05$, significant.

surgery group (31 vs. 17 patients, respectively). These adhesions were vascular, resulting in adhesion of embolized tumor to the surrounding structures and organs including stomach, colon, omentum, diaphragm, and gallbladder according to its respective location. Dissection of those adhesions resulted in significantly longer operative time in those patients (*P*<0.0001) with median of 190 min (range: 123–350 min) compared with 162 min (range: 110–340 min) in surgery upfront group. Consequently, a significantly higher mean amount of blood loss was recorded in those patients (763.7±368.5 vs. 607.3±386.4 ml, *P*=0.035) compared with surgery upfront group; however, this did not result in an increase rate of blood transfusion (*P*=0.109). Interestingly, there was no significant difference between the two surgery groups regarding the type and extent of surgical resection with similar rates of nonanatomical, major and minor anatomical hepatectomies (^{MC}P=0.949).

Using Clavien–Dindo classification to evaluate and compare the postoperative complications after liver resection in surgery upfront group versus surgery after TACE revealed comparable outcomes regarding in-hospital and 30-day morbidity (*P*=0.819). There were no differences in the perioperative morbidity and mortality rates for the two groups. In the surgery upfront group, 24 patients had a total of 43 complications, including bleeding (*n*=2), bile leak (*n*=2), ascites requiring treatment (*n*=13), hyperbilirubinemia (*n*=4), mild pleural effusion (*n*=9), wound infection (*n*=3), hematoma (*n*=1), chest

Table 3 Postoperative data, complications, and pattern of recurrence encountered among the studied patients subjected to upfront surgery and surgery after transarterial chemoembolization

Postoperative data and complications	Upfront surgery (*n*=54) [*n* (%)]	Surgery after TACE (*n*=54) [*n* (%)]	Significance
ICU stay			
No	33 (61.1)	29 (53.7)	χ^2=0.666
Yes	21 (38.9)	25 (46.3)	*P*=0.415
Duration of hospital stay (days)			
Minimum–maximum	3–7	3–9	*Z*=2.335
Median (Q1–Q3)	5 (4–5)	5 (4–6)	*P*=0.020*
Overall complications			
No	28 (53.8)	23 (42.5)	χ^2=1.810
Yes	24 (46.1)	31 (57.4)	*P*=0.178
Clavien–Dindo classification			
No complications	28 (53.8)	23 (42.6)	χ^2=1.612
Grade I	4 (7.7)	5 (9.3)	^{MC}P=0.819
Grade II	15 (28.8)	20 (37.0)	
Grade IIIa	1 (1.9)	2 (3.7)	
Grade IIIb	4 (7.7)	4 (7.4)	
Occurrence of bleeding			
No	50 (96.2)	51 (94.4)	^{FE}P=1.0
Yes	2 (3.8)	3 (5.6)	
Ascites			
No	39 (75.0)	36 (66.7)	χ^2=0.889
Yes	13 (25.0)	18 (33.3)	*P*=0.346
Liver failure			
No	52 (100.0)	53 (98.1)	^{FE}P=1.0
Yes	0 (0.0)	1 (1.9)	
Jaundice			
No	48 (92.3)	49 (90.7)	^{FE}P=1.0
Yes	4 (7.7)	5 (9.3)	
Encephalopathy			
No	52 (100.0)	53 (98.1)	^{FE}P=1.0
Yes	0 (0.0)	1 (1.9)	
Wound			
No	49 (94.2)	51 (94.4)	^{FE}P=1.0
Yes	3 (5.8)	3 (5.6)	
Chest			
No	47 (90.4)	48 (88.9)	χ^2=0.064
Yes	5 (9.6)	6 (11.1)	*P*=0.801
Bile leak			
No	50 (96.2)	51 (94.4)	^{FE}P=1.0
Yes	2 (3.8)	3 (5.6)	
Hematoma			
No	51 (98.1)	53 (98.1)	^{FE}P=1.0
Yes	1 (1.9)	1 (1.9)	
Pleural effusion			
No	43 (82.7)	43 (79.6)	χ^2=0.162
Yes	9 (17.3)	11 (20.4)	*P*=0.687
Incisional hernia			
No	48 (92.3)	50 (92.6)	^{FE}P=1.0
Yes	4 (7.7)	4 (7.4)	
30 days readmission			
No	52 (96.3)	50 (92.6)	^{FE}P=0.363
Yes	2 (3.7)	4 (7.4)	

(*Continued*)

Table 3 (*Continued*)

Postoperative data and complications	Upfront surgery (*n*=54) [*n* (%)]	Surgery after TACE (*n*=54) [*n* (%)]	Significance
Overall recurrence			
No	32 (59.2)	29 (53.7)	χ^2=0.446
Yes	22 (40.7)	25 (46.3)	*P*=0.504
Intrahepatic recurrence	22 (40.7)	25 (46.3)	*P*=0.504
Extrahepatic recurrence	5 (9.3)	3 (10.3)	^{FE}P=1.0
Time of recurrence			
<6 months	5/22 (22.7)	5/25 (20)	*P*=0.558
<12 months	9/22 (40.9)	14/25 (56)	*P*=0.286

^{FE}P, Fisher's exact test; TACE, transarterial chemoembolization; *Z*, Mann–Whitney test. *$P\leq0.05$, significant.

Table 4 Complications after transarterial chemoembolization of extrahepatic collateral feeder to hepatocellular carcinoma in group II

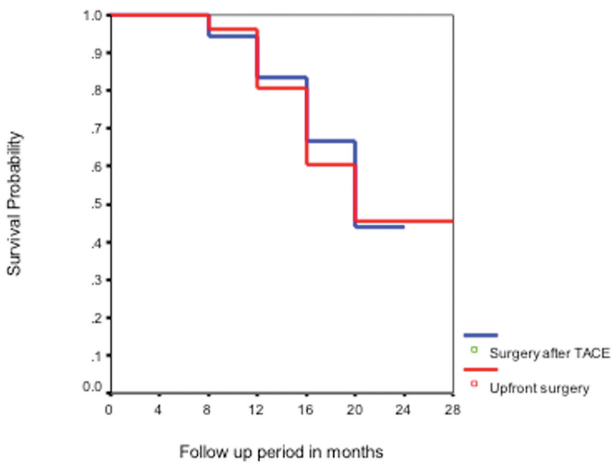
	Number of TACE	Complications	*n* (%)
RIPA	34	Shoulder pain	32 (94)
		Pleural effusion	30 (88)
		Basal lung atelectasis	12 (35)
LIPA	9	Shoulder pain	6 (67)
		Pleural effusion	3 (33)
RGA	8	No	0 (0)
LGA	9	No	0 (0)
OA	16	Abdominal pain	10 (63)
AA	6	No	0 (0)
MCA	5	No	0 (0)
RIMA	4	Cutaneous pain, itching and skin discoloration	1 (25)
RICA	2	Itching, skin necrosis	1 (50)
LA	13	Paraplegia	1 (7.7)
CA	15	Acute cholecystitis	3 (20)
		Perforation	1 (6.6)
Total	121		

AA, adrenal artery; CA, cystic artery; LA, lumbar artery; LGA, left gastric artery; LIPA, left inferior phrenic artery; MCA, middle colic artery; OA, omental artery; RGA, right gastric artery; RICA, right intercostal artery; RIMA, right internal mammary artery; RIPA, right inferior phrenic artery; TACE, transarterial chemoembolization.

infection (*n*=5), and incisional hernia (*n*=4). In the surgery after TACE group, 31 patients had 56 complications, including bleeding (*n*=3), bile leak (*n*=3), ascites requiring treatment (*n*=18), hyperbilirubinemia (*n*=5), chest infection (*n*=6), hematoma (*n*=1), liver failure (*n*=1), pleural effusion (*n*=11), encephalopathy (n=1), wound infection (n=3), and incisional hernia (n=4). Overall, 25/54 (46.3%) of patients in surgery after TACE required at least 1 day ICU stay compared with only 21/54 (38.9%) patients in upfront surgery group (P=0.217). Overall, upfront surgery group showed a statistically significant shorter duration of postoperative hospital stay compared with surgery after TACE subgroup (P=0.020). All cases in both groups achieved R0 resection on final histopathology, with no significant difference in incidence of microvascular invasion (P=0.795); however, patients who underwent surgery after TACE had statistically significant wider resection margin (2.0±0.6 vs. 1.7±0.5 mm) compared with surgery upfront group (P=0.003).

After a mean follow-up of 14.3±5.9 months (range: 2–24 months), none of the tumors in both groups showed local recurrence. No significant differences in the disease-free survival were noted between the upfront surgery and surgery after TACE groups (P=0.516) as shown in Fig. 1. During the follow-up period, 22 (40.7%) patients in surgery upfront group developed intrahepatic distant recurrence in comparison with 25 (46.3%) patients in the surgery after TACE group. There was no significant difference between the mean numbers of new (de-novo) tumors detected in surgery upfront (2.22±1.60) or surgery after TACE group (2.54±1.69; P=0.492). Moreover, the two groups showed no significant difference regarding type, and time of recurrence within 6 months or 1 year following resection (Table 4). None of the de-novo tumors had re-resection in either group. In the surgery upfront group, retreatment was performed in 22 patients, including RFA in 15 patients and TACE in seven. In the surgery after TACE group, recurrent tumors were treated by RFA (n=17) and TACE (n=5), whereas three patients could not be treated further because of poor liver function.

Figure 1



Kaplan–Meier plot showing the Disease free survival patterns for patients who were treated by either upfront surgery (blue line) or surgery after TACE (red line).

Discussion

The major drawback after curative hepatic resection of HCC is the high incidence of recurrence. The cumulative 5-year recurrence rate reported in literature is 75–100% [33]. Recurrence after curative resection is believed to originate through intrahepatic spread of the primary tumor or from de-novo multicenteric recurrence. Recurrences are usually classified into either intrahepatic (solitary or multiple) and extrahepatic recurrence [34] and according to time into early (<1 year) or late (>1 year) [35]. It was believed that early recurrences appeared to originate mainly from intrahepatic metastases, whereas late recurrences were likely to arise from a multicentric origin. The principle behind neoadjuvant TACE for resectable HCC is to decrease the tumor load by inducing necrosis to decrease the chance of metastases from the tumor after curative resection. For neoadjuvant TACE to fulfill its role, it should succeed in preventing extrahepatic metastases and decrease rate of early intrahepatic recurrence. In our study, this was not achieved, and no significant difference was observed in the pattern of recurrence or the recurrence time between the two groups. The control of extrahepatic collaterals with preoperative TACE did not have any oncological advantage in improving disease-free survival or reducing the recurrence rates, which might suggest that spillage of tumor cells during surgical manipulation might not be the main cause for HCC recurrence.

Published literature investigating clinical outcomes of surgery versus TACE for solitary large HCC yielded controversial results [2,36,37]. For resectable HCC, Zhang *et al.* [8] reported an improved disease-free survival after hepatctomy in patients having preoperative TACE in contrast to a retrospective study by Choi *et al.* [11] who reported that preoperative TACE did not significantly improve DFS or recurrence patterns after curative resection of HCC. In our study, and in accordance with the latter, there was no statistical significant difference between surgery alone (surgery upfront group) and resection after TACE in terms of the incidence (P=0.679) and type of recurrence, whether intrahepatic (P=0.679) or extrahepatic (^{FE}P=1.0). In agreement with published studies [9–12], preoperative

TACE did not improve the disease-free survival after curative resection of large exophytic HCC, and there was no clear added benefit of control of extrahepatic collaterals preoperatively.

In this study, upfront surgery group achieved 100% technical success with R0 resection in all cases, with no 30-day mortality. In spite of the large size of HCCs included in our study (mean: 9.8±2.2 cm, range: 7.2–15.6 cm), major liver resections were needed in only 11.1% of cases owing to the exophytic pattern of growth of those tumors. Technical difficulties were encountered in TACE group considering the wide spectrum of extrahepatic collateral arteries, and the selective angiography of individual collateral vessels was tedious, time consuming, and not possible to tackle all collateral feeders in one session of TACE. This interfered with effective control of the tumor. None of our patients in TACE group achieved full control of hepatic and extrahepatic feeders in a single session (mean: 2±0.8 session, range: 1–4 sessions). Failure of complete tumor control resulted from failure of control of extrahepatic feeders with the appearance of new feeders, which were technically impossible to embolize safely. As the number of TACE sessions increased, the cumulative probability of the development of de-novo extrahepatic collateral arteries also increased, owing to the neovascularity induced by ischemia together with hepatic artery attenuation resulting from repeated cannulation in sequential TACE procedures that potentially stimulate the development of parasitic supply to the peripheral zone of the corresponding liver parenchymal segment. These findings highlight the importance of the exophytic pattern of growth in large HCCs and its effect on the development of extrahepatic collateral feeders.

All of our HCCs were technically resectable, and patients who had liver resection after TACE showed a significant technical difficulty in the form of increased perihepatic adhesions (P=0.006*), which were vascular and led to a significant increase in the operative time and blood loss compared with those who had liver resection alone in (resection group). This finding is in agreement with a study by Luo *et al.* [38] who also demonstrated longer operative times (P<0.0001), more blood loss (763.7±368.5 vs. 607.3±386.4, P=0.035), and more postoperative abdominal drainage on comparing patients who had had received LR alone with those who had received TACE. Although abdominal drainage showed an increase in patients who underwent preoperative TACE, it did not reach a statistical significant value in our study. Patients who had surgery after TACE had a statistical significant longer duration of postoperative hospital stay compared with upfront surgery group. Interestingly, patients who underwent surgical resection after TACE did not show any significant difference regarding the type or extent of surgical resection compared with upfront surgery group, with similar rates of nonanatomical, major and minor anatomical hepatectomies (P=0.949) with no change of resection plan after TACE compared with pre-TACE findings. Preoperative TACE did not result in parenchymal-sparing strategy among those patients, with no patients showing a shift from major hepatetcomy plan to more limited resection plan after TACE. So overall, preoperative TACE among this subgroup of patients increased surgical difficulty and risk, added no benefit in decreasing the amount of liver parenchyma resected or decreasing the rate of major hepatectomies, and delayed the curative surgery. In addition, in 16.8% of cases, repeated TACE contributed to worsening of the biochemical parameters of those patients beyond accepted criteria for further management of the tumor.

Selective catherterization of collateral vessels with microcatheters is mandatory with placement of the catheter tip as close as possible to the specific feeder supplying the tumor to reduce the risk of embolizing nontarget branches which can lead to a number of complications depending on the embolized artery. The experience of the operator is mandatory to prevent embolic material from refluxing into nontarget branches and lowering vascular access complications, especially intimal injury, and arterial spasm might lead to technical failure with subsequent failure of tumor control. In our study, shoulder pain was common (91%) with embolization of the right inferior phrenic artery together with pleural effusion and basal lung atelectasis. Cutaneous itching associated with reddish skin patches of different color grades mounting to skin necrosis occurred with embolization of intercostal and internal mammary artery or lumbar artery. Abdominal pains occurred in 53% of cases with embolization of omental branches. Unfortunately, one case developed paraplegia owing to accidental embolization of spinal branch from lumbar artery. Acute cholecystitis occurred in 20% of cases with one progressing to gallbladder perforation in a diabetic patient resulting from cystic artery embolization.

Classical TACE is based on the fact that exclusively the hepatic artery supplies HCCs. In clinical practice, HCCs supplied by extrahepatic collateral arteries are frequently encountered even when the hepatic artery is patent [29,39]. The development of extrahepatic arterial supply for HCC is governed by tumor location, patency of hepatic artery, exophytic growth pattern, multiple sessions of TACE, and direct contact or invasion into other organs. The combined effect of exophytic growth pattern with anatomic locations of HCCs adjacent to the bare area, suspensory ligaments, and diaphragm might lead to a higher incidence of diaphragmatic blood supplies, including the inferior phrenic, internal mammary, and intercostal arteries. In our patients, the tumor location and adherence to near by organ determined the origin of the parasitic feeder. The presence and development of those collateral arteries further complexes the embolization procedure with the necessity of controlling those feeders. It is essential to try to determine first whether parasitic or collateral blood supply is present. The preassessment dynamic abdominal CT scan had a critical role in selection of our patients, and the results were confirmed during angiography performed in TACE group patients, where all patients had at least one collateral extrahepatic arterial feeder. In the view of our results, detection of those vessels at early stage should be a predictor of lower incidence of technical success than conventional TACE with a higher number of sessions needed for tumor control and increased incidence of complications.

There is no clear treatment strategy for solitary large HCC (>5 cm) in the Barcelona clinic liver cancer guidelines [40]. The biological behavior of these single large tumors that grow over time without becoming multinodular needs further characterization and may hint toward a more benign course. Up till now, there is no consensus regarding the size limit for solitary HCC undergoing surgical resection with a curative intent. In view of our results, in patients with solitary large HCC showing an exophytic growth pattern, hepatic resection should be the first line of treatment if the liver condition and volumetric assessment permits. TACE may be useful in the setting of downsizing to transplant accepted criteria. Expected outcome of TACE in term of technical success is low, and it requires multiple sessions to achieve adequate tumor control. It should be carefully evaluated, with the benefits weighted against the potential risks and complications anticipated during embolizing the collateral arteries.

Conclusion

In Child A cirrhotic patients with solitary large exophytic HCC with extrahepatic blood supply, combined hepatic resection plus TACE is associated with increased perihepatic adhesions, increased operative time, blood loss, and postoperative hospital stay compared with liver resection alone. Upfront surgical resection should be considered as a first-line therapy in those patients, as preoperative TACE does not have additional oncological benefit with no reduction in recurrence rate or improvement in disease-free survival.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1 Bruix J, Reig M, Sherman M. Evidence-based diagnosis, staging, and treatment of patients with hepatocellular carcinoma. Gastroenterology 2016; 150:835–853.

2 Yang LY, Fang F, Ou DP, Wu W, Zeng ZJ, Wu F. Solitary large hepatocellular carcinoma: a specific subtype of hepatocellular carcinoma with good outcome after hepatic resection. Ann Surg 2009; 249:118–123.

3 Okada S, Shimada K, Yamamoto J, Takayama T, Kosuge T, Yamasaki S, *et al.* Predictive factors for postoperative recurrence of hepatocellular carcinoma. Gastroenterology 1994; 106:1618–1624.

4 Brown DB, Geschwind JF, Soulen MC, Millward SF, Sacks D. Society of Interventional Radiology position statement on chemoembolization of hepatic malignancies. J Vasc Interv Radiol 2009; 20:S317–S323.

5 Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: chemoembolization improves survival. Hepatology 2003; 37:429–442.

6 Imaoka S, Sasaki Y, Shibata T, Fujita M, Kasugai H, Kojima J, *et al.* A pre-operative chemoembolization therapy using lipiodol, cisplatin and gelatin sponge for hepatocellular carcinoma. Cancer Chemother Pharmacol 1989; 23:S126–S128.

7 Majno PE, Adam R, Bismuth H, Castaing D, Ariche A, Krissat J, *et al.* Influence of preoperative transarterial lipiodol chemoembolization on resection and transplantation for hepatocellular carcinoma in patients with cirrhosis. Ann Surg 1997; 226:688–701.

8 Zhang Z, Liu Q, He J, Yang J, Yang G, Wu M. The effect of preoperative transcatheter hepatic arterial chemoembolization on disease-free survival after hepatectomy for hepatocellular carcinoma. Cancer 2000; 89:2606–2612.

9 Yamasaki S, Hasegawa H, Kinoshita H, Furukawa M, Imaoka S, Takasaki K, *et al.* A prospective randomized trial of the preventive effect of pre-operative transcatheter arterial embolization against recurrence of hepatocellular carcinoma. Jpn J Cancer Res 1996; 87:206–211.

10 Zhou WP, Lai EC, Li AJ, Fu SY, Zhou JP, Pan ZY, *et al.* A prospective, randomized, controlled trial of preoperative transarterial chemoembolization for resectable large hepatocellular carcinoma. Ann Surg 2009; 249: 195–202.

11 Choi GH, Kim DH, Kang CM, Kim KS, Choi JS, Lee WJ, *et al.* Is preoperative transarterial chemoembolization needed for a resectable hepatocellular carcinoma? World J Surg 2007; 31:2370–2377.

12 Sasaki A, Iwashita Y, Shibata K, Ohta M, Kitano S, Mori M. Preoperative transcatheter arterial chemoembolization reduces long-term survival rate after hepatic resection for resectable hepatocellular carcinoma. Eur J Surg Oncol 2006; 32:773–779.

13 Uchida M, Kohno H, Kubota H, Hayashi T, Yamanoi A, Kimoto T, *et al.* Role of preoperative transcatheter arterial oily chemoembolization for resectable hepatocellular carcinoma. World J Surg 1996; 20:326–331.

14 Koehler RE, Korobkin M, Lewis F. Arteriographic demonstration of collateral arterial supply to the liver after hepatic artery ligation. Radiology 1975; 117:49–54.

15 Miyayama S, Matsui O, Akakura Y, Yamamoto T, Nishida H, Yoneda K, *et al.* Hepatocellular carcinoma with blood supply from omental branches: treatment with transcatheter arterial embolization. J Vasc Interv Radiol 2001; 12:1285–1290.

16 Michels NA. Collateral arterial pathways to the liver after ligation of the hepatic artery and removal of the celiac axis. Cancer 1953; 6:708–724.

17 Chung JW, Park JH, Han JK, Choi BI, Kim TK, Han MC. Transcatheter oily chemoembolization of the inferior phrenic artery in hepatocellular carcinoma: the safety and potential therapeutic role. J Vasc Interv Radiol 1998; 9:495–500.

18 Hirota S, Matsumoto S, Fukuda T, Yoshikawa T, Motohara T, Ichikawa S. Solitary hepatocellular carcinoma fed by the cystic artery: limitation of transcatheter arterial embolization. Cardiovasc Intervent Radiol 1999; 22:206–209.

19 Tanigawa N, Sawada S, Okuda Y, Shinzato S, Mishima K, Asai T, *et al.* A case of small hepatocellular carcinoma supplied by the cystic artery. Am J Roentgenol 1998; 170:675–676.

20 Park SI, Lee DY, Won JY, Lee JT. Extrahepatic collateral supply of hepatocellular carcinoma by the intercostal arteries. J Vasc Interv Radiol 2003; 14:461–468.

21 Chung JW, Kim HC, Yoon JH, Lee HS, Jae HJ, Lee W, *et al.* Transcatheter arterial chemoembolization of hepatocellular carcinoma: prevalence and causative factors of extrahepatic collateral arteries in 479 patients. Korean J Radiol 2006; 7:257–266.

22 Cazejust J, Bessoud B, Colignon N, Garcia-Alba C, Planché O, Menu Y. Hepatocellular carcinoma vascularization: from the most common to the lesser known arteries. Diagn Interv Imaging 2014; 95:27–36.

23 Charnsangavej C, Chuang VP, Wallace S, Soo CS, Bowers T. Angiographic classification of hepatic arterial collaterals. Radiology 1982; 144:485–494.

24 Li Q, Ao GK, Duan F, Wang ZJ, Yan JY, Wang MQ. Incidence and therapeutic frequency of extrahepatic collateral arteries in transcatheter arterial chemoembolization of hepatocellular carcinoma: experience from 182 patients with survival time more than 3 years. Eur J Radiol 2015; 84:2555–2563.

25 Miyayama S, Matsui O, Nishida H, Yamamori S, Minami T, Shinmura R, *et al.* Transcatheter arterial chemoembolization for unresectable hepatocellular carcinoma fed by the cystic artery. J Vasc Interv Radiol 2003; 14(Pt 1):1155–1161.

26 Kodama Y, Shimizu T, Endo H, Hige S, Kamishima T, Holland GA, *et al.* Spontaneous rupture of hepatocellular carcinoma supplied by the right renal capsular artery treated by transcatheter arterial embolization. Cardiovasc Intervent Radiol 2002; 25:137–140.

27 Nakai M, Sato M, Kawai N, Minamiguchi H, Masuda M, Tanihata H, *et al.* Hepatocellular carcinoma: involvement of the internal mammary artery. Radiology 2001; 219:147–152.

28 Duprat G, Charnsangavej C, Wallace S, Carrasco CH. Inferior phrenic artery embolization in the treatment of hepatic neoplasms. Acta Radiol 1988; 29:427–429.

29 Kim JH, Chung JW, Han JK, Park JH, Choi BI, Han MC. Transcatheter arterial embolization of the internal mammary artery in hepatocellular carcinoma. J Vasc Interv Radiol 1995; 6:71–74. discussion 75–77

30 Soo CS, Chuang VP, Wallace S, Charnsangavej C, Carrasco H. Treatment of hepatic neoplasm through extrahepatic collaterals. Radiology 1983; 147:45–49.

31 Edmondson HA, Steiner PE. Primary carcinoma of the liver: a study of 100 cases among 48,900 necropsies. Cancer 1954; 7:462–503.

32 Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004; 240:205–213.

33 Tung-Ping Poon R, Fan ST, Wong J. Risk factors, prevention, and management of postoperative recurrence after resection of hepatocellular carcinoma. Ann Surg 2000; 232:10–24.

34 Shimada M, Takenaka K, Gion T, Fujiwara Y, Kajiyama K, Maeda T, *et al.* Prognosis of recurrent hepatocellular carcinoma: a 10-year surgical experience in Japan. Gastroenterology 1996; 111:720–726.

35 Poon RT, Fan ST, Ng IO, Lo CM, Liu CL, Wong J. Different risk factors and prognosis for early and late intrahepatic recurrence after resection of hepatocellular carcinoma. Cancer 2000; 89:500–507.

36 Hsu CY, Hsia CY, Huang YH, Su CW, Lin HC, Pai JT, *et al.* Comparison of surgical resection and transarterial chemoembolization for hepatocellular carcinoma beyond the Milan criteria: a propensity score analysis. Ann Surg Oncol 2012; 19:842–849.

37 Ariizumi S, Kotera Y, Takahashi Y, Katagiri S, Yamamoto M. Impact of hepatectomy for huge solitary hepatocellular carcinoma. J Surg Oncol 2013; 107:408–413.

38 Luo YQ, Wang Y, Chen H, Wu MC. Influence of preoperative transcatheter arterial chemoembolization on liver resection in patients with resectable hepatocellular carcinoma. Hepatobiliary Pancreat Dis Int 2002; 1:523–526.

39 Kim HC, Chung JW, Lee W, Jae HJ, Park JH. Recognizing extrahepatic collateral vessels that supply hepatocellular carcinoma to avoid complications of transcatheter arterial chemoembolization. Radiographics 2005; 25(Suppl 1):S25–S39.

40 Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. Hepatology 2011; 53:1020–1022.