Transarterial chemoembolization versus surgical resection for giant hepatocellular carcinoma under the different status of capsule: a retrospective study

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Background: As an independent risk factor for the recurrence of hepatocellular carcinoma (HCC), the capsule has not been investigated in giant HCC (HCC ≥10 cm in diameter). In addition, whether the first line treatment for giant HCC should be surgery or transarterial chemoembolization (TACE) remains controversial. The aim of this study was to investigate the influence of tumor capsule on the prognosis of patients with giant HCC, and to compare the prognosis between surgical resection and TACE in giant HCC patients under different status of capsule to better inform surgeons.

Methods: A retrospective review was conducted of all patients (n=83) who had been diagnosed with giant HCC and undergone surgical resection or TACE in the Affiliated Lihuili Hospital, Ningbo University, from January 2012 to December 2020. Among those who underwent surgical resection, overall survival (OS) and progression-free survival (PFS) were compared between patients with a complete capsule and with either an incomplete or no capsule. In patients with an incomplete/no capsule, survival outcomes were also compared between surgical resection and TACE. Prognostic factors for OS and PFS were analyzed in patients who underwent surgical resection.

Results: In our study, 30 surgical patients had a complete capsule (Group 1), 33 surgical patients had an incomplete/no capsule (Group 2); 20 patients who had undergone TACE had an incomplete/no capsule (Group 3). The patient demographics were comparable, expect for liver segment invasion and tumor number, which suggested these 2 factors were related with capsule. Median OS was 39 months in Group 1, 27 months in Group 2, and 10 months in Group 3. Median PFS was 17 months in Group 1, 17 months in Group 2, and 7.5 in Group 3. There were significant statistical differences in OS and PFS between Group 1 and Group 2 (P=0.036; P=0.025). In patients who underwent surgical resection surgical time, liver segments invasion, and capsule were the independent risk factor for OS.

Conclusions: In giant HCC patients, complete tumor capsule could take a better long-term outcomes than incomplete or no tumor capsule. In addition, if possible, such patients should opt for surgical resection to obtain a better prognosis.

Keywords: Hepatocellular carcinoma (HCC); large; hepatectomy; Transarterial chemoembolization (TACE); survival

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Introduction

Hepatocellular carcinoma (HCC) was the sixth most commonly diagnosed cancer and third leading cause of cancer death all over the world in 2020, with more than 900,000 new cases and 800,000 deaths every year (1). HCC tumors with a diameter more than 10 cm are known as giant hepatocellular carcinoma (G-HCC). According to the internationally recognized staging standard for HCC, Barcelona Clinic Liver Cancer (BCLC) staging system (2) and American Joint Committee on Cancer 8th edition (AJCC 8th) staging system (3), the diameter of the tumor does not affect the oncological staging of HCC, but in the clinical setting, different to ordinary HCC, the prognosis of G-HCC is always variable. A literature review found that the ratio of the capsule present around the tumor is higher in G-HCC by about 74.8–97% (4-8) than in normal HCC. The HCC capsule comprises some peritumoral fibrous tissues, prominent sinusoids, or compressed liver parenchyma (6). Torimura *et al.* found that the capsule is the protective mechanism to limit tumor growth and invasion in HCC (9). However, weather the capsule could lead to a better prognosis in HCC patients is still controversial, and no studies have reported on the significance of the capsule in G-HCC alone. Due to the higher ratio present on G-HCC, it is necessary to research the significance of the capsule in G-HCC. Moreover,

surgical resection may be the only curative therapeutic modality (10) and transarterial chemoembolization (TACE) is a recognized effective treatment for G-HCC (11). Studies on the above two treatments were mostly limited to huge HCC (tumor diameter >5 cm) rather than giant HCC (tumor diameter >10 cm). Jin *et al.* found that surgery seems to be more effective than TACE for a solitary large HCC of BCLC stage A (P<0.01) (12). However, because of the more aggressive tumor biology, G-HCC patients accompanied by vascular invasion, satellite nodules always be difficult to take resection and had the high rate of recurrence after surgical resection (13-15), therefore some scholars choose the TACE for G-HCC, Xue *et al.* found the survival rates of huge HCC patients who received TACE was 33% at 1 year 13% at 3 years and 10% at 5 years, they thought TACE was suitable and safe for huge HCC and is particularly suitable for patients with good liver function and BCLC B stage (16). However, the first-line treatment for G-HCC is also controversial. In this study, we attempted to address the above 2 problems. The aim of this study was to compare the survival outcomes between patients with a complete capsule and those with an incomplete/no capsule. Moreover, we aimed to find a better first-line treatment strategy between surgical resection and TACE in patients with different capsule status. We present the following article in accordance with the STROBE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2473/rc).

Highlight box

Key findings:
- We found that in giant HCC patients, complete tumor capsule could take a better long-term outcomes. In addition, if possible, giant HCC patients should opt for surgical resection to obtain a better prognosis.

What is known and what is new?
- Capsule size or status was reported as an independent risk factor in hepatocellular carcinoma in many studies. In addition, both surgical resection and TACE was reported to be effective in huge HCC. However capsule and treatment options have not been investigated in giant HCC before.
- We found that complete capsule is an independent protect factor in giant HCC and surgical resection should be the first line therapy for these patients.

**What is the implication, and what should change now?**
- It should be recognized that giant HCC with complete capsule should be surgically resected whenever possible to achieve a better prognosis, even though the tumor staging may be unfavorable.

Methods

Patients

This retrospective study involved standard care performed at a single medical institution.

We searched the medical records of the Affiliated Lihuili Hospital, Ningbo University, to derive all patients confirmed of HCC by clinical and pathological diagnosis from January 2012 to December 2020. A total of 528 confirmed cases of HCC were screened in this search. The inclusion criteria were as follows: (I) the diameter of tumor ≥10 cm; (II) the first-line treatment of patients was only curative surgical resection or TACE; (III) the patient's general condition and liver function status were suitable for surgery or TACE; (IV) after the surgery or TACE, the sequential treatment of patients was only TACE. The exclusion criteria were as follows: (I) patients who had received other antitumor treatments; (II) patients who died
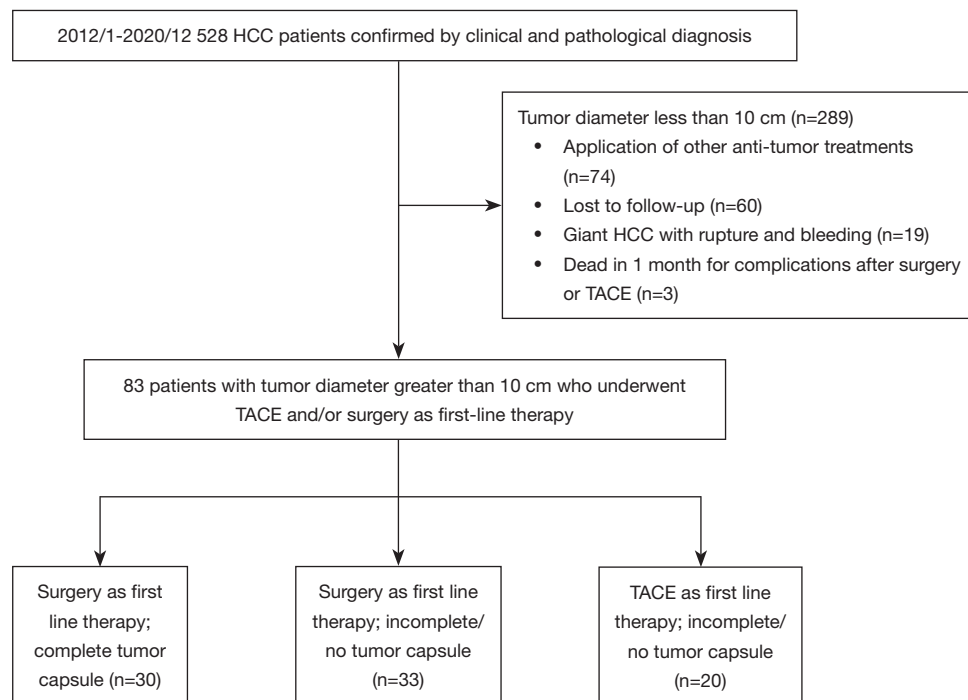
Figure 1 Flow chart of patient selection. HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization.

due to surgical or TACE complications in 1 month of the intervention; (III) patients who were lost to follow-up. (IV) The patients developed rupture and hemorrhage of liver cancer during hospitalization. In the end, a total of 83 consecutive patients (73 males and 10 females; mean age, 57±11 years; range: 30–80 years) were enrolled in our study and were grouped as follows: (I) those who had a complete capsule (hereinafter referred to as capsule+ patients) and underwent surgical resection n=30 (Group 1); (II) those who had an incomplete capsule or no capsule (hereinafter referred to as capsule-patients) and underwent surgical resection n=33 (Group 2); (III) capsule-patients who underwent TACE, not surgery n=20 (Group 3). The patient recruitment pathway and inclusion criteria are displayed in *Figure 1*.

Routine preoperative laboratory examinations included liver and renal function tests, hepatitis B and C immunology, serum α-fetoprotein (AFP), Child-Pugh score, platelet count (PLT), serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum total bilirubin (TB), serum albumin (ALB), prothrombin time (PT), and gamma-glutamyl transpeptidase (GGT). The preoperative diagnosis of HCC was based on the criteria of Chinese Society of Clinical Oncology (CSCO) (12). The platelet-to-

neutrophil ratio (PNR) was obtained by dividing the PLT by the neutrophil count. The neutrophil-to-lymphocyte ratio (NLR) was obtained by dividing the neutrophil count by the lymphocyte count. The cutoff values of AFP, TB, ALB, GGT, PNR, PLR, NLR, PT, and tumor diameter were determined by the Youden index calculated by the receiver operating characteristic (ROC) curves. Judgment of tumor capsule was as follows: in cases involving surgical resection, we reviewed the patient's surgical records to determine the tumor capsule based on intraoperative findings and in patients who underwent TACE, we made judgments based on preoperative imaging examinations such as computed tomography (CT) and magnetic resonance imaging (MRI). According to Cannella *et al.*, the role of extracellular contrast agent (ECA-MRI) and CT in capsular determination is reliable: their sensitivity was more than 75% and their specificity was more than 80% (4). To reduce the chance of bias, we only considered capsules obtained by imaging in patients who underwent TACE. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics review board of the Affiliated Lihuili Hospital, Ningbo University (No. KY2021PJ036) and the requirement for written informed consent was waived.

Treatment and follow-up

Hepatectomy

Liver resection (LR) was performed by experienced surgeons. Surgical planning was based on tumor size, tumor location, and liver function. The hepatectomy method contains anatomical resection and non-anatomical resection. We applied Pringle's maneuver with cycles of clamping and unclamping times of 1 to 15 and 5 minutes each time, respectively, and controlled central venous pressure below 4 mmHg during parenchyma dissection to control intraoperative bleeding.

TACE

Our choice of treatment measures was strictly in accordance with the China liver cancer staging (CNLC) (17), but not all patients who met the Ia-Ib stage were suitable for surgery. Due to tumor size, growth site, number of liver segments invaded, age, severe cirrhosis, and the patient's personal preference; despite their Ia-Ib staging, they might have had risks such as many postoperative complications, poor postoperative prognosis, and insufficient postoperative liver volume after surgery. Finally, 20 patients who only underwent TACE were enrolled in this study. Our TACE procedure usually adopts the Seldinger method: percutaneous femoral artery intubation, digital subtraction angiography (DSA) was performed to clarify the characteristics of blood vessels and tumors, chemotherapeutic drugs combined with lipiodol were mixed, and then chemoembolization was performed.

Follow-up

In surgery patients: abdominal B-ultrasound and AFP were reviewed every 3 months after surgery, and upper abdominal enhanced CT or enhanced magnetic resonance were reviewed every 6 months. Recurrence or progression of a tumor were evaluated according to the response evaluation criteria in solid tumors: revised (RECIST 1.1) (18) standard combined with clinical indicators (AFP+AFP-L3+DCP). Cases who achieved tumor progression or recurrence were only treated by TACE.

Among the TACE patients, follow-up measures involved the following: CT or MRI; tumor markers; liver and kidney function, and routine blood tests were reviewed 4–6 weeks after the first TACE treatment. If the imaging examination showed that the lipiodol accumulation in the liver tumor lesions was dense, and the tumor tissue was necrotic without growth and new lesions, TACE was temporarily not performed, and such patients were defined as stable disease (SD). As for the frequency of follow-up, it depended on the results of follow-up; for SD patients, the follow-up interval could have been 1–3 months or longer. The patients included in this study did not receive other anti-tumor treatments after TACE.

Statistical analysis

The primary outcome was overall survival (OS). The secondary outcomes were as follows: (I) progression-free survival (PFS); (II) disease control rate (DCR); (III) objective response rate (ORR). The software SPSS 22.0 (IBM Corp., Armonk, NY, USA) and R language (version 4.0.4; The R Foundation for Statistical Computing, Vienna, Austria) was used for statistical analysis. Independent sample t-test was used for continuous variables which were consistent with positive distribution. Univariate analysis of variance (ANOVA) test and non-parametric Kruskall–Wallis (K-W) test were performed on disordered variables or grade variables. Univariate and multivariate Cox regression analysis was used for survival analysis of patients. Patients' prognosis was analyzed by Kaplan–Meier (K-M) survival curve combined with log rank function. All tests were considered statistically different with P<0.05.

Results

Baseline characteristics of patients

This single center study recruited 83 patients with a median age of 57.0 (range: 30–80) years. Among them, 73 (89.1%) were male, and 77 (93.9%) were HBsAg positive. A total of 63 (75.9%) patients underwent LRs and 20 (24.1%) underwent TACE. The median tumor diameter was 13.7 cm (range: 10–20 cm). The median length of follow-up was 2.13 years overall. In patients who underwent surgical resections, the median intraoperative blood loss was 650 mL (range: 100–2,000 mL); 42 (66.7%) patients had microscopic vascular invasion; 28 (44.4%) patients were in BCLC stage A, 9 (14.3%) were in BCLC stage B, 26 (41.3%) were in BCLC stage C. In TACE group 7 (35%) patients were in BCLC stage A, 5 (25%) were in BCLC stage B, and 8 (40%) were in BCLC stage C. For the convenience of survival analysis, we divided the surgical group into capsule-positive and negative groups (Group 1; Group 2), and separately screened the capsule-negative patients in the TACE group (Group 3) for baseline comparison. The

clinicopathological data, including demographic factors, inflammatory factors, tumor factors, and surgical factors of the patients are summarized in *Table 1* and *Table 2*.

Factors associated with capsule negativity

The single factor chi-square test revealed the following:

tumors invaded more liver segments in capsule-negative patients (P=0.017), in Group 2, 1 (6%) patient had 1 invaded liver segment, 18 (53%) patients had 2 invaded liver segments, 8 (24%) patients had 3 invaded liver segments, 5 (15%) patients had 4 invaded liver segments, 1 (2%) patients had 6 invaded liver segments. In addition, the patients with negative capsules tended to have a higher

Table 1 Clinical characteristics of the patients between group1 and group2

Variable	Capsule(–), n=33	Capsule(+), n=30	P value
Age, years	56±10	57±11	0.586
Gender			0.176
Female	3 (10%)	5 (17%)	
Male	30 (90%)	25 (83%)	
PS			0.093
0	33 (100%)	26 (90%)	
1	0	4 (10%)	
Liver segment invasion			0.017*
1	1 (6%)	0	
2	18 (53%)	12 (40%)	
3	8 (24%)	7 (24%)	
4	5 (15%)	8 (28%)	
5	0	2 (5%)	
6	1 (2%)	1 (3%)	
Surgical time, minutes	235±96	259±62	0.357
Blood lost, mL	547±445	771±547	0.082
Child-Pugh			0.096
A	33 (100%)	26 (90%)	
B	0	4 (10%)	
BCLC stage			0.174
A	17 (53%)	11 (34%)	
B	6 (18%)	3 (11%)	
C	10 (29%)	16 (55%)	
AJCC 8th			0.075
Ib	17 (53%)	11 (34%)	
IIIa	7 (21%)	2 (7%)	
IIIb	6 (18%)	9 (31%)	
IV	3 (8%)	8 (25%)	

Table 1 (*continued*)

Table 1 (*continued*)

Variable	Capsule(–), n=33	Capsule(+), n=30	P value
Postoperative TACE (yes/no)	21/12	22/8	0.185
Tumor diameter $\bar{x}$	12	16	0.323
AFP $\bar{x}$	37143	41462	0.871
ALBI grade			0.209
1	17 (53%)	12 (40%)	
2	16 (47%)	17 (59%)	
3	0	1 (1%)	
NLR $\bar{x}$	2.4	3.8	0.088
PNR	62±23	53±30	0.160
PLR	146±72	150±64	0.806
Liver cirrhosis (yes/no)	33/0	30/0	0.476
GGT $\bar{x}$	112	141	0.355
PT	12±3	13±2	0.124
Tumor number (single/multiple)	23/10	25/5	0.405
Tumor satellite (yes/no)	6/27	13/17	0.268
MVI			0.313
0	11 (35%)	9 (28%)	
1	10 (29%)	7 (24%)	
2	12 (35%)	13 (48%)	
MAV (yes/no)	8/25	14/16	0.196
PVTT (yes/no)	3/30	7/23	0.606
Extra lesion (yes/no)	1/32	6/24	0.114
Anatomic liver resection (yes/no)	9/24	14/16	0.103
HBsAg (+/–)	32/1	28/2	0.093
Tumor differentiation			0.435
High	2 (9%)	2 (3%)	
Medial	18 (53%)	12 (41%)	
Poor	13 (38%)	16 (56%)	

Data are presented as n or mean ± standard deviation. *, this factor was statistically significant (P<0.05). BCLC, Barcelona Clinic Liver Cancer; AJCC, American Joint Committee on Cancer; MVI, microvascular invasion; PVTT, portal vein tumor thrombus; MAV, macrovascular invasion; TACE, transarterial chemoembolization; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; GGT, gamma-glutamyl transpeptidase; PT, prothrombin time. PS, Performance Status score (Zubrod-ECOG-WHO); AFP, Alpha-FetoProtein; ALBI, albumin-bilirubin grade; PNR, platelet-to-neutrophil ratio.

Table 2 Clinical characteristics of the patients between group 2 and group 3

Variable	Capsule(–) & TACE, n=20	Capsule(–) & surgery, n=33	P value
Age, years	55±11	56±10	0.415
Gender			0.430
Female	2 (10%)	3 (10%)	
Male	18 (90%)	30 (90%)	
PS			0.051
0	14 (70%)	33 (100%)	
1	6 (30%)	0	
Liver segment invasion			0.057
1	1 (5%)	1 (6%)	
2	1 (5%)	18 (53%)	
3	4 (20%)	8 (24%)	
4	11 (55%)	5 (15%)	
5	2 (10%)	0	
6	1 (5%)	1 (2%)	
Child-Pugh			0.333
A	17 (85%)	33 (100%)	
B	2 (10%)	0	
C	1 (5%)	0	
BCLC stage			0.789
A	7 (35%)	17 (53%)	
B	5 (25%)	6 (18%)	
C	8 (40%)	10 (29%)	
Tumor diameter $\bar{x}$	12	12	0.375
AFP $\bar{x}$	73,995	37,143	0.106
ALBI grade			0.159
1	4 (20%)	17 (53%)	
2	15 (75%)	16 (47%)	
3	1 (5%)	0	
NLR $\bar{x}$	4.9	2.4	0.397
PNR	45±23	62±23	0.345
PLR	155±82	146±72	0.828
Liver cirhosis (yes/no)	20/0	33/0	
GGT $\bar{x}$	265	112	0.042*
PT	14±4	12±3	0.145
Tumor number (single/multiple)	6/14	23/10	<0.001*
MAV (yes/no)	8/12	8/25	0.865
PVTT (yes/no)	5/15	3/30	0.562
Extra leision (yes/no)	3/17	1/32	0.988
HBsAg (+/−)	17/3	32/1	0.520

Data are presented as No. or mean ± standard deviation. *, this factor was statistically significant (P<0.05). BCLC, Barcelona Clinic Liver Cancer; MVI, microvascular invasion; PVTT, portal vein tumor thrombus; MAV (macrovascular invasion); TACE, transarterial chemoembolization; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; GGT, gamma-glutamyl transpeptidase; PT, prothrombin time; AFP, alpha fetoprotein; PS, Performance Status score (Zubrod-ECOG-WHO); ALBI, albumin-bilirubin grade; PNR, platelet-to-neutrophil ratio.
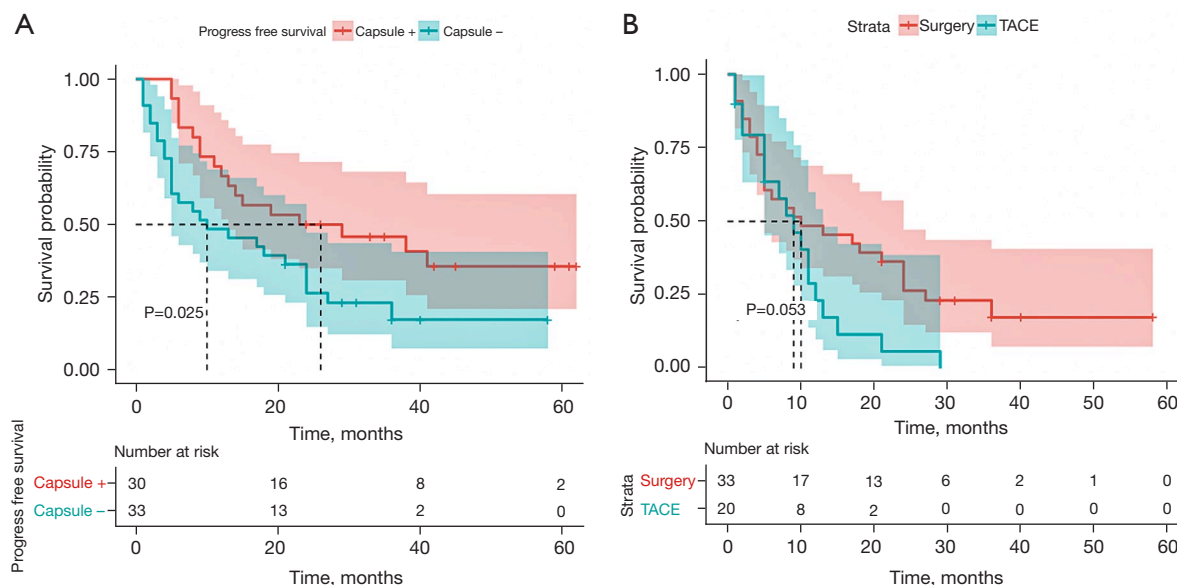
Figure 2 Kaplan-Meier survival curves for PFS. (A) PFS between positive and negative capsules in surgical patients. (B) PFS after TACE and surgery in a capsule-negative patient. PFS, progression-free survival; TACE, transarterial chemoembolization.

number of tumors (P<0.001).

PFS

At the end of follow-up 43 (68.7%) patients who underwent surgical resection and 18 (85.7%) patients who underwent TACE showed HCC progression. The 1-, 3-, and 5-year cumulative PFS rates were 57.1%, 17.5%, and 3.2% in the surgery group, respectively, among them, the 1-, 3-, and 5-year cumulative PFS rates were 58.8%, 26.5%, and 6.7%, respectively, in Group 1 (median PFS: 17 months), and 55.5%, 6.9%, 0%, respectively, in Group 2 (median PFS: 17months). In Group 3, the 1-, 3-, and 5-year cumulative PFS rates were 20%, 0%, and 0%, respectively (median PFS: 7.5 months). There was a statistically significant difference in PFS between Group 1 and Group 2 (P=0.025, *Figure 2A*), there was no significant difference in PFS between Group 2 and Group 3 (P=0.053, *Figure 2B*).

OS

At the end of follow-up, 25 (39%) patients in the surgery group and 15 (71.4%) patients in the TACE group had died. The 1-, 3-, and 5-year cumulative OS rates were 85.7%, 44.5%, and 1.6% in the surgery group; among them, the 1-, 3-, and 5-year cumulative OS rates were 88.2%, 58.8%, and 3.2% in Group 1 (median OS: 39 months), and 82.8%,

27.6%, and 3.2% in Group 2 (median OS: 27 months). In Group 3, the 1-, 3-, and 5-year cumulative OS rates were 45%, 0%, and 0%, respectively (median OS: 10 months). There was a statistically significant difference in OS between Group 1 and Group 2 (P=0.036, *Figure 3A*) and also between Group 2 and Group 3 (P=0.0082, *Figure 3B*).

Independent prognosis factor in patients who underwent surgical resection

Univariable and multivariable analyses were performed in the patients who under went surgical resection respectively. The results are listed in *Table 3* and *Table 4*. There were 4 factors correlated with PFS and 5 factors correlated with OS. All significant factors (P<0.1) in the univariable analysis were entered into the multivariable analysis via the Cox regression mode. The results showed that surgical time [hazard ratio (HR):1.009, 95% confidence interval (CI): 1.001–1.017, P=0.025], liver segment invasion (HR: 2.174, 95% CI: 1.056–4.476, P=0.035) and capsule (HR: 1.21, 95% CI: 1.12–4.72, P=0.041) were shown to be the independent risk factors for OS.

Discussion

G-HCC has always been a challenge for surgeons. Some studies have shown that the integrity of the capsule is
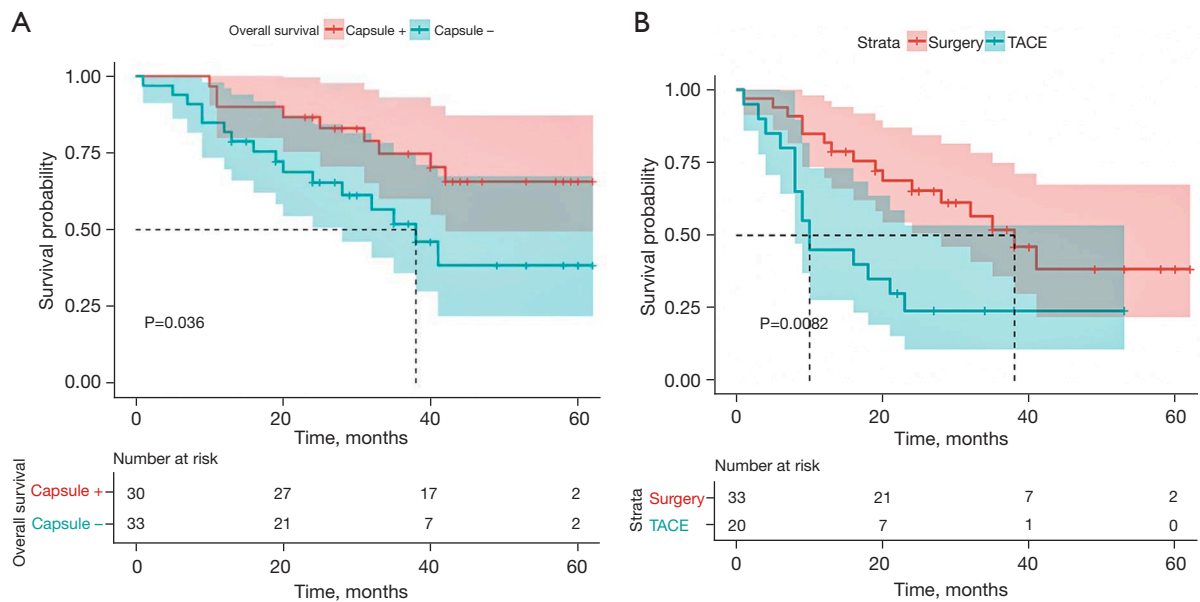
Figure 3 Kaplan-Meier survival curves for OS. (A) OS between positive and negative capsules in surgical patients. (B) OS after TACE and surgery in a capsule-negative patient. OS, overall survival; TACE, transarterial chemoembolization.

indeed a high-risk factor for early recurrence of HCC (19-21). However, there have been no studies to investigate the significance of the capsule in G-HCC alone. In addition, G-HCC was often deemed to be a candidate for surgery, and some locoregional therapy, like TACE, was recommended (22). We aimed to determine whether surgery is justified in G-HCC, regardless of if it has a capsule.

Our study shows that surgical resection provides longer 1-, 3-, and 5-year OS and PFS in patients with a complete capsule than it does patients with an incomplete or absent capsule. In addition, in patients who have an incomplete capsule or no capsule, surgical resection also provides longer 1-, 3-, and 5-year OS than TACE. An incomplete capsule or no capsule often means more segmental invasion and a greater number of tumors. Surgical time is the independent risk factor for early recurrence in G-HCC without a capsule after surgery.

Since 2014, Chou *et al.* have successively reported that the tumor capsule of HCC is highly correlated with microvascular invasion (MVI), suggesting a poor prognosis (5). Our findings are broadly similar to theirs; different to MVI; from a clinical point of view, we found that tumor number and liver segment invasion were related to the capsule. The reason why G-HCC is more likely to have a capsule is because the vast majority G-HCC grows

rapidly, compressing surrounding hepatocytes or tissues to form capsule, and rapid growth of tumors often indicates its malignant oncological features (23). An incomplete capsule tumor or no capsule tumor invade more liver segments and have more tumor numbers. Conversely, according to the tumor capsule protection theory of Torimura *et al.*, the incompleteness or absence of the capsule may lead to the potential micrometastasis of the tumor or invasion of the surrounding vasculature such as the portal venous system (9).

Treatment strategies for G-HCC are also controversial. Theoretically, surgical treatment is recommended for single G-HCC (24); however, the vast majority of G-HCC is often multiple tumors or accompanied by intrahepatic metastasis, and are classified as BCLC stage C or AJCC stage III-IV. In our study there were 34 (42%) patients classified as BCLC stage C, so in these patients to choose surgical resection or palliative treatment like TACE is controversial. To make sure which treatment (LR or TACE) is the more appropriate for G-HCC, Bogdanovic *et al.* did their research and found that the LR group was associated with longer OS than the TACE group before matching (P=0.032) and after propensity score matching (P=0.023) (25), which is consistent with our findings. In this study, we focused on which treatment is more suitable for patients with an incomplete capsule or no capsule. We think that a tumor with an incomplete capsule or no capsule has more aggressive oncological behavior,

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Table 3 Univariate and multivariate analysis of PFS in patients who underwent surgery

Variable	Univariate analysis		Multivariable analysis	
	P value	HR (95% CI for HR)	P value	HR (95% CI for HR)
Age	0.79	1 (0.97–1)		
Gender	0.64	0.82 (0.34–1.9)		
Capsule	0.027*	2 (1.1–3.7)	1.21	1.7 (1.1–3.2)
PS	0.28	0.34 (0.046–2.5)		
HBsAg	0.33	2.7 (0.37–20)		
Liver cirrhosis	0.066*	1.5 (0.97–2.3)	0.16	1.36 (0.89–2.1)
AFP	0.88	1 (1–1)		
GGT	0.8	1 (1–1)		
ALBI grade	0.14	1.6 (0.86–2.8)		
PNR	0.19	0.99 (0.98–1)		
PLR	0.8	1 (0.99–1)		
NLR	0.45	1 (0.96–1.1)		
PT	0.51	0.95 (0.82–1.1)		
Tumor diameter	0.72	1 (0.99–1)		
Tumor differentiation	0.86	0.96 (0.58–1.6)		
Tumor number	0.83	0.95 (0.58–1.5)		
Satellite	0.52	1.2 (0.66–2.3)		
MVI	0.88	1 (0.72–1.5)		
MAV	0.58	1.2 (0.65–2.2)		
PVTT	0.7	0.85 (0.38–1.9)		
Liver segment	0.055*	1.2 (1–1.5)	0.47	1.1 (0.84–1.4)
Extra hepatic invasion	0.43	1.5 (0.57–3.7)		
Child-Puph	0.12	2.5 (0.78–8.3)		
BCLC stage	0.045*	1.4 (1–1.9)	0.37	1.2 (0.8–1.8)
AJCC 8th	0.22	1.2 (0.91–1.5)		
Anatomic resection	0.19	1.5 (0.81–2.8)		
Surgical time	0.9	1 (1–1)		
Blood lose	0.93	1 (1–1)		

*, variables that can be included in the analysis of cox multivariate analysis (P<0.1). HR, hazard ratio; CI, confidence interval; MVI, microvascular invasion; PVTT, portal vein tumor thrombus; MAV (macrovascular invasion); TACE, transarterial chemoembolization; NLR, neutrophil-lymphocyte ratio; PNR, platelet-toneutrophil ratio; PLR, platelet-neutrophil ratio; GGT, gamma-glutamyl transpeptidase; PT, prothrombin time; AFP, alpha fetoprotein; PS, Performance Status score (Zubrod-ECOG-WHO); ALBI, albumin-bilirubin grade; PFS, progress free survival; BCLC, Barcelona stage of liver cancer; AJCC, American Joint Committee on Cancer.

Table 4 Univariate and multivariate analysis of OS in patients who underwent surgery

Variable	Univariate analysis		Multivariable analysis	
	P value	HR (95% CI for HR)	P value	HR (95% CI for HR)
Age	0.53	1 (0.97–1.1)		
Gender	0.28	0.56 (0.19–1.6)		
Capsule	0.049*	2.3 (0.99–5.2)	0.041	1.21 (1.12–4.72)
PS	0.92	1.1 (0.15–8.3)		
HBsAg	0.13	0.32 (0.076–1.4)		
Liver cirrhosis	0.36	1.3 (0.77–2)		
AFP	0.86	1 (1–1)		
GGT	0.13	1 (1–1)		
ALBI grade	0.59	1.2 (0.58–2.6)		
PNR	0.7	1 (0.98–1)		
PLR	0.098*	1 (1–1)	0.306	1.005 (0.995–1.016)
NLR	0.047*	1.1 (1–1.2)	0.713	1.115 (0.624–1.994)
PT	0.82	0.98 (0.83–1.2)		
Tumor diameter	0.67	0.99 (0.93–1)		
Tumor differentiation	0.62	0.85 (0.44–1.6)		
Tumor number	0.57	0.82 (0.42–1.6)		
Satellite	0.51	1.3 (0.58–2.9)		
MVI	0.92	1 (0.65–1.6)		
MAV	0.71	0.86 (0.38–1.9)		
PVTT	0.98	1 (0.38–2.7)		
Liver segment	0.044*	1.3 (1–1.8)	0.035	2.174 (1.056–4.476)
Extra hepatic invasion	0.83	0.86 (0.2–3.6)		
Child-Puph	0.31	2.1 (0.5–8.9)		
BCLC stage	0.44	1.2 (0.77–1.8)		
AJCC 8th	0.43	1.1 (0.81–1.6)		
Anatomic resection	0.3	1.5 (0.69–3.4)		
Surgical time	0.026*	1 (1–2.3)	0.025	1.009 (1.001–1.017)
Blood lose	0.97	1 (1–1)		

*, variables that can be included in the analysis of cox multivariate analysis (P<0.1). HR, hazard ratio; CI, confidence interval; MVI, microvascular invasion; PVTT, portal vein tumor thrombus; MAV, macrovascular invasion; TACE, transarterial chemoembolization; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; GGT, gamma-glutamyl transpeptidase; PT, prothrombin time; AFP, alpha fetoprotein; OS, overall survival; PS, Performance Status score (Zubrod-ECOG-WHO); ALBI, albumin-bilirubin grade; PNR, platelet-to-neutrophil ratio; AJCC stage, The eighth edition of the American Joint Committee on Cancer (AJCC) melanoma staging system; BCLC, Barcelona stage of liver cancer.

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faster growth rates, and more minor metastases which cannot be recognized visually or radiologically. TACE delivers chemotherapeutic drugs to the blood-rich tumor and its surroundings through the hepatic artery may lead to a better prognosis; however, our study shows that no matter with an incomplete capsule or without a capsule, surgery provides better long-term survival than TACE, and this may be associated with a large tumor load, difficulty in thorough TACE treatment, and tumor drug resistance. In addition, G-HCC is often complicated with vascular carcinoma thrombus, which seriously affects the efficacy of TACE.

In today's era of so-called targeted immunity, it is superficial to discuss the choice between surgery and TACE in HCC alone, because both surgery and TACE have limited efficacy in the long-term treatment of HCC, so this paper only discusses the choice of the first treatment. The treatment of liver cancer is complex, and the choice of treatment mode for each individual is individualized such as postoperative adjuvant TACE; the use of targeted drugs such as sorafenib renvaritinib; the use of immunogenic drugs such as sintilimab, camrelizumab, atilizumab, and so on, which have all brought new ideas for systemic and local treatment of tumors and promising the prognosis. Due to the fast growth speed and much more invaded liver segments or vasculatures, by the time G-HCC is diagnosed, the tumor stage is usually later. Our experience is that, for such patients, if surgical treatment can be performed, they should not hesitate to choose surgery, and if the operation is difficult, they should be comprehensively evaluated as soon as possible. Targeted drugs and immunotherapeutic drugs are actively used as the treatment background supplemented by TACE, radiotherapy, and other local treatments to degenerate and transform the tumors. In fact, the concept of down-stage therapy and conversion therapy has been very popular in recent years.

There are many limitations to this article. First this was a retrospective study with small sample of patients who underwent surgical resection or TACE of G-HCC, which is a disadvantage that cannot be overcome entirely; what we can do is try to be as realistic as possible in imaging interpretation and data collection. Second, this was a single center study reported from Eastern Asia, with patients with hepatitis B as the main contingent, which has limited guiding significance for the treatment of G-HCC with hepatitis C and alcoholic fatty liver disease as are common in the west. We will try to include more samples in future studies to address this shortcoming. Third, patients' choice

of treatment was highly subjective, which had an objective impact on OS and PFS of the patients in this study. In the end, according to the patients who underwent surgical resection in our study, the follow-up of imaging and tumor marker were required every 6 months and every 3 months, however imaging and tumor marker follow-up of patients who underwent TACE in our study was 1–1.5 months, these differences might result in different PFS.

Conclusions

In giant HCC patients who undergo surgical resection, a complete capsule could be associated with better OS and PFS than an incomplete/no capsule. In addition, surgical resection could provide better OS than TACE in giant HCC.

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Footnote

Reporting Checklist: Both authors have completed the STROBE reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2473/rc

Data Sharing Statement: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2473/dss

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki

(as revised in 2013). Ethics committee approval was granted by the ethics review board of the Affiliated Lihuili Hospital, Ningbo University (No. KY2021PJ036) and the requirement for written informed consent was waived.

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