*Original Article*

# Management of Huge HCC: Surgical Resection versus TACE-A Ten-Year Experience in a Single Institution

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**Background**: Treatment for huge or 10 cm and larger hepatocellular carcinoma (HCC) is complex with regards to the size and multifocality of this tumor. Treatment options include surgical resection or transarterial chemoembolization (TACE).

**Objective**: To evaluate the outcomes of surgical resection and TACE in management of huge HCC.

**Materials and Methods**: Between 2010 and 2019, 154 huge HCC patients with potentially resectable tumors were enrolled and evaluated by a multidisciplinary team (MDT) for treatment plans between surgical resection and TACE. The clinicopathological characteristic and overall survival (OS) between surgical resection and TACE were collected and analyzed.

**Results**: After MDT review, 115 patients were eligible for management. Sixty-three patients underwent surgical resection. TACE was performed in 52 patients. Patients in the surgical resection group had less severe comorbid disease with 14 patients (22.2%) versus 28 patients (53.8%) (p<0.001], less incidence of cirrhosis at 40 patients (63.5%) versus 45 patients (86.5%), (p=0.005) and less incidence of portal vein tumor thrombus at 11 patients (17.5%) versus 21 patients (40.3%), (p=0.003) compared to patients in the TACE group. The 1-, 3-, 5-year OS rates for surgical resection were 81%, 54%, and 39%, and 10.2%, 8.2%, and 2% in the TACE group (p<0.001) with mean follow up of four years. Morbidity and mortality rate in surgical resection were 34.9% and 1.5%, respectively. Posthepatectomy grade C complication was zero.

**Conclusion**: Surgical resection in huge HCC in selected cases achieve better outcomes than TACE with acceptable morbidity and mortality rate.

**Keywords**: Surgical resection; Huge Hepatocellular carcinoma; Transarterial chemoembolzation

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Size of hepatocellular carcinoma (HCC) is one of the key factors in determining disease management according to the Barcelona clinic of liver cancer (BCLC) guideline. The BCLC guideline over the past decade has recommended performing liver resection (LR) in a single HCC size of less than 5 cm, classified as BCLC A. It offers a 5-year overall survival (OS) of 60% to 80%. A single, large tumor of more than 5 cm, or multiple tumors, which are more than three tumors, is classified as BCLC B, whereby transarterial chemoembolization (TACE) is the main treatment for this group[1].

Improvements in perioperative care and techniques of LR have made the treatment for LR in large HCCs progressed. However, huge HCCs, defined as size of 10 cm or larger, remain a surgical challenge due to surgical risks, especially tumor rupture during manipulation or intraoperative bleeding during LR. When these tumors exhibit aggressive characteristics in terms of vascular invasion and satellite lesions, tumor prognosis becomes poor. In general practice, TACE is still offered as a treatment for huge HCC[2-4].

At King Chulalongkorn Memorial Hospital (KCMH), a multidisciplinary team (MDT) evaluates the management of HCC. LR will be attempted in resectable HCC in patients with good liver function. The aim of the present study was to outline the management of huge HCC patients at KCMH and study the outcomes of the treatment, especially LR and TACE in huge HCC patients.

## Materials and Methods

A retrospective review was conducted in patients with huge HCC underwent treatment between 2010

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and 2019 at a single institution, KCMH.

Diagnosis of HCC was based on The American Association for the Study of Liver Diseases (AASLD) criteria[5]. The International Statistical Classification of Diseases and Related Health Problems Tenth Revision (ICD 10) code C22.0 was used to identify inpatients with a diagnosis of HCC. The inclusion criteria were patients with a single tumor or multifocal HCCs, with the largest tumor size being 10 cm or more in diameter. The exclusion criteria were the presence of extrahepatic disease (M1), concomitant cancer, Child-Pugh score C, incomplete data base, and loss of follow-up.

Based on the above criteria, 154 patients whose tumor sizes were 10 cm or more in diameter were enrolled into the present study, but 39 patients were subsequently excluded with 20 due to the presence of extrahepatic metastasis, four due to concomitant cancer, one was classified as Child-Pugh C, eight due to loss of follow-up, and six had incomplete data records. Finally, 115 patients were analyzed, and details are shown in Figure 1.

Patient characteristics, laboratory data, image findings, treatment modality either TACE or LR, complications, and follow up data were reviewed from the outpatient and the inpatient records. Patients' underlying diseases were categorized using the Charlson Comorbidity Score (CCS)[6]. Postoperative complications were classified using the Clavien-Dindo Classification[7]. Perioperative mortality defined death within 30 days of surgery or during the admission. Posthepatectomy liver failure was categorized by the International Study Group of Liver Surgery's definition[8].

### Preoperative evaluation for liver resection

All patients with potential resectable tumors were evaluated for LR. Criteria for LR composed of medically fit patients, well preserved liver function classified as Child-Pugh A, no sign of significant portal hypertension, tumor confined in one lobe no matter of single or multiple tumors, and no tumor thrombus in main portal vein or bilateral portal vein. TACE would be performed in patients who did not fall in the criteria for LR or patients who refused surgery.

Sequential TACE and PVE would be scheduled in case of borderline function liver remnant (FLR) volume of less than 40% in cirrhotic liver or less than 25% to 30% in normal liver. In general, TACE would be performed first, followed by portal vein embolization (PVE) one or two weeks after recovery from TACE. FLR volume would be subjected to reevaluation four to six weeks after PVE. Patients with preoperative TACE before LR did not apply to the TACE group.

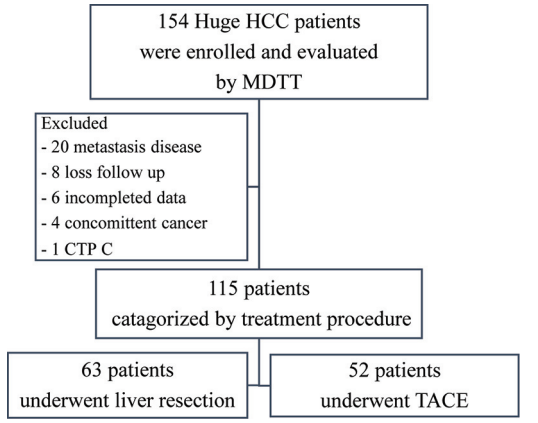



**Figure 1.** Flow chart of patients with huge HCC.

### Diagnosis of cirrhosis

The imaging criteria of the findings applied to diagnose cirrhosis were surface and parenchyma nodularity, fatty change, and parenchyma heterogeneity[9]. Pathologic finding of cirrhosis was used to confirm diagnosis in patients who underwent LR.

### Surgical procedures

The operative procedure was started with an upper midline incision. Assessment of resectability was confirmed by surgical exploration and intraoperative liver ultrasonography. If the tumor was resectable, an incision was extended to the upper right quadrant incision, or mirror left incision, and a curative resection was performed. If the exposure were limited, an extension to the thoracoabdominal approach for the right-sided tumor or inverted T-incision for the left-sided tumor would be applied.

For a right hepatectomy, the Glissonian approach of the right portal pedicle was preferred if the tumor was far from the right portal pedicle. If bile duct tumor thorombus (BDTT) or major portal vein tumor thrombus (PVTT) was present, individual ligation were performed instead. For left hepatectomy, individual ligation was routinely performed. An anterior approach combined with liver hanging, especially for the right-sided tumor was applied for liver parenchymal transection. Multiorgan resection was performed to obtain a free-resection margin for the tumor that adhered to adjacent organs.

### TACE

TACE was performed by a specially trained interventional radiologist who used fluoroscope guidance to identify and inject cisplatin with lipiodol. After the procedure, all patients were admitted for observation for any complication of angiography and post TACE syndrome.

### Postoperative care and follow-up

Patients who underwent LR were routinely transferred back to the surgical ward, except for high anesthetic-risk patients or those who underwent extensive surgical procedures, an admission to the intensive care unit (ICU) would be required. Enhanced recovery after surgery (ERAS) protocols for liver surgery were applied in all patients[10]. Two weeks after treatment, the patients routinely underwent clinical examinations at the outpatient department. Imaging, either computed tomography (CT) scan or magnetic resonance imaging (MRI), and blood tests for alpha-fetoprotein (AFP) were performed within the first three months after surgical resection, at three to six months' intervals during the first two years, then every six months until recurrence. If recurrence was suspected, or detected by imaging, full metastasis work up was performed to detect all metastatic lesions and plans for treatment were designed.

Patients post-performed TACE were transferred back to the surgical ward and observed for post TACE syndrome. Two weeks after discharge, the patients were routinely followed up by clinical examinations at the outpatient department. Imaging, either CT scan or MRI, were scheduled within the first three months to detect possible viable tumors or new lesions. TACE would be repeated if the imaging demonstrated such occurrences.

### Definition of clinical endpoints

The OS was defined as the interval between the date of treatment and time of death caused by HCC or the last treatment date. Recurrence-free survival (RFS) was defined as the interval between the date of treatment and the first relapse in cases of LR.

### Statistical analysis

Categorical variables were expressed as percentage, and continuous variables data within the normal distribution were shown as mean and standard deviation, otherwise as median and interquartile range. Pearson's chi square was used to calculate p-values for categorical variables. Independent t-tests or the Mann-Whitney U tests was used, when appropriate, to calculate p-values for quantitative variables.

The OS and RFS rates were calculated using the Kaplan-Meier model with log-rank test. A p-value less than 0.05 was considered statistically significant. The statistical analyses were performed with the IBM SPSS Statistics, version 25.0 (IBM Corp., Armonk, NY, USA). Approval for the present study was obtained by KCMH's Ethics Committee (IRB number 078/64).

## Results

One hundred fifteen patients were reviewed by the MDT, 63 patients were candidate for LR, while 52 patients including 26 patients with portal hypertension,13 patients with severe comorbid disease, five patients with main portal vein tumor thrombus, six patients with bilobar tumors, and two patients who refused surgery, underwent TACE.

### Demographic and clinical data

Patient data, laboratory investigations, image findings are shown in Table 1. Mean age was 58 years. Ninety-eight patients (85.2%) were male, and 17 patients (14.8%) were female. Forty-two patients (36.5%) had severe comorbidity, categorized by the CCS level of 3-4. Eighty-five patients (73.9%) were presented with HCC associated with cirrhosis. The causes of cirrhosis were chronic hepatitis B (HPB) virus infection in 57 patients (67%), chronic hepatitis C (HPC) virus infection in seven patients (8.2%), alcohol in seven patients (8.2%), Non-alcoholic Steatohepatitis NASH in one patient (1%), and cryptogenic causes in 13 patients. Previous ruptured tumor was found in 10 patients (8.7%). AFP within the normal range or less than 10 mg/mL was found in 23 patients (20%) and 38 patients (33%) were presented with high AFP or more than 1,000 ng/mL.

The median tumor size was 13 cm, and the largest tumor size was 28 cm in diameter. A single tumor was detected in 74 patients (64.3%) and 41 patients (35.7%) had multiple tumors. Image findings demonstrated HCC with PVTT in 33 patients (28.7%). One patient had HCC with BDTT.

A comparison of the demographics and clinical data between LR and TACE groups, with the statistical significances shown in Table 1, were as follows, patients in the LR group when compared to those in the TACE group had less severe comorbid disease or CCS of more than 2 in 14 patients (22.2%) versus 28 patients (53.8%), ($p<0.001$), less incidence of cirrhosis in 40 patients (63.5%) versus 45 patients

**Table 1.** Demographics and clinical data between LR and TACE groups

| Demographic data (n=115) | Entire cohort (n=115) | Liver resection (n=63) | TACE (n=52) | p-value |
|---|---|---|---|---|
| Patient characteristics | | | | |
| Age (year); mean±SD | 58±12 | 56.5±12.3 | 60 (12) | 0.155 |
| Sex; n (%) | | | | 0.013* |
| • Male | 98 (85.2) | 49 (77.7) | 49 (94.2) | |
| • Female | 17 (14.8) | 14 (22.3) | 3 (5.8) | |
| Charlson comorbidity score; n (%) | | | | <0.001* |
| • ≤2 | 73 (63.5) | 49 (77.8) | 24 (46.2) | |
| • >2 | 42 (36.5) | 14 (22.2) | 28 (53.8) | |
| Liver status; n (%) | | | | 0.005* |
| • Non-cirrhosis | 30 (26.1) | 23 (36.5) | 7 (13.5) | |
| • Cirrhosis | 85 (73.9) | 40 (63.5) | 45 (86.5) | |
| - CTP A | 69 (60.0) | 40 (63.6) | 29 (55.8) | |
| - CTP B | 16 (13.9) | 0 (0.0) | 16 (30.8) | |
| Presence of portal hypertension; n (%) | 27 (23.5) | 0 (0) | 27 (52) | <0.001* |
| Previous ruptured tumor; n (%) | 10 (8.7) | 7 (11.1) | 3 (5.8) | 0.312 |
| Laboratory investigation | | | | |
| HBsAg positive status; n (%) | 57 (49.6) | 32 (50.8) | 25 (48.1) | 0.772 |
| Anti-HCV positive status; n (%) | 7 (6.1) | 1 (1.6) | 6 (11.5) | 0.026* |
| PLT ($\times 10^3/\mu L$); median [IQR] | 239,000 [157,000] | 250,000 [150,000] | 218,500 [144,500] | 0.241 |
| INR; mean±SD | 1.11±0.12 | 1.09±0.11 | 1.14±0.15 | 0.030* |
| TB (mg/dL); median [IQR] | 0.7 [0.47] | 0.61 [0.35] | 0.88 [0.81] | 0.001* |
| Albumin (g/dL); mean±SD | 3.6±0.56 | 3.7±0.59 | 3.43±0.5 | 0.009* |
| AFP (ng/mL); median [IQR] | 323.6 [16,122] | 161.4 [5,957] | 597.6 [36,530] | 0.058 |
| Image findings | | | | |
| Size (cm); median [IQR] | 13 [4] | 13.4 [4] | 14 [4.3] | 0.189 |
| Number of tumors; n (%) | | | | |
| • Solitary | 74 (64.3) | 45 (71.4) | 29 (55.8) | |
| • Multiple | 41 (35.7) | 18 (28.6) | 23 (44.2) | 0.081 |
| Presence of PVTT; n (%) | 33 (28.7) | 11 (17.5) | 21 (40.3) | 0.003* |

SD=standard deviation; IQR=interquartile range; TACE=transarterial chemoembolization; HCV=hepatitis C virus; PLT=platelet; INR=international normalized ratio; TB=total bilirubin; AFP=alpha-fetoprotein; PVTT=presence with portal vein tumor thrombus

(86.5%), (p=0.005), and no significant portal hypertension, more preserved liver function and less incidence of PVTT in 11 patients (17.5%) versus 21 patients (40.3%), (p=0.003).

### Liver resection group

Thirty-four patients (53.9%) underwent TACE from other hospitals and were transferred to the present study institution for further treatment. Preoperative TACE and subsequent PVE was performed in six patients.

Major LR was performed in 52 patients (82.5%). Extended organ resection was performed in 15 patients (23.8%) and the other 11 patients (17.5%) were segmentectomy. All patients had R0 resection.

The median operative time was four hours. The median operative blood loss was 800 mL. The median length of stay (LOS) after surgical resection was nine days. The median length of postoperative ICU stay was one day.

Postoperative complications according to the Clavien-Dindo classification occurred in 22 patients (34.9%). The most common complication was pleural effusion that required drainage in four of the six patients. Intraabdominal collection was detected in four patients, and percutaneous drainage was intervened in all patients. Bile leakage developed in four patients. However, one patient developed severe sepsis due to bile leak and led to death, thus, a mortality rate of 1.5%.

Twenty-nine patients (46%) developed postoperative liver failure, at grade A in 23 patients and grade B in six patients.

### TACE group

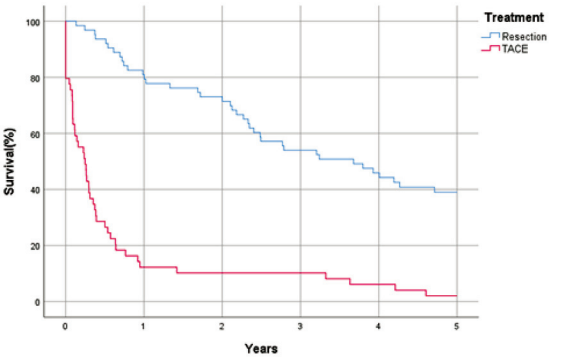
Twenty patients (38.4%) underwent one episode of TACE due to the progression of disease during follow up. No patient in this group lived longer than four months. The remaining 32 patients had TACE twice on average, due to the presence of viable tumor or new lesion formation during follow-up.

The median LOS after the first episode of TACE was two days. There was no postoperative mortality after TACE in this cohort.

### Clinical outcomes

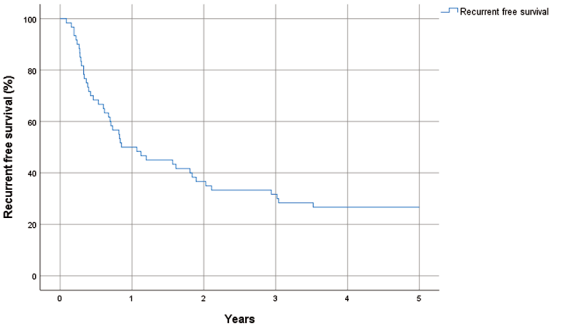
The median follow-up time after treatment for the entire cohort was 12 months (IQR 48 months), with 44 months (IQR 40 months) in the LR group and three months (IQR 5 months) in the TACE group. The median OS in the LR group was 38 months (95% CI 33.132 to 43.632), and the 1-, 3-, and 5-year OS rates were 81%, 54%, and 39%, respectively. Meanwhile, the median OS in the TACE group was eight months (95% CI 3.912 to 12.144), and 1-, 3-, and 5-year OS rates were 10.2%, 8.2%, and 2%, respectively, ($p<0.001$) (Figure 2).

The median RFS in the LR group was 26 months (95% CI 19.656 to 31.452) and the 1-, 3-, and 5-year RFS rates of patients in the LR group were 50%, 36.7%, and 26.7%, respectively (Figure 3).




| | Median | 1 year | 3 years | 5 years |
|---|---|---|---|---|
| Resection | 38 months | 81% | 54% | 39% |
| TACE | 8 months | 10.2% | 8.2% | 2% |

**Figure 2.** Overall survival of the entire cohort.




| | Median | 1 year | 3 years | 5 years |
|---|---|---|---|---|
| Resection | 26 months | 50% | 36.7% | 26.7% |

**Figure 3.** Recurrent-free survival in liver resection group.

## Discussion

Curative treatments for HCC according to the BCLC guideline include LR, liver transplantation, and local ablative treatment. Patient performance status, size of tumor, number of tumors, sign of portal hypertension, and liver function are the determining factors applied to outline the treatment options. According to the guideline, LR is the treatment of choice for patients with a solitary tumor and medically fit with a well-preserved liver function. It is reported that a 5-year survival in patients with LR for HCC of less than 5 cm is 60% to 80%[1,4].

Local ablation is not effective and liver transplantation is contraindicated in huge HCC of 10 cm or larger. To this extent, LR is the only curative treatment for these lesions. LR in huge HCC is not only technically challenging due to the risks of bleeding and tumor rupture during manipulation[11] but involves risks from postoperative complication.

Moreover, this type of tumor is aggressive in terms of vascular invasion and satellite lesions, which make poor prognosis. Due to multiple tumors or heterogenic characteristics associated with huge HCC, they may be classified into BCLC A or BCLC B, according to the BCLC guideline.

Data on management of huge HCC remains inconclusive. Many studies, especially from Asia have reported that OS for surgical resection was better in comparison to TACE[12] despite not fully abiding by the BCLC guidelines in terms of resectable criteria for HCCs.

The present study approach for the management of patients with huge HCC is to conduct an evaluation of all patients by the MDT and to encourage LR in patients with a potentially resectable tumor. LR would be offered in medically fit patients, with well-reserved liver function classified as Child-Pugh A, no sign of significant portal hypertension, tumor confined in one lobe irrespective of single or multiple tumors, and no tumor thrombus in the main portal vein or the bilateral portal vein.

In the present study, patients in the LR group

**Table 2.** Overall results from pervious literatures compared with the present study

| Author | Years | Period | No. of patients | 5-year OS | 5-year RFS | Morbidity | Mortality |
|---|---|---|---|---|---|---|---|
| Allemann et al[14] | 2013 | 1997-2009 | 22 | 45% | 27% | 23% | 0% |
| Ariizumi et al[3] | 2013 | 1990-2008 | 119 | 56% | 29% | N/A | 5.6% |
| Shrager et al[15] | 2013 | 1992-2010 | 103 | 18.8% | 11.5% | 21.5% | 6.9% |
| Hwang et al[11] | 2015 | 2000-2012 | 471 | 35.5% | 24% | N/A | 1.7% |
| Lim et al[16] | 2015 | 1995-2012 | 149 | 28% | 17% | 43.6% | 5.4% |
| Chang et al[17] | 2016 | 2002-2010 | 912 | 35% | N/A | N/A | N/A |
| Wakayama et al[18] | 2017 | 1990-2013 | 53 | 49.2% | 14.2% | N/A | 0.35% |
| Fang et al[19] | 2018 | 2007-2017 | 84 | 41.1% | 15.5% | 100% | 0% |
| The present study | | 2010-2019 | 63 | 39% | 26.7% | 34.9% | 1.9% |

OS=overall survival; RFS=recurrence-free survival; N/A=not applicable

when compared with the TACE group had statistically significant results. They had less severe comorbid disease at CCS of more than 2, 14 patients (22.2%) versus 28 patients (53.8%), p<0.001), less incidence of cirrhosis at 40 patients (63.5%) versus 45 patients (86.5%), p=0.005, and no significant portal hypertension, more preserved liver function and less incidence of PVTT at 11 patients (17.5%) versus 21 patients (40.3%), p=0.003.

Due to the tumor size, major LR was performed in 52 patients (82.5%). To prevent or reduce the risks of posthepatectomy liver failure, preoperative liver assessment and liver volumetry were the important factors for preoperative evaluation[13]. In case of inadequate FLR volume, sequential TACE followed by PVE was performed to increase liver volume.

In the present cohort, despite using the Child-Pugh A score, coupled with the clinical evidence of an absence of significant portal hypertension and adequate liver volume of FLR, posthepatectomy liver failure grade A developed in 23 patients (36.5%) and grade B in six patients (9.5%). No patient had posthepatectomy liver failure grade C.

The survival analyses between patients treated by LR and TACE were analyzed by the Kaplan-Meier survival analysis with a patient follow-up of up to 14 years. In the LR group, the median OS was 38 months and the 1-, 3-, and 5-year OS rates were 81%, 54%, and 39%, respectively. Meanwhile, the median OS was eight months and the 1-, 3-, and 5-year OS rates were 10.2%, 8.2%, and 2%, respectively in the TACE group. The longest surviving patient from the present cohort is still alive more than 13 years without any recurrence. The 1-, 3-, and 5-year RFS rates of patient with huge HCC underwent LR were 50%, 36.7%, and 26.7%, respectively.

These overall results are comparable to previous studies that demonstrated 5-year OS rates of 18.8% to 49.2%[3,11,14-19] and relapse-free survival rates of 11.5% to 29%[3,11,14-16,18,19]. Morbidity and mortality of the present study were 34.9% and 1.5%, respectively. These are acceptable according to the EASL recommendation[20] and not inferior to the previous studies as shown in Table 2.

The recently updated BCLC 2022 guideline, used as the mainstay guideline for treatment of HCC has recommended that LR be performed in patients with a single tumor, regardless of tumor size[21]. These latest recommendations are in line with those suggested by the APASL 2017 guideline[22].

The present study has limitations due to the retrospective design and small cohort.

## Conclusion

LR in huge HCC provided better long-term survival for patients in comparison to TACE. For medically fit patients with well-preserved liver function and no signs of portal hypertension, LR should be encouraged as a viable treatment of huge HCC.

## What is already known on this topic?

LR offers long-term survival in patients with HCC BCLC stage A, especially tumor size less than 5 cm.

## What this study adds?

In huge HCC, or 10 cm or larger, due to multifocality of tumor, some patients are categorized into BCLC B. Option of treatments in this tumor includes LR and TACE. Comparing to TACE, LR still provides better long-term survival. LR should be performed in patients with resectable HCC, no matter the size of tumor.

## Conflicts of interest

The authors declare no conflict of interest.

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