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BRIEF ARTICLE

Role of surgical resection for multiple hepatocellular carcinomas

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Abstract

AIM: To clarify the role of surgical resection for multiple hepatocellular carcinomas (HCCs) compared to transarterial chemoembolization (TACE) and liver transplantation (LT).

METHODS: Among the HCC patients who were managed at Yonsei University Health System between January 2003 and December 2008, 160 patients who met the following criteria were retrospectively enrolled: (1) two or three radiologically diagnosed HCCs; (2) no radiologic vascular invasion; (3) Child-Pugh class A; (4) main tumor smaller than 5 cm in diameter; and (5) platelet count greater than 50 000/mm^3. Long-term outcomes were compared among the following three treatment modalities: surgical resection or combined radiofrequency ablation (RFA) (n = 36), TACE (n = 107), and LT (n = 17). The survival curves were computed using the Kaplan-Meier method and compared with a log-rank test. To identify the patients who gained a survival benefit from surgical resection, we also investigated prognostic factors for survival following surgical resection. Multivariate analyses of the prognostic factors for survival were performed using the Cox proportional hazard model.

RESULTS: The overall survival (OS) rate was significantly higher in the surgical resection group than in the TACE group (48.1% *vs* 28.9% at 5 years, $P < 0.005$). LT had the best OS rate, which was better than that of the surgical resection group, although the difference was not statistically significant (80.2% *vs* 48.1% at 5 years, $P = 0.447$). The disease-free survival rates were also significantly higher in the LT group than in the surgical resection group (88.2% *vs* 11.2% at 5 years, $P < 0.001$). Liver cirrhosis was the only significant prognostic factor for poor OS after surgical resection. Clinical liver cirrhosis rates were 55.6% (20/36) in the resection group and 93.5% (100/107) in the TACE group. There were 19 major and 17 minor resections. *En bloc* resection was performed in 23 patients, multisite resection was performed in 5 patients, and combined resection with RFA was performed in 8 patients. In the TACE group, only 34 patients (31.8%) were recorded as having complete remission after primary TACE. Seventy-two patients (67.3%) were retreated with repeated TACE combined with other therapies. In patients who underwent surgical resection, the 16 patients who did not have cirrhosis had higher 5-year OS and disease-free survival rates than the 20 patients who had cirrhosis (80.8% *vs* 25.5% 5-year OS rate, $P = 0.006$; 22.2% *vs* 0% 5-year disease-free survival rate, $P = 0.048$). Surgical resection in the 20 patients who had cirrhosis did not provide any survival benefit when compared with TACE (25.5% *vs* 24.7% 5-year OS rate, $P = 0.225$). Twenty-nine of the 36 patients who underwent surgical resection experienced recurrence. Of the patients with cirrhosis, 80% (16/20) were within the Milan criteria at the time of recurrence

after resection.

CONCLUSION: Among patients with two or three HCCs, no radiologic vascular invasion, and tumor diameters ≤ 5 cm, surgical resection is recommended only in those without cirrhosis.

Key words: Hepatocellular carcinoma; Hepatectomy; Liver transplantation; Chemoembolization; Cirrhosis

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INTRODUCTION

Surgical resection is the established treatment modality for hepatocellular carcinoma (HCC) in patients with preserved liver function, and surgical outcomes have been greatly improved with mortality rates of 0%-6.4% and excellent 5-year survival rates of more than 50%[1-3]. However, for patients with multiple HCCs, unfavorable disease-free and overall survival (OS) rates following surgical resection have led to the contraindication of surgical treatment. This contraindication is reflected in the guidelines suggested by the American Association for the Study of Liver Disease[4] and the European Association for the Study of the Liver[5] based on the Barcelona Clinic Liver Cancer (BCLC) staging system. Thus, liver transplantation is recommended as the best option for patients with multiple HCCs, but a worldwide shortage of donor organs greatly limits the application of this recommendation. Therefore, although multidisciplinary strategies are used in the treatment of multiple HCCs, multiple HCCs still pose a therapeutic challenge and are a matter of debate.

Currently, the main treatment modality for multiple HCCs is transarterial chemoembolization (TACE). Although several expert centers have recently reported encouraging durable long-term outcomes of surgical resection for multiple HCCs (50%-60% at 5 years) in patients with well-preserved liver function[6,7], few comparative studies of surgical resection and liver transplantation (LT).

ACE have been reported[8,9]. Therefore, we designed this study to clarify the role of surgery for multiple HCCs by comparing the long-term outcomes following surgical resection, TACE, and LT and investigating prognostic factors in patients who underwent surgical resection.

MATERIALS AND METHODS

Patient evaluation and follow-up

We analyzed a single-institution database of 3928 patients who received their initial treatments for HCCs at Yonsei University Health System, Seoul, South Korea between January 2003 and December 2008. The Institutional Review Board of Yonsei University Health System approved this study. Of the patients who underwent surgical resection (n = 304), TACE (n = 854), and LT (n = 45), the patients who met the following criteria were enrolled in this retrospective, single-cohort study: (1) two or three radiologically diagnosed HCCs; (2) no radiologic vascular invasion; (3) Child-Pugh class A; (4) main tumor smaller than 5 cm in diameter; and (5) a platelet count greater than 50 000/mm^3. Small satellite nodules found in the resected specimen were not included in this study.

The cutoff value of tumor size for therapeutic decision making is a debated issue. The 7th edition of cancer staging of the American Joint Committee on Cancer describes main tumor size greater than 5 cm in multiple tumors as an independent prognostic factor for survival[10]. Additionally, a study comparing the pathologically proven necrosis rate following TACE reported the following frequencies of complete necrosis according to tumor size: 66.7%, 30% and 0% for ≤ 3.0 cm, 3.1-5.0 cm, and > 5.0 cm, respectively[11]. Although TACE has been performed as palliative care for larger HCCs, the OS rates of patients with tumors larger than 5 cm in diameter are very poor[12,13]. In addition to tumor size, the presence of vascular involvement of the tumor is a significant prognostic factor for poor outcome. The 5-year survival rates among patients with tumors with and without macroscopic vascular invasion are significantly different (48% ± 3% *vs* 14% ± 5%, $P < 0.001$)[14]. Therefore, patients with a tumor ≥ 5 cm in diameter or with macroscopic vascular involvement were excluded from this study because those patients were unsuitable for curative therapy.

Ultimately, we included 36 patients who underwent surgical resection or combined resection with radiofrequency ablation (RFA), 107 patients who received TACE, and 17 patients who underwent LT, and we compared long-term outcomes following the respective treatments.

Patients were evaluated preoperatively by abdominal ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI), and hepatic angiography, if indicated. All patients were assessed using alpha-fetoprotein (AFP), protein induced by vitamin K absence or antagonist Ⅱ (PIVKA Ⅱ), hepatitis B surface antigen, anti-hepatitis C viral antibody, liver biochemistry, coagulation test, and indocyanine green retention rate at 15 min (ICG R15).

The selection of therapeutic options was determined by the anatomical locations of the tumors, liver functional reserve, and patient preference. TACE was generally considered when the tumor was ineligible for complete surgical removal, low remnant liver volume was expected after resection, or the patients declined operative inter-

vention. The patients who had an available liver donor underwent LT.

Eradicating all of the multifocal tumors required a multimodality approach using not only *en-bloc* resection but also separate multi-site resection or resection combined with RFA. All of the patients who underwent surgical resection were routinely assessed by intra-operative US. The effectiveness and safety of combined hepatectomy with RFA for multi-site HCCs were reported by Choi *et al*[15], and our previous work has also shown comparable results between en-bloc resection and multi-site resection or combination hepatectomy with RFA[16]. Separate multi-site resection or resection plus RFA was performed for the multifocal tumors ineligible for en-bloc resection because of bilobar involvement or when there was not enough hepatic function reserve after *en-bloc* resection. Wedge resection was considered for superficial tumors, and RFA was performed for tumors less than 3 cm in diameter that were located deep in the liver.

The median follow-up period for the patients who underwent surgical resection was 38.6 mo (range: 1-94 mo). Surveillance after treatment was conducted with regular monitoring of AFP, PIVKA Ⅱ, and US or CT every three to six months. Suspicious intrahepatic recurrence was confirmed by MRI, hepatic angiography, or image-guided fine-needle biopsy, if needed.

To identify the patients who gained a survival benefit from surgical resection, we also investigated prognostic factors for survival following surgical resection. Twelve clinical variables recorded at the time of diagnosis were analyzed. The variables included age at diagnosis; sex; serum albumin; alanine aminotransferase (ALT) and aspartate aminotransferase levels; ICG R15; serum AFP level; clinical liver cirrhosis; main tumor size and number of tumors on preoperative image studies; lobar distribution of the tumor; and type of operation.

Clinically diagnosed liver cirrhosis was defined as follows: (1) history of overt complications of liver cirrhosis, such as ascites, variceal bleeding, and hepatic encephalopathy; (2) evidence of clinical portal hypertension, including esophageal or gastric varices, or splenomegaly (maximal diameter > 12 cm) with platelet count < 100 000 mm^3; and (3) liver morphology suggesting the presence of cirrhosis on preoperative image studies, including hypertrophy of the left lobe and/or caudate lobe, relative volume reduction of the right lobe, nodularity of the liver surface, presence of regenerative or dysplastic nodules, or the presence of a portosystemic shunt[17-19]. All of the analysis in the current study were performed using a clinical diagnosis of liver cirrhosis to evaluate its clinical usefulness. Minor resection was defined as hepatectomy of two or fewer liver segments.

Statistical analysis

Continuous variables are presented as the mean ± SD and were compared by Student's *t* test. Categorical variables are expressed as frequencies with percentages and were compared by the χ^2 test. Cumulative overall and disease-free survival rates were computed by the Kaplan-Meier method, and differences between the survival curves were compared using a log-rank test. Multivariate analyses of the prognostic factors for survival were performed using the Cox proportional hazard model and included the factors that had *P* values less than 0.1 upon univariate analysis. Statistical analyses were performed using SPSS 15 for Windows (SPSS Inc., Chicago, IL, United States). Statistical significance was set at a *P* value less than 0.05.

RESULTS

Clinical characteristics of the surgical resection group and TACE group

The patients who underwent TACE were older and had lower platelet counts, higher ALT levels, and a higher rate of clinical liver cirrhosis than those in the resection group. Clinical liver cirrhosis rates were 55.6% (20/36) in the resection group and 93.5% (100/107) in the TACE group. Surgical resection was performed more frequently in patients with larger diameter tumors (Table 1).

Operative procedures in the surgical resection group and additional treatments in the TACE group

Table 2 lists the operative procedures and combined treatments with RFA in the resection group. There were 19 and 17 major and minor resections, respectively. *En bloc* resection was performed in 23 patients, multi-site resection was performed in 5 patients, and combined resection with RFA was performed in 8 patients. In the TACE group, only 34 patients (31.8%) were recorded as having complete remission after primary TACE. Seventy-two patients (67.3%) were retreated with repeated TACE, one patient was retreated with repeated TACE and intra-arterial chemotherapy, two patients were retreated with RFA, two patients were retreated with radiation therapy, one patient was retreated with percutaneous ethanol injection, two patients were retreated with intra-arterial chemotherapy and systemic chemotherapy, two patients were retreated with intra-arterial chemotherapy and radiation therapy, and five patients were retreated with holmium therapy.

Long-term outcomes according to treatment modality

The OS rate was significantly higher in the surgical resection group than in the TACE group (48.1% *vs* 28.9% at 5 years, $P < 0.005$) (Figure 1A). LT had the best OS rate, which was better than that of the surgical resection group, although the difference was not statistically significant (80.2% *vs* 48.1% at 5 years, $P = 0.447$) (Figure 1A). The disease-free survival rates were also significantly higher in the LT group than in the surgical resection group (88.2% *vs* 11.2% at 5 years, $P < 0.001$) (Figure 1B).

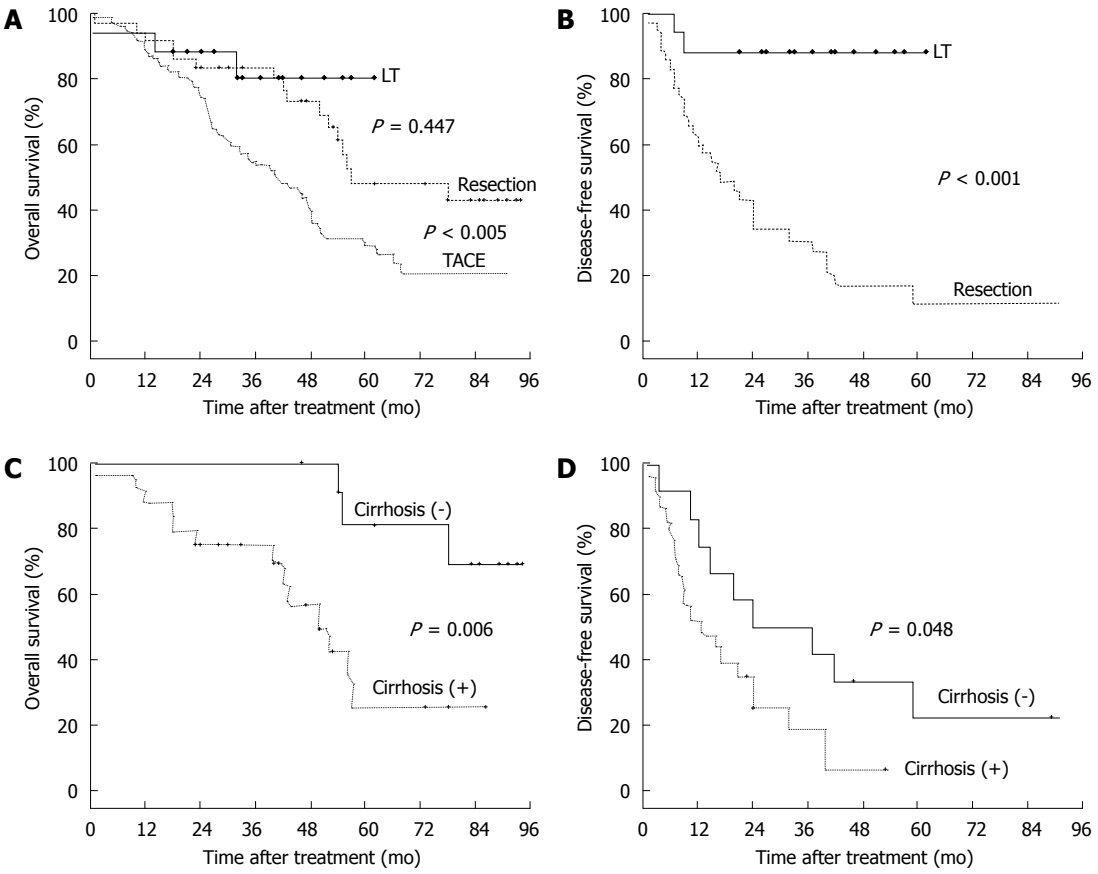

Figure 1 The overall and disease-free survival curves according to treatment modality and presence of liver cirrhosis in surgical resection patients. A: The 1-, 3- and 5-year overall survival (OS) rates were 94.1%, 80.2% and 80.2%, respectively, in the liver transplantation (LT) group; 91.7%, 83.3% and 48.1%, respectively, in the resection group; and 88.7%, 55.6% and 28.9%, respectively, in the transarterial chemoembolization (TACE) group. The OS rate was significantly higher in the surgical resection group than in the TACE group ($P < 0.005$). LT showed the best OS rate (better than the surgical resection group, but not statistically significant, $P = 0.447$); B: The 1-, 3- and 5-year disease-free survival rates were 88.2%, 88.2% and 88.2% in the LT group and 60%, 30.3% and 11.2% in the resection group, respectively. The disease-free survival rates were also significantly higher in the transplantation group than in the surgical resection group ($P < 0.001$); C: The 1-, 3- and 5-year OS rates were 100%, 100% and 80.8% in patients without cirrhosis (-) and 87.5%, 75% and 25.5% in patients with cirrhosis (+), respectively ($P = 0.006$); D: The 1-, 3- and 5-year disease-free survival rates were 75.0%, 50.0% and 22.2% in patients without cirrhosis (-) and 52.3%, 18.7% and 0% in patients with cirrhosis (+), respectively ($P = 0.048$).

Table 1 Clinical characteristics of the surgical resection patients *vs* the transarterial chemoembolization patients

Variable	Surgical resection (n = 36)	TACE (n = 107)	P value
Age (yr)	54.3 ± 8.6	61.2 ± 9.3	< 0.001
Gender (male:female)	34:2	86:21	0.047
Platelet (k/mm^3)	153.4 ± 53.9	121.0 ± 51.8	0.002
Albumin (g/dL)	4.05 ± 0.50	3.93 ± 0.48	0.203
ALT (IU/L)	36.4 ± 15.8	59.0 ± 40.4	0.001
AST (IU/L)	41.2 ± 25.8	53.2 ± 44.7	0.130
HBsAg	28 (77.8)	67 (62.6)	0.099
Clinical liver cirrhosis	20 (55.6)	100 (93.5)	< 0.001
Tumor number			0.549
2	30 (83.3)	90 (84.1)	
3	6 (16.7)	17 (15.9)	
Main tumor size (cm)			0.005
< 3	19 (52.8)	17 (47.2)	
⩾ 3	29 (27.1)	78 (72.9)	
AFP > 1000 IU/mL	2 (5.6)	8 (7.5)	0.696

Data are expressed as absolute n (%) or mean ± SD. M: Male; F: Female; TACE: Transarterial chemoembolization; ALT: Alanine aminotransferase (reference range, 5-46 IU/L); AST: Aspartate aminotransferase (reference range, 13-34 IU/L); HBsAg: Hepatitis B surface antigen; AFP: α-fetoprotein.

Table 2 Operative procedures in the resection group

Degree of resection	Operative procedure	Number of patients (n = 36)
Major resection (n = 19)	Extended right hepatectomy	1
	Right hepatectomy only	12
	+ wedge resection	1
	+ RFA	1
	Left hepatectomy only	1
	+ wedge resection	1
	Central bisectionectomy only	2
Minor resection (n = 17)	Left lateral sectionectomy only	3
	+ RFA	1
	Sectionectomy only	2
	+ wedge resection	2
	+ RFA	2
	Bisegmentectomy only	1
	+ wedge resection	1
	+ RFA	2
	Segmentectomy only	1
	+ RFA	1
	Wedge resection + RFA	1

En bloc resection (n = 23); multi-site resection (n = 5); resection plus radiofrequency ablation (RFA) (n = 8).

Table 3 Prognostic factors for overall survival in surgical resection patients

Variable	Patients (n = 36)	1-yr OS	3-yr OS	5-yr OS	P value
Age (yr)					0.146
≤ 60	27	88.9%	81.5%	42.3%	
> 60	9	100%	88.9%	66.7%	
Gender					0.245
Male	34	91.2%	82.4%	45.1%	
Female	2	100%	100%	100%	
Serum albumin (g/dL)					0.642
≤ 3.5	10	90.0%	60.0%	48.0%	
> 3.5	26	92.3%	87.7%	46.1%	
ALT (IU/L)					0.593
≤ 50	27	92.6%	81.5%	53.7%	
> 50	9	88.9%	71.1%	23.7%	
AST (IU/L)					0.87
≤ 50	31	90.3%	80.6%	52.4%	
> 50	5	100%	100%	50.0%	
ICG R 15 (%)					0.992
≤ 14	25	92.0%	84.0%	47.1%	
> 14	9	88.9%	77.8%	58.3%	
α-fetoprotein					0.471
≤ 1000 IU/mL	32	90.6%	81.3%	47.3%	
> 1000 IU/mL	4	100%	100%	50.0%	
Cirrhosis					0.023
No	16	100%	93.8%	69.9%	
Yes	20	85.0%	75.0%	26.5%	
Main tumor size (cm)					0.629
< 3.0	17	94.1%	86.3%	43.1%	
≥ 3.0	19	89.5%	73.7%	52.6%	
Number of tumors					0.061
2	31	90.3%	80.6%	40.7%	
3	5	100%	100%	100%	
Lobar distribution of tumors					0.892
One lobes	24	91.7%	83.3%	49.4%	
Two lobe	12	91.7%	83.3%	48.6%	
Operation type					0.568
En bloc resection	23	91.3%	82.6%	43.4%	
Multiple resection or combined with RFA	13	92.3%	84.6%	57.1%	

OS: Overall survival; RFA: Radiofrequency ablation; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ICG R 15: Indocyanine green retention rate at 15.

Prognostic factors for OS in patients who underwent surgical resection

Cirrhosis was the only significant prognostic factor for poor OS after resection in both the univariate (P = 0.023) and multivariate analyses (P = 0.034, odds ratio = 0.552, 95%CI: 0.105-0.915) (Table 3). Clinically diagnosed liver cirrhosis was correlated with pathological cirrhosis with a positive predictive value of 100%, a negative predictive value of 75%, a sensitivity of 83.3%, and a specificity of 100%.

Long-term outcomes of patients who underwent surgical resection according to the presence of cirrhosis

The 1-, 3- and 5-year OS rates were 100%, 100% and 80.8%, respectively, in 16 patients without cirrhosis, and 87.5%, 75% and 25.5%, respectively, in 20 patients with cirrhosis (P = 0.006) (Figure 1C). The disease-free 1-, 3- and 5-year survival rates were 75.0%, 50% and 22.2%, respectively, in patients without cirrhosis and 52.3%, 24.9% and 0%, respectively, in patients with cirrhosis (P = 0.048) (Figure 1D). The OS rates were not different between the surgical resection group and the TACE group among the patients with cirrhosis (87.5%, 75.0% and 25.5% *vs* 91.8%, 61.7% and 24.7% at 1-, 3- and 5-year, respectively, P = 0.225) (Figure 2).

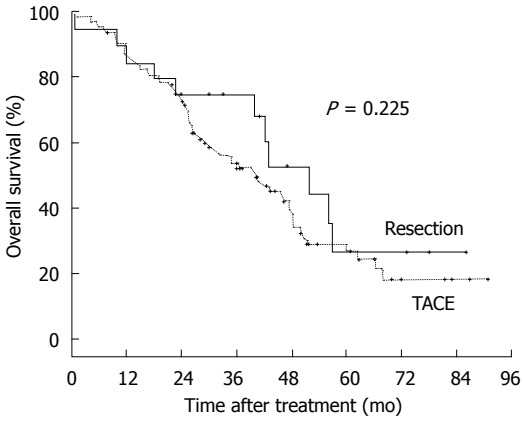

Figure 2 Overall survival curves of surgical resection and transarterial chemoembolization in patients with liver cirrhosis. Among patients with cirrhosis, the overall survival (OS) rates were not different between the surgical resection group and the transarterial chemoembolization (TACE) group (25.5% *vs* 24.7% 5-year OS rate, P = 0.225).

Recurrence pattern after surgical resection

Twenty-nine of the 36 patients who underwent surgical resection experienced recurrence. Of the 29 patients with recurrence, 1 (4%) had a marginal recurrence on the resection margin, 21 (84%) had intra-hepatic recurrences, and 3 (12%) had extra-hepatic recurrences with one in the lung and two in bone. All of the patients with marginal and intra-hepatic recurrence were retreated by TACE. Chemotherapy, radiation therapy, and a clinical trial were used to treat extra-hepatic recurrences. Notably, of the patients with cirrhosis, 80% (16/20) were within the Milan criteria at the time of recurrence after resection.

DISCUSSION

Our study demonstrates that surgery for patients with multiple HCCs is recommended in patients without cirrhosis. Our data revealed that the survival of patients who underwent surgical resection was better than that of patients who received TACE. However, the survival of patients with HCCs was affected not only by HCC itself, but also by underlying liver disease. The majority of patients (93.5%, 100/107) who received TACE had liver cirrhosis. Therefore, when the survival of the patients in the surgical resection group was compared with the TACE group according to the presence of cirrhosis, surgical resection showed no survival benefit in cirrhotic patients.

To confirm the efficacy of surgical resection for mul-

tiple HCCs, its superiority over non-surgical treatment (TACE) should be proven. A recent retrospective cohort study by Ho *et al*[8] reported that hepatectomy yields better survival than TACE even in patients with multiple HCCs in various stages. The authors compared the prognosis of the patients according to stages in different staging systems; however, as the authors note, their study had several weaknesses. Although each staging system represents the prognosis of the patients who have HCC, and in particular, the BCLC system accounts for portal hypertension and the bilirubin level in addition to the Child-Pugh classification in staging, the liver function status in each stage encompasses a wide range and the prognosis in the subgroups of each stage differs significantly[20]. Additionally, the patients in each stage of their study were heterogeneous. Therefore, it is unclear whether the degree of underlying liver disease was evenly distributed between the compared groups. In our study, we limited the inclusion criteria to patients with platelet counts greater than 50 000/mm^3 in addition to a Child-Pugh A classification to exclude patients who had severely advanced liver cirrhosis, for whom surgery is contraindicated due to likely postoperative deterioration of liver function and poor prognosis[17,21].

Liver cirrhosis is a well-known potent predictive factor for OS in patients with HCC[14,22,23], as shown in our patient cohort. According to our analysis, the survival rates of cirrhotic patients with multiple HCCs who underwent surgical resection were extremely disappointing. The 5-year OS rate of the patients with cirrhosis was 25.5%, which was significantly worse than that of the patients without cirrhosis (69.3%, $P = 0.006$) (Figure 1C and D). Furthermore, the outcomes of surgical resection and TACE in the patients with cirrhosis were not different (Figure 2). Therefore, surgical resection for multiple HCCs would be beneficial in patients without cirrhosis, but it remains debatable in patients with cirrhosis.

Despite the fact that surgical resection for multiple HCCs showed acceptable OS rates in our study as well as in several other publications[6-8,22,24], a high recurrence rate is a major drawback of surgical resection as a curative therapy. According to our data, the 5-year disease-free survival rates were 0% in patients with cirrhosis and 22.2% in non-cirrhotic patients. Thus, our single cohort study demonstrated that LT might be the preferred treatment option to offer the chance of a cure for multiple HCCs; the OS and disease-free survival rates were 80.2% and 88.2%, respectively (Figure 1A and B). However, in addition to inevitable immuneesuppressive therapy, which has an adverse oncologic effect, the scarcity of liver donors is another great obstacle to the wide application of LT.

Which loco-regional therapy is superior as a bridge to LT is an issue because of the long waiting time on the transplant list, which results in patients progressing and falling outside the transplant criteria. According to Llovet *et al*[25], approximately 10% of patients are dropped from the transplant list during the waiting period because of tumor progression or liver failure. TACE and RFA have been studied in detail and widely used as a bridge therapy in several transplant centers, but the efficacy of these modalities has not yet been established[26-28].

Recently, Belghiti *et al*[29] proposed three different roles of resection for HCC prior to LT: (1) As a primary therapy, resection can delay or avoid transplantation and can be followed by salvage transplantation for recurrence and deteriorated liver function; (2) As an initial therapy, resection can provide pathologic information about the whole specimen, which enables selection of the best candidates for transplantation; and (3) As a bridge therapy, resection can offer the best control of HCC in patients listed for LT through the possibility of downstaging and providing detailed pathologic information. In addition to these benefits, liver resection can provide superior control and a good survival rate[29,30]. Furthermore, several studies report that 60%-80% of patients who recur after resection for HCC are still amenable to transplantation, and these results are not different between patients with solitary and oligonodular primary HCCs[22,31,32]. Our results also showed that 80% of the recurred patients with cirrhosis following resection were within the Milan criteria. Thus, surgical resection for cirrhotic patients with multiple HCCs might be performed as a bridge to LT. Surgical resection as a bridge is justified by the improved safety of liver surgery and no survival impairment in the event of subsequent LT[31].

Recent studies demonstrated that salvage LT does not compromise the operative morbidity and mortality compared with primary LT[31,33,34]. In contrast, Adam *et al*[35] reported that secondary LT is associated with a higher operative morbidity and mortality; they also argued that patients treated by resection when they were initially transplantable had a higher recurrence rate with more frequent extrahepatic metastasis and vascular invasion, which impair the transplantability and long-term survival of the patients. Therefore, it is too early to conclude whether resection can be performed as bridge therapy. Nevertheless, these efforts to use the limited number of donor organs effectively are necessary, as is further investigation of this issue.

We did not analyze the outcomes according to the types of multiple HCCs in the present study because our data included patients who received resection combined with RFA, which did not allow for pathologic analysis. Discrimination of intrahepatic metastasis (IM) and *de novo* multicentric (MC) HCCs may be important because generally, IMs that have acquired metastatic ability exhibit more aggressive biologic behavior[36,37] and thus influence therapeutic strategy decisions. According to the guidelines of the Liver Cancer Study Group of Japan[38], IM is diagnosed if the tumors definitely originated from portal vein tumor thrombi, if the tumors arose in multiple satellite nodules surrounding a main tumor, or if a satellite tumor near the main tumor shows similar or

poorer histological differentiation than the main tumor. Otherwise, multiple HCCs that do not meet these conditions are deemed *de novo* MC tumors. Although these conventional pathological criteria are convenient, they are relatively subjective. Currently, the most precise method to determine the origin of HCC is DNA clonal analysis[39,40], and clinical differentiation between IM and MC is not possible preoperatively. If a credible diagnosis could be possible for preoperative distinction of the origin of multiple nodules, it might be helpful for the selection of therapy.

In conclusion, surgical resection for HCCs with two or three radiologically identified tumors, no radiologic vascular invasion, and diameters less than 5 cm is recommended for patients without cirrhosis but debatable for patients with cirrhosis. LT might be the best treatment option for patients with multiple HCCs. The retrospective design and the small number of cases are limitations of this-single cohort study. Therefore, further multi-center trials and randomized, controlled, prospective studies are needed, especially to examine the role of surgical resection in cirrhotic patients with multiple HCCs.

COMMENTS

Background

Although surgical resection is the established treatment modality for hepatocellular carcinoma (HCC) in patients with preserved liver function, however, for patients with multiple HCCs, unfavorable disease-free and overall survival (OS) rates following surgical resection have led to the contraindication of surgical treatment. Therefore, although multidisciplinary strategies are used in the treatment of multiple HCCs, multiple HCCs still pose a therapeutic challenge and are a matter of debate. There has been a lack of studies for the efficacy of surgical resection in patients with multiple HCCs.

Research frontiers

The survival of patients with HCCs was affected not only by HCC itself but also by underlying liver disease. Some studies have reported the superiority of surgical resection for multiple HCCs over non-surgical treatment. However, long-term outcomes of the patients according to not only stage but also the degree of underlying liver disease may help to select a proper treatment modality.

Innovations and breakthroughs

Their study demonstrates that surgery for patients with multiple HCCs is recommended in patients without clinical cirrhosis. When the survival of the patients in the surgical resection group was compared with the transarterial chemoembolization group according to the presence of cirrhosis, surgical resection showed no survival benefit in cirrhotic patients. This study is worthy because the surgical outcomes of the patients with multiple HCCs were compared according to the degree of underlying liver disease.

Applications

Liver cirrhosis is a well-known potent predictive factor for OS in patients with HCC. According to the analysis, the survival rates of cirrhotic patients with multiple HCCs who underwent surgical resection were extremely disappointing. Therefore, surgical resection for multiple HCCs is recommended for patients without cirrhosis but still debatable for patients with cirrhosis. Further multi-center trials and randomized, controlled, prospective studies are needed.

Peer review

This study provides clinical outcomes of surgical resection for multiple HCCs compared with the transarterial chemoembolization and liver transplantation. This issue is still debatable in patients with cirrhosis. The retrospective design and the small number of cases are limitations of this study.

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