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ORIGINAL ARTICLE

Retrospective Study

Outcome of transarterial chemoembolization-based multi-modal treatment in patients with unresectable hepatocellular carcinoma

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Abstract

AIM: To investigate the efficacy and safety of transarterial chemoembolization (TACE)-based multimodal treatment in patients with large hepatocellular carcinoma (HCC).

METHODS: A total of 146 consecutive patients were included in the analysis, and their medical records and radiological data were reviewed retrospectively.

RESULTS: In total, 119 patients received TACE-based multi-modal treatments, and the remaining 27 received conservative management. Overall survival (P < 0.001) and objective tumor response (P = 0.003) were significantly better in the treatment group than in the conservative group. After subgroup analysis, survival benefits were observed not only in the multi-modal treatment group compared with the TACE-only group (P = 0.002) but also in the surgical treatment group compared with the loco-regional treatment-only group (P < 0.001). Multivariate analysis identified tumor stage (P < 0.001) and tumor type (P = 0.009) as two independent pre-treatment factors for survival. After adjusting for significant pre-treatment prognostic factors, objective response (P < 0.001), surgical treatment (P = 0.009), and multi-modal treatment (P = 0.002) were identified as independent post-treatment prognostic factors.

CONCLUSION: TACE-based multi-modal treatments were safe and more beneficial than conservative management. Salvage surgery after successful downstaging resulted

in long-term survival in patients with large, unresectable HCC.

Key words: Hepatocellular carcinoma; Multimodal treatment; Transarterial chemoembolization; Salvage surgery

Core tip: The aim of this study was to investigate the efficacy of transarterial chemoembolization (TACE)-based multimodal treatment in patients with large hepatocellular carcinoma. The primary findings of this study were as follows: (1) The overall survival was significantly longer in the treatment group than in the conservative group; (2) Survival benefits were observed not only in the surgical treatment group (TACE + resection or transplantation) compared with the localized treatment group (TACE + ablation/radiotherapy) but also in the combination treatment group compared with the TACE-only group; and (3) Objective response, surgical treatment, and multimodality were independent factors for survival.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most-common cancer worldwide and the third most-common cause of cancer mortality[1]. In clinical practice, the majority of HCC patients are diagnosed at an inoperable stage, and prognosis is assumed to be poor. The recent guidelines issued by the European Association for the Study of the Liver (EASL) and American Association for the Study of Liver Disease (AASLD) endorse the Barcelona Clinic Liver Cancer (BCLC) staging system[2,3]. BCLC guidelines have the advantage of combining performance status, liver function, and tumor extent to classify patients into early (A), intermediate (B), advanced (C), and terminal (D) stages, and it links staging with treatment modalities and with an estimation of life expectancy. This guideline recommends transarterial chemoembolization (TACE) in BCLC-B and sorafenib in BCLC-C as standard treatments. Although BCLC guidelines have been extensively validated, a heterogeneous population of patients with intermediate-stage HCC or with advanced-stage HCC has consistently raised issues in clinical practice. Because multiple variables affect the clinical course of HCC, no single treatment strategy can be applied to all patients. Therefore, therapy should be tailored to each patient's individual needs using a multidisciplinary approach, particularly in cases of unresectable, large HCC.

The most widely used loco-regional therapies for the treatment of intermediate stage HCC involve TACE. In early 2000, two randomized controlled trials (RCTs) and systematic reviews reported that TACE improves the survival of patients with unresectable HCC compared with those who receive supportive treatment[4-7]. Although TACE is typically contraindicated in advanced HCC patients with portal vein (PV) invasion because of the potential risk of hepatic insufficiency, it has been suggested that TACE can be safely performed, even in those patients with PV invasion[8]. Therefore, it has also been used in patients with advanced HCC with PV invasion as a palliative treatment, and several studies have reported that it confers a survival benefit to these advanced patients[9-11]. However, limited studies have evaluated the proper treatment and the efficacy of TACE in cases of large HCCs (> 10 cm) with or without vascular invasion, which are frequently observed in clinical practice. The aim of this study was to evaluate the efficacy and safety of TACE-based multimodal treatment in patients with unresectable, large HCC.

MATERIALS AND METHODS

Patients

This was a retrospective study aimed at evaluating the therapeutic efficacy of combination therapy with TACE and other treatment modalities for large HCC in comparison with that of optimal supportive treatment. The HCC database at our center was retrospectively reviewed between June 1995 and December 2007. The inclusion criteria for eligibility in this study were as follows: (1) treatment-naïve adult patients who were newly diagnosed with HCC at our center; (2) HCC of over 10 cm in size; (3) Eastern Cooperative Oncology Group performance status of 0-2; and (4) Child-Turcotte-Pugh functional class of A (score of 5 or 6). Patients with distant extrahepatic metastasis and severe comorbidity and those who were transferred to another center without receiving treatment were excluded. This study was approved by the local ethics committee.

The diagnosis of HCC was made either pathologically or based upon elevated serum alpha-fetoprotein levels (> 200 ng/mL) with typical radiological findings (arterial hypervascularity and venous/late-phase washout). All patients were staged according to the modified Union for International Cancer Control staging system[12]. The gross type of HCC was defined based on the extent of demarcation, as described in a previous study[10].

Therapeutic modalities including TACE

Almost all therapeutic approaches were selected by the HCC tumor board team, which consisted of

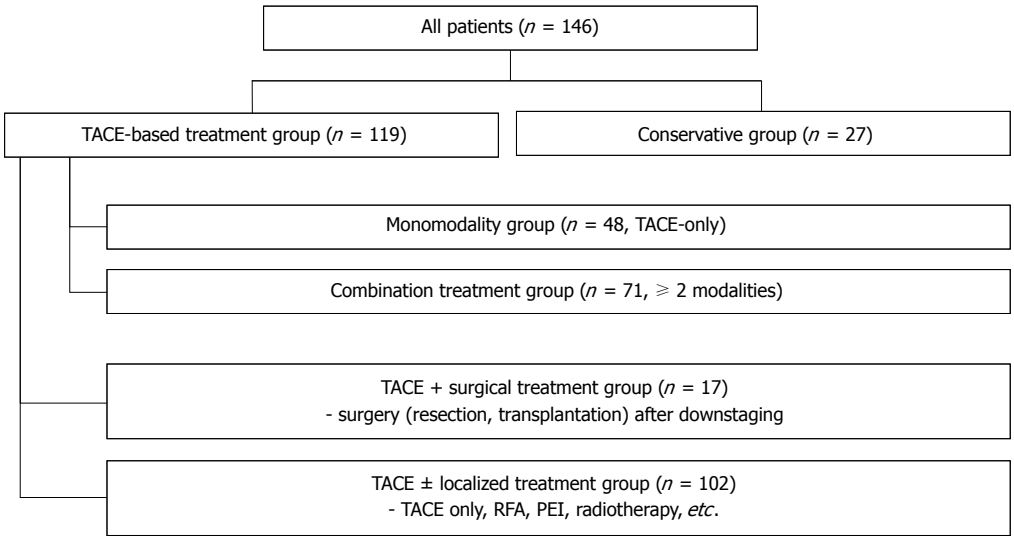

Figure 1 Treatment protocol. TACE: Transarterial chemoembolization; RFA: Radiofrequency ablation; PEI: Percutaneous ethanol injection.

hepatologists, surgeons, interventional radiologists, medical oncologists and radiation oncologists. All patients in the treatment group underwent a transarterial infusion of epirubicin (50 mg/m^2) and cisplatin (60 mg/m^2) in a mixture of 5-10 mL Lipiodol® (Guerbet, Aulnay-Sous-Bois, France) *via* femoral approach, which was accompanied by embolization using gelfoam in selected cases. The patients received an additional systemic infusion of 5-fluorouracil (5-FU) (200 mg/m^2) for 12 h after completing the transarterial procedure[10]. Unless there was a contraindication, the TACE sessions were repeated every 4-6 wk, and other additional therapies were performed as necessary for the downstaging of the tumor. Additional therapeutic modalities included radiofrequency ablation (RFA), percutaneous ethanol injection (PEI), radiation therapy and systemic chemotherapy with the ECF regimen (epirubicin + cisplatin + 5-FU). Surgical resection or transplantation was considered for those patients who were downstaged following local therapy. Before surgical resection or transplantation, chest computed tomography (CT) and positron emission tomography (PET) CT scans were performed to exclude the presence of extra-hepatic metastasis. Liver transplantations were performed in the patients who met the University of California, San Francisco (UCSF) criteria (Figure 1).

All patients who met the inclusion criteria were recommended to receive the treatment that had been determined by the tumor board. The patients who refused HCC treatment against medical advice, with the exception of those receiving symptomatic support, were classified as the conservative care group. Sorafenib could not be administered to the treatment group and conservative group because it was not available during the study period.

Assessment of treatment response and adverse effects

Treatment response was assessed after every TACE session using dynamic enhanced CT or magnetic resonance imaging (MRI), and the best response during serial TACE was taken as the overall response. Tumor response was evaluated according to the modified Response Evaluation Criteria in Solid Tumors (RECIST)[13]. A complete response (CR) was defined as the disappearance of any intra-tumoral arterial enhancement, a partial response (PR) was defined as a ⩾ 30% decrease in the sum of the diameters of viable lesions, progressive disease (PD) was defined as a ⩾ 20% increase in the sum of the diameters of viable lesions, and stable disease (SD) was defined as any case that did not qualify as either PR or PD.

The primary endpoint of this study was overall survival (OS), and the secondary endpoint was objective response (OR). OS was defined as the time from the first session of TACE to death, and OR was defined as the sum of the complete response and partial response. The treatment-related adverse events were assessed for 1-2 wk after each treatment using the National Cancer Institute Common Toxicity Criteria v3.0, and grade 3 or 4 toxicities were noted.

Statistical analysis

Statistical analyses were performed using the Statistical Package for Social Science software (SPSS 14.0 for Windows; SPSS, Inc., Chicago, IL). The results are presented as the number (%) or median (range), as appropriate. The Mann-Whitney test and Fisher's exact test or the χ^2 test were used for comparisons between the treatment group and the conservative group. Categorical variables were evaluated using Fisher's exact test or the chi-square test. Cumulative survival rates were estimated using the Kaplan-Meier method, and differences were analyzed using the log-rank test. To identify the independent factors for survival among pre-treatment variables and treatment-related variables, we used Cox proportional hazard regression models with backward elimination. In the multivariate analysis using treatment-related variables, hazard

Table 1 Baseline characteristics of the patients *n* (%)

Variables	All (*n* = 146)	Treatment group (*n* = 119)	Conservative group (*n* = 27)	*P* value
Age (yr)	52 (30-79)	52 (30-77)	58 (41-79)	0.014
Gender, male	130 (89.0)	111 (93.3)	19 (70.4)	0.002
Etiologies, *n*				0.385
HBV/HCV/Alcohol/others	115/7/8/16	95/4/7/13	20/3/1/3	
AFP (ng/mL)	546.7 (0.7-5719.0)	471.2 (0.7-5719.0)	1210.0 (3.1-2613.0)	0.652
Maximal tumor size (cm)	12.0 (10.0-20.0)	12.0 (10.0-20.0)	11.2 (10.0-17.0)	0.459
Tumor type				0.551
Well-demarcated	99 (67.8)	82 (68.9)	17 (63.0)	
Poorly-demarcated	47 (32.2)	37 (31.1)	10 (37.0)	
Location of main tumor				0.369
Left	24 (16.4)	18 (15.1)	6 (22.2)	
Right	122 (83.6)	101 (84.9)	21 (77.8)	
PVT				0.637
Present	108 (74.0)	89 (74.8)	19 (70.4)	
Absent	38 (26.0)	30 (25.2)	8 (29.6)	
Stage, modified UICC				0.491
Stage Ⅲ	67 (45.9)	53 (44.5)	14 (51.9)	
Stage Ⅳ-A	79 (54.1)	66 (55.5)	13 (48.1)	

HBV: Hepatitis B virus; HCV: Hepatitis C virus; AFP: Alpha-fetoprotein; PVT: Portal vein thrombosis; UICC: Union for International Cancer Control.

ratios were adjusted for significant variables in the multivariate analysis of pre-treatment variables due to the possibility of multi-collinearity. The variables that showed significant or marginal association ($P < 0.1$) by univariate analysis were subsequently included in multivariate analysis. A P value of less than 0.05 was considered statistically significant.

RESULTS

Patient characteristics

Using the aforementioned selection criteria, a total of 146 consecutive patients were enrolled in this study. The baseline characteristics of the patients are summarized in Table 1. A total of 119 patients (81.5%) were treated with the TACE-based multimodal procedure, and 27 (18.5%) received supportive treatment. One hundred and thirty patients (89.0%) were male, and the median age of the 146 patients was 52 years (range, 30-79 years). The etiology of the underlying liver disease was hepatitis B virus in 115 (78.8%), hepatitis C virus in 7 (4.8%), and alcoholism in 8 patients (5.5%). One hundred and eight patients (74.0%) had evidence of PV thrombosis (PVT) at baseline. There was no significant difference between the two groups in terms of the etiology of underlying disease, serum alpha-fetoprotein (AFP) level, maximal tumor size, tumor type, proportion of PVT, and stage. The median age of patients in the treatment group was lower than that of patients in the conservative group ($P = 0.014$), and male patients were more common in the treatment group ($P = 0.002$).

Treatment response

In the treatment group, a total of 513 TACE sessions were performed with a median of 3 sessions per patient (range: 1-17). In total, 71 (59.7%) out of 119 patients received combination therapy. As for treatment modality, a median of 2 methods (range: 1-5 methods) was administered. Systemic chemotherapy was administered in 46 patients, radiotherapy in 25, ablation therapy, such as RFA or PEI, in 21, surgical resection in 13, and liver transplantation in 4 patients.

Tumor responses were assessable in 122 of 146 patients (83.6%), while 24 (16.4%) were not assessable due to poor patient condition or loss to follow-up. The intent-to-treat analysis revealed that 14 of 102 patients (13.7%) experienced complete remission (CR), 15 (14.7%) experienced partial remission (PR), 31 (30.4%) experienced stable disease (SD), and 42 (41.2%) developed progressive disease (PD) in the treatment group. Therefore, the objective response rate was 28.4%, and 60 patients (58.8%) achieved successful disease control (CR + PR + SD) in the treatment group. In the conservative group, SD and PD were observed in 3 (15.0%) and 17 patients (85.0%), respectively, and there was no CR and PR. The objective response rate of the treatment group was significantly higher than that of the conservative group (28.4% *vs* 0.0%, $P = 0.003$). The disease control rate was also better in the treatment group than in the conservative group (58.8% *vs* 15.0%, $P < 0.001$) (Table 2).

Survival and prognostic factors

The median follow-up period was 8.5 mo (range: 0.8-129.4 mo), and the median overall survival (OS) in this study was 8.7 mo (95%CI: 7.0-10.4 mo). OS was significantly longer in the treatment group than in the conservative group (median of 10.3 mo *vs* 4.0 mo, $P < 0.001$) (Figure 2A). Following subgroup analysis, survival benefits were observed not only in the surgical treatment group (TACE + resection or transplantation) compared with the localized treatment group (TACE +

Table 2 Objective response and disease control rate *n* (%)

	Objective response	Non-response	Disease control	Progressive disease
Treatment group (n = 102)	29 (28.4)	73 (71.6)	60 (58.8)	42 (41.2)
Conservative group (n = 20)	0 (0)	20 (100)	3 (15)	17 (85)
P value	0.003		< 0.001	

Evaluation of tumor response was not possible in 17 (14.3% within treatment group) and 7 (25.9%, within conservative group) out of 146 patients.

Table 3 Estimated 6-, 12-, 18- and 24-mo survival rate

	6 mo	12 mo	18 mo	24 mo
Treatment group, total (n = 119)	72.0%	43.0%	28.2%	23.5%
Surgical treatment (n = 17)	88.2%	76.5%	64.7%	64.7%
Localized treatment (n = 102)	69.3%	37.3%	22.0%	16.4%
Conservative group (n = 27)	18.5%	3.7%	0%	0%
P value	< 0.001	< 0.001	< 0.001	< 0.001

RFA, PEI or radiotherapy) (median of 31.6 mo *vs* 9.1 mo, $P < 0.001$) (Figure 2B) but also in the combination treatment group (TACE + other modalities) compared with the TACE-only group (median of 12.8 mo *vs* 8.1 mo, $P = 0.002$) (Figure 2C). The estimated survival rates at 6, 12, 18, and 24 mo were 72.0%, 43.0%, 28.2%, and 23.5%, respectively, for the treatment group, whereas the estimated 6- and 12-mo survival rates were 18.5% and 3.7% for the conservative group (Table 3).

Univariate analysis revealed the following 4 potential prognostic factors related to survival among the baseline characteristics in the treatment group: age ($P = 0.062$), tumor type ($P < 0.001$), portal vein thrombosis ($P < 0.001$), and tumor stage ($P < 0.001$). Upon multivariate analysis, tumor type [hazard ratio (HR) = 1.849; 95%CI: 1.165-2.934, $P = 0.009$] and stage (HR = 2.828; 95%CI: 1.740-4.595, $P < 0.001$) were identified as independent factors for survival (Table 4). Multivariate analysis for identifying the influences of treatment response and treatment modality revealed that objective response (HR = 2.870; 95%CI: 1.678 - 4.910, $P < 0.001$), surgical treatment (HR = 2.301; 95%CI: 1.227-4.317, $P = 0.009$), and multi-modality (HR = 1.835; 95%CI: 1.242-2.714, $P = 0.002$) were also independent factors for survival (Table 5).

Subgroup analysis of baseline characteristics in the treatment group

Because the surgical treatment significantly influenced patient survival, we compared the baseline characteristics between the surgical treatment group and non-surgical treatment group (Table 6). There were no statistically significant differences between two groups. However, the surgical treatment group tended to have more favorable prognostic factors, such as well-demarcated tumors, no PVT, and lower tumor stage ($P = 0.051$, $P = 0.094$, and $P = 0.071$, respectively).

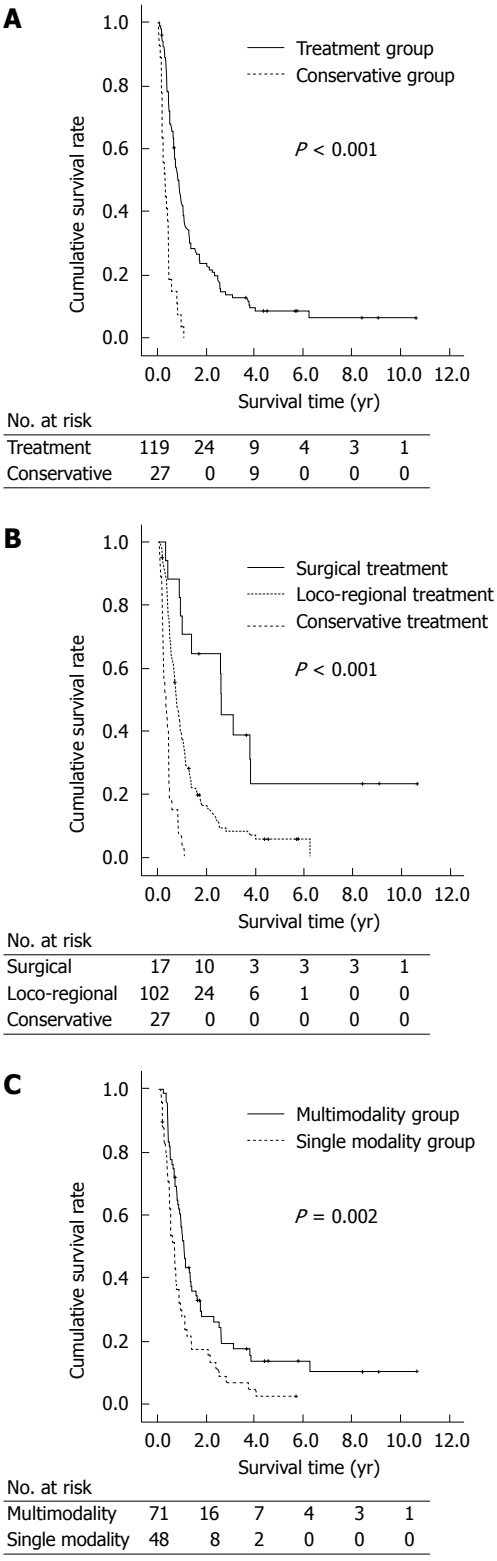

Figure 2 Overall survival according to the Kaplan-Meier method. Significantly better overall survival rates were observed in the treatment group compared with the conservative group ($P < 0.001$) (A), in the surgical treatment group compared with the loco-regional treatment group ($P < 0.001$) (B), and in the multi-modal treatment group compared with the single modality group ($P = 0.002$) (C).

Table 4 Pre-treatment prognostic factors for survival in the treatment group

Factors	Univariate analysis			Multivariate analysis		
	HR	95%CI	*P* value	HR	95%CI	*P* value
Age (< 60 yr *vs* ⩾ 60 yr)	0.634	0.393-1.023	0.062			
Gender (female *vs* male)	0.768	0.373-1.584	0.475			
Child-Turcotte-Pugh score (5 *vs* 6)	1.292	0.839-1.990	0.245			
AFP (< 1000 ng/mL *vs* ⩾ 1000 ng/mL)	1.346	0.914-1.982	0.132			
Maximal tumor size (< 15 cm *vs* ⩾ 15 cm)	1.342	0.842-2.140	0.216			
Tumor type (well-demarcated *vs* poorly-demarcated)	2.689	1.721-4.203	< 0.001	1.849	1.165-2.934	0.009
Portal vein thrombosis (absent *vs* present)	2.430	1.519-3.888	< 0.001			
Stage (Ⅲ *vs* Ⅳ-A)	3.344	2.108-5.304	< 0.001	2.828	1.740-4.595	< 0.001

AFP: Alpha-fetoprotein.

Table 5 Treatment-related prognostic factors in the treatment group

Factors	Univariate analysis			Multivariate analysis		
	HR	95%CI	*P* value	HR[1]	95%CI	*P* value[2]
Objective response (present *vs* absent)	3.591	2.129-6.056	< 0.001	2.87	1.678-4.910	< 0.001
Surgical treatment (yes *vs* no)	2.9	1.634-5.147	< 0.001	2.301	1.227-4.317	0.009
Multimodality (yes *vs* no)	1.743	1.198-2.536	0.004	1.835	1.242-2.714	0.002

[1]Adjusted HR for tumor type and stage; [2]*P* for adjusted hazard ratio.

Table 6 Comparison of baseline characteristics between the surgical treatment group and the non-surgical treatment group *n* (%)

Variables	All (*n* = 119)	Surgical treatment group (*n* = 17)	Non-surgical treatment group (*n* = 102)	*P* value
Age (yr)	52 (30-77)	52 (30-74)	51.5 (32-77)	0.814
Gender, male	111 (93.3)	15 (88.2)	96 (94.1)	0.320
Etiologies (*n*)				0.704
HBV/HCV/Alcohol/others	95/4/7/13	12/1/1/3	83/3/6/10	
AFP (ng/mL)	471.2 (0.7-5719.0)	261.8 (0.7-5719.0)	603.6 (1.9-5102.0)	0.879
Maximal tumor size (cm)	12 (10.0-20.0)	12(10.0-16.0)	12 (10.0-20.0)	0.904
Tumor type				0.051
Well-demarcated	82 (68.9)	15 (88.2)	67 (65.7)	
Poorly-demarcated	37 (31.1)	2 (11.8)	35 (34.3)	
Location of main tumor				0.085
Left	18 (15.1)	5 (29.4)	13 (12.7)	
Right	101 (84.9)	12 (70.6)	89 (87.3)	
PVT				0.094
Present	89 (74.8)	10 (58.8)	79 (77.5)	
Absent	30 (25.2)	7 (41.2)	23 (22.5)	
Stage, modified UICC				0.071
Stage Ⅲ	53 (44.5)	11 (64.7)	42 (41.2)	
Stage Ⅳ-A	66 (55.5)	6 (35.3)	60 (58.8)	

HBV: Hepatitis B virus; HCV: Hepatitis C virus; AFP: Alpha-fetoprotein; PVT: Portal vein thrombosis; UICC: Union for International Cancer Control.

Treatment-related toxicity

Grade 3 and grade 4 treatment-related toxicities were investigated in the treatment group. The most common G3-4 toxicities were serum transaminase elevation (45.4%) and gastrointestinal toxicity, such as nausea, vomiting and anorexia (29.4%), jaundice (26.9%), neutropenia (23.5%), thrombocytopenia (16.0%), and anemia (14.3%). However, the toxicities were transient and successfully managed using conservative treatment. In addition, there were no significant life-threatening adverse effects related to the treatment.

DISCUSSION

Although the surveillance program for high-risk patients has improved the early detection of HCC and decreased tumor-related mortality[14], a substantial proportion of patients present with a large HCC (⩾ 10 cm diameter)[6]. The prognosis of large HCC is very poor because tumor size is a significant risk factor for vascular invasion and intra- and extra-hepatic spreading[15-17]. In patients with large HCC, surgical resection or TACE are the generally accepted treatment options. The BCLC guidelines recommend sorafenib

for the treatment of advanced HCC patients with PVT. However, despite recent advances in treatment, it is unclear which option is the optimal treatment modality for these patients. In this study, we showed that TACE-based treatments confer survival benefits to patients with large HCC ($P < 0.001$). Moreover, combination therapy with TACE and an additional treatment was associated with a better outcome than that of TACE alone, especially in cases of curative resection or liver transplantation ($P < 0.001$).

The BCLC staging system includes multiple variables affecting the course of HCC and treatment response, including liver function, performance status, cancer-related symptoms and tumor stage[2,3]. In addition, it assigns each stage with a survival rate and a treatment algorithm. However, this staging system not only fails to suggest an appropriate combination treatment strategy but also does not provide suggestions on salvage therapy, because it only recommends a single treatment option as the first line of therapy at each stage. Because of the heterogeneity in presentation and diversity of patient responses to therapy, no single treatment strategy can be applied to all patients, and multimodal treatment is required to manage HCC patients in clinical practice. Many studies supporting a multimodal treatment approach for HCC have been performed, particularly with TACE. The combination therapy with TACE and percutaneous ablation, such as PEI or RFA, has been shown to be superior to TACE alone or percutaneous ablation therapy alone[18-20]. Some studies have also shown that combination therapy with TACE and radiotherapy improves patient survival, compared with TACE alone[21,22]. Recently, substantial numbers of clinical trials assessing the efficacy of sorafenib in combination with TACE have been completed or are currently underway[23-25]. However, it is still unclear whether multimodal treatments provide better outcomes in patients with large HCC because few studies have been performed on this group, and no randomized controlled studies have been conducted. In this study, we showed that TACE-based therapy improved patient survival compared with supportive care in patients with large HCC ($P < 0.001$), and combination therapy with TACE and an additional treatment modality prolonged overall survival compared with that of TACE alone ($P < 0.001$) (Figure 2). In addition, multi-modal treatment was identified as a significant prognostic factor by multivariate analysis ($P = 0.002$) (Table 5). Although TACE procedure has the risk of severe complications, such as hepatic arterial occlusion, liver abscess, and spontaneous rupture of tumor[26], there were no serious complications observed in this study. These results suggest that TACE-based treatment may be safe and effective and that multimodal treatment is associated with better prognosis in patients with large HCC and preserved liver function.

Surgical resection is the mainstay of treatment for resectable tumors. Recently, Min *et al*[27] reported that surgical resection is associated with better outcomes than TACE in patients with large HCC ($\geqslant$ 10 cm). However, a substantial proportion of large HCC are unresectable because of intrahepatic or extrahepatic metastasis or the risk of post-operative hepatic dysfunction. The treatment of these unresectable HCCs is mainly palliative, aiming to relieve symptoms, and if possible, prolong survival. With improvements in regional and systemic therapies, some treatments that originally aim at palliation can downstage tumors from unresectable to resectable. Although the downstaging of HCC prior to hepatic resection has not been widely investigated, some previous studies have shown that successful downstaging can improve patient prognosis[28-30]. The tumor downstaging strategy has been studied more frequently in association with liver transplantation than resection. The use of successful downstaging therapy in patients with HCC exceeding the accepted transplant criteria has revealed excellent post-transplant results[31-33]. In addition, patients who received surgical treatment after downstaging using TACE had significantly longer survival than those who received TACE with loco-regional treatment in this study ($P < 0.001$), and surgical treatment was an independent prognostic factor for survival ($P = 0.009$). In practice, multimodal treatment including surgical treatment prolonged the survival time over 10 years in a representative example (Figure 3). These results suggest that salvage surgery after successful downstaging leads to better outcomes in patients with large, unresectable HCC. Therefore, clinicians should attempt downstaging in these cases using aggressive treatment and a multimodal strategy and consider surgical treatment, such as resection or transplant, as an option if downstaging is successful.

As HCC treatments have been developed, novel transarterial approaches, such as TACE with drug-eluting beads (DEB) or transarterial radioembolization (TARE), have been introduced. Recent studies have reported that the use of TACE with DEB leads to better outcomes compared with conventional TACE in the treatment of patients with advanced HCC[34,35]. In addition, TARE appears to be safe in the treatment of more advanced disease, including portal vein invasion and large HCC[36,37]. These modalities were not included as a treatment option in this study. However, considering the advantages of these transarterial treatments, multimodal strategies using these approaches are also expected to provide benefits to patients with unresectable HCC, and further prospective studies are necessary.

This study had some limitations. First, a retrospective design was used, which could have led to selection bias. However, we consecutively enrolled patients during the study period, and there were no significant differences between the treatment group and conservative group. Second, the combination therapies used in the TACE-based treatment group included heterogeneous modalities, such as sys-

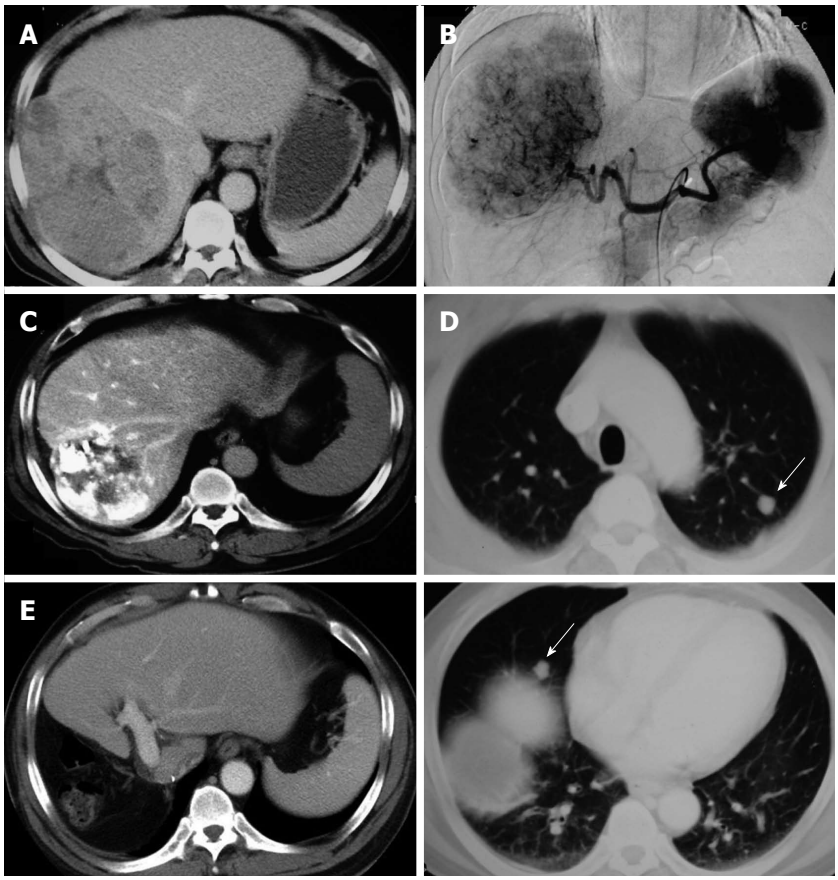

Figure 3 Representative example of multi-modal treatment. A: A 46-year-old male patient had a large hepatocellular carcinoma measuring 11 cm in diameter in the right hepatic lobe; B: TACE was performed; C: After 6 sessions of TACE, 7 sessions of PEI, 6 cycles of systemic chemotherapy, and external radiation therapy, the tumor mass was remarkably reduced; D: After right hepatectomy, 2 cycles of adjuvant chemotherapy were administered. However, two metastatic nodules occurred, one in each lung without hepatic recurrence at 5 mo after right hepatectomy (arrow); E: Wedge resection for metastatic lung nodules was performed, and no hepatic and pulmonary recurrences were observed until 12 years after hepatectomy and metastasectomy (arrow). TACE: Transarterial chemoembolization; PEI: Percutaneous ethanol injection.

temic chemotherapy, RFA, PEI, and radiation therapy. Moreover, some patients who achieved successful downstaging received surgical resection or transplantation. Although these additional treatments used in combination with TACE resulted in better outcomes, this study may have been inherently biased due to the heterogeneous treatments. Thus, prospective studies are necessary to resolve this issue. Third, patients who were treated with sorafenib, which is a molecular-targeted agent, were not included in this study. We included a substantial number of patients with advanced HCC (BCLC stage C). In the BCLC staging system, sorafenib is recommended as a first-line option in advanced stage HCC[2,3]. However, it was not available during the study period in Korea, and consequently, it could not be used as a treatment option in this study. Although sorafenib has been proven to improve survival in randomized controlled trials, its therapeutic advantages are modest[38,39]. Thus, many clinical trials of combined loco-regional treatment and sorafenib have recently been conducted to improve patient outcome[25,40].

In conclusion, TACE-based treatment in combination with other modalities was shown to be safe and more beneficial compared with conservative management in patients with large HCC and preserved hepatic function. Multimodal treatment was more effective than that of TACE only, and salvage surgery after successful downstaging achieved promising long-term results, suggesting that it is valuable in the treatment of patients with large, unresectable HCC. These results should be investigated further by prospective randomized controlled trials.

COMMENTS

Background

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide and the third most common cause of cancer mortality. Although the Barcelona Clinic Liver Cancer staging system has been validated extensively, a heterogeneous population of patients with intermediate or advanced stage HCC has consistently raised issues in clinical practice. In addition, because multiple variables affect the clinical course of HCC, no single treatment strategy can be applied to all patients.

Research frontiers

Transarterial chemoembolization (TACE) is known to improve the survival of patients with unresectable HCC, compared to those who receive supportive treatment. Although TACE is typically contraindicated in advanced HCC patients with portal vein invasion (PV), it has been suggested that TACE can be safely performed even in those patients with PV invasion. Therefore, it has been

used in patients with advanced HCC with PV invasion as a palliative treatment. However, only a limited number of studies have evaluated the proper treatment and the efficacy of TACE in cases of large HCCs (> 10 cm).

Innovations and breakthroughs

The authors revealed that overall survival and objective tumor response were significantly better in the TACE-based treatment group than in the conservative group. After subgroup analysis, survival benefits were observed not only in the multi-modal treatment group compared with the TACE-only group but also in the surgical treatment group compared with the loco-regional treatment-only group. Tumor stage and tumor type were two independent pre-treatment factors for survival. After adjusting for significant pre-treatment prognostic factors, objective response, surgical treatment, and multi-modal treatment were independent post-treatment prognostic factors.

Applications

In cases of advanced HCC, clinicians should attempt downstaging using aggressive treatment and a multimodal strategy and consider surgical treatment, such as resection or transplant, as an option if downstaging is successful.

Terminology

Multimodal treatment is a treatment strategy that combines various techniques, either as the first-line therapy or as a second-line approach after the failure of a monotherapy.

Peer-review

The authors present an important, retrospective study on the outcome of TACE in 146 patients with large HCC, defined as > 10 cm tumor diameter. Most patients underwent multimodal treatment, and a small subgroup could be downstaged to receive salvage surgery or transplantation.

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