Diffuse infiltrative hepatocellular carcinoma: analysis of response and prognostic factors influencing survival after transcatheter arterial chemoembolization

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Purpose

Hepatocellular carcinoma (HCC) is one of the most common cancers in the world, with its incidence increasing in the industrialized countries (1). The extensive ultrasound screening programs have helped detect HCCs at an early stage that are amenable to various treatment options such as hepatic resection, percutaneous ethanol injection, and thermoablation. Although those curative treatment options are known to improve survival, they can be carried out in only 30% of patients with HCCs (2).

Treatment of infiltrative HCCs are challenging because of following reasons: i) most patients with infiltrative HCCs present with advanced disease because infiltrative HCC may be difficult to diagnose given that it commonly lacks a well-demarcated boundary on cross-sectional imaging and can thus blend into the background of the cirrhotic liver (3,4), ii) it is difficult to evaluate the tumor extent within the liver due to poorly-delineated tumor boundary, and iii) because of its large, diffuse nature and propensity to involve the portal vein, diffuse infiltrative HCC may be difficult to treat and treatment may increase the risk of serious complications (5). Therefore, treatment options for patients with diffuse, infiltrative HCCs are limited and data on the presentation, treatment, and outcome of patients with infiltrative HCCs are not well characterized (5).

Transcatheter arterial chemoembolization (TACE) has been considered for certain patients with unresectable HCC for palliative purposes (6). Previous studies have clearly shown the survival benefit for certain patients with unresectable HCC who undergo chemoembolization (7,8). However, the safety and efficacy of TACE for diffuse, infiltrative HCC are not well studied (5). In this study, We evaluated the tumor response, survival period, and the factors associated with survival after TACE in patients with infiltrative HCC.
Methods and Materials

Patient Characteristics

Our institutional review board approved this retrospective study. The medical and imaging records of the patients enrolled in this study were thoroughly reviewed. Between January 2007 and January 2010, a total of 52 patients with infiltrative HCCs underwent TACE in our institution. There were 43 men and nine women with ages ranging from 39-73 years (mean 56 y ± 9). Most of these patients (88%) had underlying liver cirrhosis diagnosed on imaging. Hepatitis B surface antigen was positive in 48 patients. The criteria for the diagnosis of HCCs were based on the guidelines of the American Association for the Study of Liver Diseases (9). The number of patients in classes A and B, referring to the degree of liver function according to the Child-Pugh class, was 22 and 30, retrospectively. The dominant tumor size ranged from 7-22 cm (mean 14.6 ± 3.5 cm) in maximal dimension before the initial treatment. Portal vein invasion (main, lobar, or segmental) was observed in 46 patients (88%). According to the AJCC staging system (10), the number of patients in stage IIIA, IIIB, IIIC, IVA, and IVB were 3, 38, 2, 3, and 6.

Transcatheter Arterial Chemoembolization

Superior mesenteric and common hepatic angiographies were performed to assess the vascular anatomy, vascularity of the tumor, tumor extent and portal vein patency. Following selective cannulation of the right lobar, left lobar, or proper hepatic artery using a microcatheter, 0.5 mg/mL of cisplatin, dissolved in distilled water, was infused into the hepatic artery according to the location of tumor for 15 minutes. The infused dose of cisplatin was 2 mg/kg (4 mL/Kg) of the patient's weight. Then, an emulsion of iodized oil (Lipiodol, Laboratoire Guerbet, Cedex, France) and cisplatin were infused into the segmental feeding artery, followed by embolization with 1mm diameter absorbable gelatin sponge particles (Gelfoam; Upjohn, Kalamazoo, MI, USA) until arterial flow stasis was achieved.

Follow-up

Radiotherapy was planned after the identification of portal vein tumor thrombosis at initial presentation or follow-up imaging after TACE and was started 2-3 weeks after TACE. The decisions of additional radiotherapy after TACE were based on patient and physician preferences at the time. Follow-up CT was performed 1 month after each TACE session to assess tumor response to treatment and to allow a timely decision on subsequent treatment. Tumor response was classified into four grades (complete response, partial response, stable disease, and progressive disease) according to the European Association for the study of the Liver (EASL) criteria, as previously described (11,12). Repeat TACE was indicated when there were new tumors, when there was tumor...
growth, or when residual tumor was detected. Treatment was terminated if the patient could not tolerate the procedure because of a decline in clinical status.

**Evaluation of Data**

Tumor response was categorized as regression, including complete response and partial response, or nonregression, including stable and progressive disease. Mortality resulting from TACE was defined as death within 30 days from the time of TACE. According to the SIR reporting standards (13), we defined major complications as any event that results in additional treatment including an increased level of care, hospital stay beyond observation status (including readmission after initial discharge), permanent adverse sequelae including substantial morbidity and disability, and death. All other complications were classified as minor. The overall patient survival was measured in months from the time of the first chemoembolization.

The following prognostic factors for patient survival were evaluated: age, sex, tumor size, Child-Pugh class, alphafetoprotein (AFP) level, additional radiotherapy for portal vein tumor thrombosis, and tumor response. Tumor size and serum AFP level were dichotomized into two groups on the basis of the median values.

**Statistical analysis**

Statistical analysis was conducted using SPSS software (version 18.0; SPSS, Inc, Chicago, Illinois). We used $\chi^2$ to determine whether there was any difference in the major complications rate according to the Child-Pugh class. The cumulative survival curves were created according to the Kaplan-Meier method and were compared with the results of the log-rank test. Univariate and multivariate Cox regression analysis was performed to assess factors associated with patient survival. We included significant factors or factors that showed a trend toward statistical significance in a multivariate model ($P < 0.1$) in the univariate analysis.
Results

Complications and tumor response after TACE

The median number of treatment sessions was 2 per patient (range 1-17 sessions). Postembolization syndrome developed in 19 of the 52 study patients (37%), although it resolved within seven days with no treatment. Chemoembolization-related major complications occurred in nine (17%) patients. The major complications rate was significantly higher in patients with Child-Pugh B (25.8%, 8/31) than in patients with Child-Pugh A (4.7%, 1/21) (P = 0.049). Acute renal failure occurred in four patients, although these patients eventually recovered after medical treatment. Hepatic failure manifested by encephalopathy or ascites or both occurred in four patients. Hepatic abscess occurred in one patient and was successfully treated by percutaneous drainage and antibiotic therapy. One patient with Child-Pugh class B died within 30 days from the time of chemoembolization because of postchemoembolization-related hepatic failure. The patient mortality rate was 2% (1 of 52).

Tumor response evaluation after TACE was possible in 49 patients (94%, 49/52). After TACE, no patient showed complete response, 9 patients (18%, 9/49) showed partial response, 23 patients showed stable disease (47%, 23/49), and 17 (35%, 17/49) patients showed progressive disease despite the therapy. Objective tumor regression (#partial response) was achieved in 9 patients (18%, 9/49) after TACE.

Follow-up and Patient survival

Thirty-two of the 52 study patients (62%) were treated using additional radiation therapy for PVT after TACE. During the follow-up period (mean, 10.1 months), 50 patients died and 2 remained alive, with the median patient survival period being 5.7 months. The patient survival rates were 48% at 6 months, 25% at one year, and 12% at two years after chemoembolization (Fig 1).
Fig. 1: The graph shows the overall cumulative survival rates in all 52 patients with infiltrative hepatocellular carcinomas.

References: Radiology, Asan medical center - Seoul/KR

Factors Associated with Patient Survival

The following variables of P < .1, as seen on univariate analysis, were entered into the multivariate Cox regression model: Child-Pugh class; tumor response; adjuvant radiation therapy after TACE. Multivariate analysis also confirmed that, the Child-Pugh class (P = 0.02), adjuvant radiation therapy after TACE (P = 0.003), and tumor response after TACE (P = 0.004) were significant factors associated with patient survival after TACE (Table 1). The Kaplan-Meier curves determined with these three factors are shown in Figure 2~4.
Table 1: Multivariate Cox Regression Analysis of the Prognostic Factors for the Patient Survival Period

<table>
<thead>
<tr>
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Fig. 2: The Kaplan-Meier curves show the patient survival rates according to the Child-Pugh classification. The median survival period was 10.0 months for patients with
Child-Pugh class A disease and 3.4 months for patients with Child-Pugh class B or C disease (P = .001).

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**Fig. 3:** The Kaplan-Meier curves show the patient survival rates according to the adjuvant radiation therapy after TACE. The median survival period was 8.0 months for patients who underwent adjuvant radiation therapy after TACE and 2.2 months for patients who did not undergo adjuvant radiation therapy after TACE (P < .001).

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Fig. 4: The Kaplan-Meier curves show the patient survival rates according to the tumor response. The median survival period was 9.7 months for patients with partial response, and 7.3 months for patients with stable disease, and 2.7 months for patients with progressive disease.

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Conclusion

Infiltrative HCC is defined as a subtype of liver cancer that presents as an ill-defined, diffuse lesion. It is known to comprise 7 to 13% of HCCs (4,14). Since infiltrative HCC almost always manifests as an extensive, diffuse tumor, there are few treatment options other than TACE. For fear of hepatic failure and grave prognosis due to poor hepatic reserve, TACE has been regarded as a strong relative contraindication for infiltrative HCC (15). For this reason, although TACE is generally accepted as the only available treatment option, the efficacy of TACE on infiltrative HCC has rarely been studied. However, Kenuertz et al (5) and Jang et al (16) have recently reported that TACE is both safe and feasible in select patients with infiltrative HCC.

In our study, the median survival of 52 eligible patients was 5.7 months. The 1-year survival rate was 25% and the 2-year survival rate was 12%. The results were quite comparable to those reported by Jang et al (16) (median survival, 5.4 months, survival rate at 1 year, 29.4%, survival rate at 2 year, 15.9%). Approximately 60% of patients showed partial or stable disease after TACE. There was only 1(2%) patient who died within 30 days of TACE, which was very similar to the peri-procedural mortality of 2.1% reported by Kenuertz et al (5). Our data demonstrated that TACE was well-tolerated in patients with infiltrative HCC and could prolong patient survival.

Our multivariate analysis showed that tumor response (PR vs SD, odd ratio [OR] 1.869, SD vs PD odd ratio [OR] 4.991, p=0.004), hepatic reserve (Child-Pugh class B, odds ratio [OR] 2.138, p=0.02) and adjuvant radiation therapy after TACE (odd ratio [OR] 0.358, p=0.003) were significant independent prognostic factors for patient survival. We discovered that patients with either partial or stable disease had a better survival rate than in those with progressive disease. In the same context as recent reports (16), our study suggested that poor hepatic reserve was associated with poor patient survival.

Once portal vein thrombosis on initial or follow-up imaging is detected, adjuvant radiotherapy may be considered. The rationale for the combined therapy was that PVT-focused adjuvant radiotherapy in patients with advanced HCC may decrease intravascular tumor growth and maintain portal flow, preserving the liver function, inhibiting intrahepatic tumor spread, and thus allowing additional TACE (17-19). Yoon et al. found that adjuvant radiation therapy combined with TACE offers a safe and feasible treatment option for advanced HCC with portal vein tumor thrombosis (20). In their report (20), median survival period after combination of TACE and radiotherapy for 412 HCC patients with portal vein tumor thrombosis was 10.6 months. In the current series, 32 patients (62%, 32/52) in total received additional radiotherapy and these patients showed better survival rate (median survival period: 8 months) than those who did not (2.2 months). Thus, we suggest that this combined approach provides a survival benefit in patients with infiltrative HCC, given that majority of patients with infiltrative HCCs may
have combined portal vein tumor thrombosis and radiotherapy may be effective to treat portal vein tumor thrombosis (20).

When a physician encounters patients with infiltrative HCCs, fear of a severe post-procedural complication arising from extensive tumor necrosis may be an obstacle to aggressive treatment (15). In deed, in the current study, TACE-related major complications developed in 9 patients (17%), which was higher than that (3%) of previous study reporting results of TACE for 362 patients with HCCs (6). The complication rate in the current study was comparable to 12.5% of previous study (16) reporting results of TACE in patients with infiltrative HCC. However, the majority of TACE-related complication occurred in patients with poor hepatic reserve in the current study: the major complications rate was significantly higher in patients with Child-Pugh B (25.8%, 8/31) than in patients with Child-Pugh A (4.7%, 1/21) (P = 0.049). Thus, we believe that TACE can be safely performed in infiltrative HCC patients with good hepatic reserve as the initial treatment.

The limitations of the current study include inclusion of patients treated at only a single center, the lack of a control group, and the retrospective nature of the work. Prospective randomized study evaluating safety and efficacy of TACE for infiltrative HCC would be required in the future.

In conclusion, TACE may be well tolerated and may be effective to prolong survival of infiltrative HCC patients with preserved liver function. In addition, combination of TACE and radiation therapy may provide a survival benefit in patients with infiltrative HCC.
References


Personal Information

Corresponding author: Jin Hyoung Kim, M.D.

Department of Radiology and Research Institute of Radiology, University of Ulsan College of Medicine, Asan Medical Center, 86 Asanbyeongwon-Gil, Songpa-Gu, Seoul 138-736, Korea

TEL: 82-2-3010-4384

FAX: 82-2-476-0090

E-mail address: m1fenew@daum.net