原　　著

EFFICACY OF A COMBINATION OF TRANSARTERIAL CHEMOEMBOLIZATION AND RADIATION THERAPTY FOR PATIENTS WITH HEPATOCELLULAR CARCINOMA INELIGIBLE FOR RESECTION OR RADIOFREQUENCY ABLATION

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Abstract

Purpose: The local control rate of trans-arterial chemoembolization (TACE) for the patients with hepatocellular carcinoma (HCC) was unsatisfactory compared to resection or radiofrequency ablation (RFA). To increase the local control rate for tumors, we performed radiation therapy followed by TACE in our institution. The purpose of this study was to evaluate the efficacy and toxicity of the TACE and radiotherapy combination in HCC patients ineligible for resection or RFA.

Material and Methods: Between January 2017 and April 2020, 33 patients with HCC ineligible for resection or RFA were treated with a combination of TACE and radiation therapy. Eight patients were initial cases, and 25 were recurrent or residual cases. A total dose of 40–60 Gy in 5–20 fractions was delivered to the 50–90% isodose line.

Results: The median follow-up period was 16 months (range, 6-47 months); the objective response rate was 66.7%; and the 1- and 2-year overall survival rates, 72.7% and 62.5%, respectively. The objective response rate for HCCs <5 cm was 79.2%; the 1- and 2-year overall survival rates, 91.7% and 62.5%, respectively; median progression-free survival, 13.5 months (range, 3-47 months), and the 1- and 2-year local progression-free survival rates, 95.8% and 85.7%, respectively. There was one case each of grade 2 radiation esophagitis and ascites after three months of irradiation.

Conclusion: The combination of TACE and radiation therapy shows good local control and acceptable toxicity, particularly in HCCs <5 cm and may be a good treatment option.

Key words: hepatocellular carcinoma, radiation therapy, stereotactic body radiotherapy, transarterial chemoembolization, radiofrequency ablation, treatment outcome

Introduction

Transarterial chemoembolization (TACE) is indicated when patients with hepatocellular carcinoma (HCC) are ineligible for resection and local radiofrequency ablation (RFA) [1,2]. However, the local control rate of TACE was inferior to that of resection and RFA [3,4]. Conversely, radiation therapy (RT) alone is considered to be a supplementary treatment and is used as a part of a multidisciplinary treatment protocol in cases where TACE is considered ineffective. Recently, treatment modalities such as intensity-modulated radiotherapy and image-guided radiation technology have shown advancements, making it possible to irradiate tumors with a definitive treatment dose while sparing the surrounding normal tissue, and high local control rates have been reported. In particular, in the case of relatively small tumors, a high dose of irradiation with stereotactic body radiation therapy (SBRT) is equivalent to surgery or RFA because of its high local control rate [5-9]. However, there is not enough evidence for SBRT to be used in patients with HCC, and whether we should perform SBRT for small HCC tumors is controversial. Thus, SBRT cannot be considered as a standard therapy option.

The present study aimed to evaluate the efficacy and safety of the combination of TACE and radiotherapy for patients with HCC, especially small tumors, ineligible for resection or RFA.

Material and Methods

Patient Characteristics

Overall, 36 patients with HCC unamenable to surgical resection and RFA received RT at our institution between January 2017 and April 2020. Three patients with multiple HCCs or distant metastases were excluded from the study. Finally, 33 patients with solitary HCC treated with TACE and RT were included in this retrospective study.

The diagnosis of HCC was based on the histopathological examination or the characteristic imaging findings of three-phase dynamic computed tomography (CT) scans, such as arterial hyperattenuation and portal hypoattenuation. The study was approved by the ethics committee of our hospital and conformed to the principles outlined in the Declaration of Helsinki. All patients were required to sign informed consent forms before receiving the scheduled combination of RT and TACE.

Treatment Procedure

TACE

The patients underwent TACE with iodized oil (Lipiodol, Guerbet, Tokyo, Japan) 4-8 weeks prior to RT. All TACE procedures were performed by an interventional radiologist with >15 years of experience. TACE was performed through the femoral artery using the Seldinger technique under local anesthesia. We confirmed that there were multiple feeding arteries on angiography; subsequently, a coaxial microcatheter was selectively inserted into all hepatic feeding arteries of a segment or subsegments containing the target tumor. We then administered an iodized oil–epirubicin hydrochloride emulsion (Nihonkayaku, Tokyo, Japan) into the feeders. The volume of iodized oil ranged from 2 to 5 ml. Finally, a small amount of gelatin sponge particles

(G-GSP, Nihonkayaku, Tokyo, Japan) mixed with contrast material was used to induce embolization until the feeding artery flow was completely occluded.

Radiation Therapy

A plain CT scan was performed on all patients 5-7 days after TACE to evaluate the deposition of the lipiodol-epirubicin mixture. If the lipiodol accumulation was not sufficient for the fiducial marker to be placed, 1-3 gold fiducials were implanted percutaneously into the liver at the peripheral lesion of the target tumors. A CT scan was performed three or four weeks later with a slice thickness of 2 mm. Respiratory motion was coordinated by voluntary breath-holding at the end-inspiratory phase, and in all cases, five breath-hold scans were acquired to measure the breathing-related tumor motion on every breath-hold. Daily image guidance was performed using cone-beam CT to localize the target lesion before treatment delivery. The gross tumor volume (GTV) was defined as the tumor volume containing the remains of iodized oil from TACE and early enhancement in the arterial phase of dynamic CT. The clinical target volume (CTV) is usually defined as a 3 mm margin around the GTV. For the internal target volume (ITV), an internal margin of 3–5 mm was added around the CTV according to the movement of the target positions on each breath-hold. For the planning target volume (PTV), a margin of 2 mm was applied around the ITV as a setup margin. Two-arc dynamic conformal radiation (DCA) or volumetric modulated arc therapy (VMAT) was planned using a radiation treatment planning system (Eclipse, version 13; Varian Medical Systems, Palo Alto, CA, USA). Beams of 10 MV X-rays were delivered using a linear accelerator (Clinac iX; Varian Medical Systems, Palo Alto, CA, USA). Only two initial HCC patients received RT with DCA, while 31 patients received RT with VMAT. A total dose of 40-60 Gy was delivered in 5-20 fractions. The doses and fractionation were evaluated by the dose coverage of 50-95% of the volume of the PTV. The dosage was modified depending on the liver function, patient's age, activity in daily life, and normal tissue constraints. Normal tissue constraints were >20 Gy to >20% of the normal liver (liver minus GTV), a maximum exposure limit for a 10-cc area of the esophagus, stomach, and bowel of 25 Gy, and a maximum dose to the spinal cord of <25 Gy.

Evaluation

All patients were examined and underwent follow-up dynamic CT or magnetic resonance imaging (MRI) every 3 to 6 months after SBRT completion. Tumor responses were assessed according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST) [10,11]. Local recurrence was defined as progressive disease (PD) or a new appearance of a lesion within or at the PTV margin in patients receiving SBRT. Toxicity was evaluated using the Common Terminology Criteria for Adverse Events, version 5.0. Radiation-induced liver disease was defined as an anicteric elevation in the alkaline phosphatase level of at least twice the upper normal level or elevated transaminase levels of at least 5-fold, without PD and the development of nonmalignant ascites. Acute and subacute toxicities were defined as adverse events occurring within the first 3 and 3–6 months, respectively, after SBRT. Late toxicities related to liver and other toxicities were defined as those occurring within 6–12 months and from 6 months to the last follow-up, respectively.

Statistical Analysis

Survival rates were calculated from the date of the SBRT. Kaplan-Meier survival analysis was used to estimate the overall survival (OS), local progression-free survival (LPFS), and progression-free survival (PFS). SPSS® software (version 19.0; IBM Corp., Armonk, NY) was used for statistical analyses.

Results

The median age was 77 years (range, 51-87 years). Twenty-eight patients were men and five were women. The underlying liver diseases were type C hepatitis for 22 cases, alcoholic hepatitis for 5 cases, and nonalcoholic steatohepatitis for 6 cases. The Child-Pugh classification for liver function was grade A in 30 cases and grade B in 3 cases. Eight patients were initial HCC cases, while twenty-five were recurrent or residual cases. A CT scan performed before treatment showed the diameters of the tumors to be 1.3-14.0 cm with a median of 4.0 cm (Table 1). The median follow-up range in all cases was 16 months (range, 6–47 months). TACE and RT were administered as scheduled treatments to all patients. During treatment planning for RT, lipiodol in the targeted tumor was fully retained in only 16 patients. The median interval between TACE and RT was 5 weeks (range, 4–8 weeks). No patients were lost to follow-up. Of the 33 patients, 24 (72.7%) were still alive. Six months after treatment, all patients underwent dynamic CT/MRI. According to mRECIST, the number of cases with complete response (CR), partial response (PR), stable disease (SD), and PD were 9 (27.3%), 13 (39.4%), 11 (33.3%), and 0 (0%), respectively. The 1- and 2-year OS rates were 72.7% and 62.5%, respectively. The median PFS was 12 months (range, 3-47 months). The 1- and 2-year LPFS rates were 87.3% and 78.7%, respectively.

Table 1. Characteristics of patients with hepatocellular carcinoma (HCC) who received TACE and RT (n = 33)

Gender (male/female)	28/5
Median age, range of years	77 (51-87)
T-stage (T1a/T1b/T2/T3/T4)	3/1/19/3/7
Background:	
Anti-HCV-positivity	22
Alcoholism	5
Nonalcoholic steatohepatitis	6
Child-Pugh score (5/6/7)	24/6/3
Median tumor size; mm (range)	4.0 (1.3-14)
Location (central/liver surface)	20/13
Initial case/recurrent case	8/25
Median total dose (range)	60 (40-60)
Median fraction dose (range)	4 (2-8)

TACE, transarterial chemoembolization; HCV, hepatitis C virus

In the set of tumors under 5 cm, the median follow-up time was 19.5 months (range 6-47 months). Twenty of the 24 patients (83.3%) were still alive. The number of cases with CR, PR, SD, and PD were 9 (37.5%), 10 (41.7%), 11(33.3%), and 5 (20.8%), respectively. The objective response rate

Table 2. Toxicities over grade 2 after the combination of RT and TACE in patients with HCC

	Toxicity: No. of patients (%)			
Toxicities (grade)	Grade 1-2	Grade 3	Grade 4	Grade 5
Transient fatigue	28 (84.8)	0 (0)	0 (0)	0 (0)
Elevated fever	25 (75.8)	0 (0)	0 (0)	0 (0)
Elevated transaminases	10 (30.3)	0 (0)	0 (0)	0 (0)
Hyperbilirubinemia	2 (6.1)	0 (0)	0 (0)	0 (0)
Esophagitis	2 (6.1)	0 (0)	0 (0)	0 (0)
Ascites	1 (3.0)	0 (0)	0 (0)	0 (0)

TACE: transarterial chemoembolization, HCC: hepatocellular carcinoma

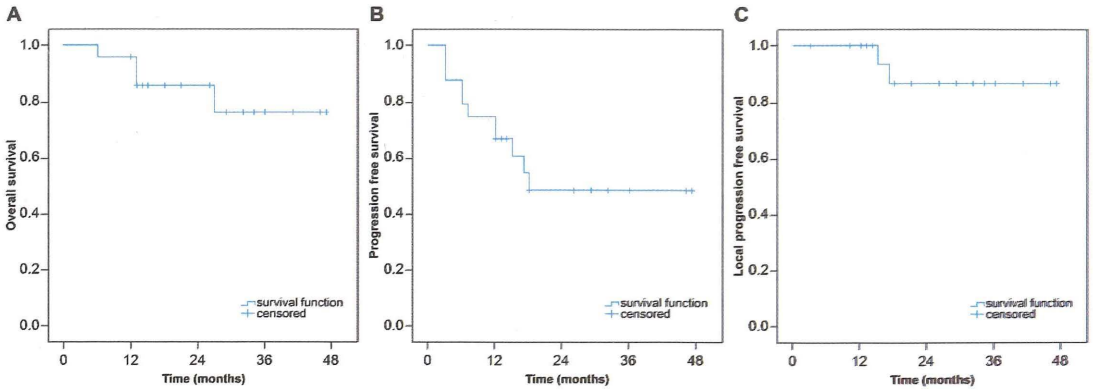

Fig. 1. (A) Kaplan-Meier curve of overall survival (OS) of patients treated with TACE and radiation therapy for HCCs less than 5cm. (B) Kaplan-Meier curve of progression free survival treated with TACE and radiation therapy for HCCs less than 5cm. (C). Kaplan-Meier curve of local progression free survival of patients treated with TACE and radiation therapy for HCCs less than 5cm.

(CR+PR) was 79.2% (19/24). The OS at one and two years was 91.7% and 62.5%, respectively. The median PFS was 13.5 months (range, 3-47 months). The 1 and 2-year LPFS rates were 95.8% and 85.7%, respectively (Fig. 1). During the follow-up period, 17 out of the 33 patients showed recurrence. Local recurrence occurred in only two cases, intrahepatic outfield failure (recurrence in the liver beyond the PTV) occurred in nine cases, and distant metastasis occurred in four cases (Fig 2). A summary of the adverse events is shown in Table 2.

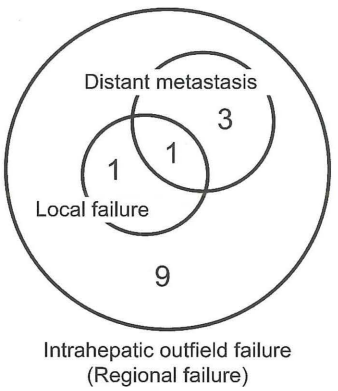

Fig. 2. Patterns of failure for this study are illustrated.

Grade 1 and 2 treatment-related toxicities as a post-embolization syndrome were as follows: fatigue, 28 cases (84.8%); fever, 25 cases (75.8%); increase in alanine aminotransferase (ALT)/aspartate aminotransferase (AST) levels, 10 cases (30.3%); and hyperbilirubinemia; 2 cases (6.1%). One patient had grade 2 radiation esophagitis. No cases of grade 3 radiation-induced gastroduodenal bleeding or perforation were observed. Grade 1 ascites without tumor progression or portal vein tumor thrombus was observed in a single case 3 months after irradiation, which improved with conservative treatment alone. Two cases of portal vein thrombosis were observed 3 months after irradiation. Both cases were asymptomatic and were treated conservatively by administering anticoagulants. The enhanced CT performed 1 month later showed the disappearance of the portal thrombus. None of the cases showed an increase of more than 2 points in the Child-Pugh score. No grade 3-5 adverse events were observed.

Discussion

TACE is often recommended for patients with HCC who are ineligible for resection and RFA and without distant metastases. However, compared to resection or RFA, the treatment results of TACE are unsatisfactory for reasons such as incomplete necrosis. Therefore, to increase the local control rate for tumors, RT is used together with TACE. In cases of inoperable HCC, RT is

performed in addition to TACE. Data showing an improvement in prognosis have been reported in multiple prospective and retrospective studies. The data of survival rates for 1 and 2 years varies from 41.8% to 93.3% and 19.9% to 73.3%, respectively. Several meta-analyses have compiled and reported these data [12-16]. When comparing treatment using only TACE with combined treatment using TACE and RT, the randomized controlled trials showed that the survival rates for 1, 2, 3, and 5 years were higher when TACE and RT were used in combination [17,18]. The total data for all cases used in our study showed that the OS rates for 1 and 2 years were 72.7% and 62.5%, respectively. The median PFS was 12 months (range, 3-47 months). The 1- and 2-year local control (LC) rates were 87.5% and 78.7%, respectively. When looking at the LC rates at 1 year, three of four cases had HCCs >5 cm with portal venous tumor thrombus (PVTT). Among the 25 patients with HCCs <5 cm, there were only four deaths during the median follow-up period of 19.5 months, and 21 patients survived. The OS rate at 1 year was 96%. The LC rates for 1 and 2 years were 96% and 86%, respectively. Several studies on relatively small HCCs treated with SBRT reported an OS rate of 74–100% at 1 year, and an LC of 91–100%, 84–95%, and 92–96%, at 1, 2, and 3 years, respectively. The LC results in the present study were similar to those of other studies.

In this study, the conditions for determining the adaptation of this combination therapy of TACE and radiation therapy for patients with relatively small HCCs (<5 cm) were tumor size (>3 cm) or the tumor location where RFA was not suitable. The unacceptable conditions for RFA are when there is poor ultrasound resolution at sub-diaphragmatic lesions or when there is a high risk of perforation near the portal vein, hepatic vena cava, hepatic vein, caudate lobe, or surface of the liver. Treating these HCC areas with TACE alone has often been the standard therapy. However, most HCCs in these regions have multiple fine feeding arteries, such as the caudate lobe branch or peribiliary plexus from the central lesion of the liver and extrahepatic collateral circulations. Moreover, it seems extremely difficult to achieve complete necrosis of a tumor using TACE alone.

In all the cases in which we considered multiple feeding arteries, and despite the fact that an experienced interventional radiologist performed TACE, there was no case in which a sufficient accumulation of lipiodol emulsion was dispersed throughout the perimeter of the tumor, including the margin lesion. This is not a problem of insufficient skill; rather, a complete embolization can be performed as a result of embolization in a wide area. We believe that TACE alone is not sufficient to control HCC in lesions of the liver for an extended period. We determined that a reasonable approach would be to apply RT after TACE. A high local control rate for small HCCs owing to SBRT has been reported. Thus, we believe that there is a significant advantage in using SBRT in conjunction with TACE. The advantage is in both the reduction of the tumor and the ability to obtain accurate contouring of the tumor. Of these two, accurate contouring is particularly important. In cases of recurrent tumors or PVTT, the effect of previous treatment and the early enhancement in the arterial phase of dynamic CT due to arterial-portal shunt or PVTT can cause difficulties in accurate target contouring on the planning CT. Even with image fusion of the treatment planning CT and dynamic CT/MRI, it is difficult to surpass the method using the accumulation of lipiodol emulsion for accuracy of contouring; therefore, we believe that this advantage is significant.

In our study, the dose per fraction was relatively low compared to that in other reports regarding SBRT for small HCC tumors. According to a majority of these reports, the dose per fraction was 8-10 Gy in 3-6 fractions. In our study, the reason for the low dose per fraction was because the majority of the patients were of advanced age, and most tumors were located adjacent to at-risk organs such as the duodenum, esophagus, and large intestine. Several studies evaluating the effect of SBRT on small HCC tumors have reported a probability of less than 5% for serious adverse events such as gastrointestinal perforation [19-22]. However, in the case of elderly patients and patients with esophageal varices, the occurrence of gastrointestinal toxicities is a serious event that carries a high probability of becoming life-threatening. Therefore, we hesitate to use SBRT with a large dose per fraction, which means that it is difficult to obtain an accurate dose conversion using the linear-quadratic model. In our study, only one patient had grade 3 radiation esophagitis, and this patient was treated with DCA irradiation. Subsequently, when we changed the treatment to VMAT, no grade ≥ 3 gastrointestinal toxicity was observed. Other toxicities, such as fever, fatigue, and liver dysfunction, were observed in most cases following TACE as a post-embolization syndrome. However, all symptoms were transient and treated with conservative therapy. Within 6 months of irradiation, there was no radiation-induced liver disease without tumor progression. The high percentage of patients with relatively good liver function may have contributed to the low toxicities, yet this combination therapy was considered very safe. This study has several limitations. First, this was a retrospective single-center study. Second, the observation time was relatively short. The third and last limitation was the small number of cases.

In conclusion, our current results demonstrate that the combination of TACE and RT for patients with HCC unamenable to surgical resection and RFA achieves promising response, LC rates, and low toxicities, especially for small solitary HCC tumors. A longer follow-up period will be required to confirm these findings. Further prospective studies are needed to investigate the effects of this treatment.

Conflict of interest

The authors report no conflicts of interest. The authors alone are responsible for the content in and writing of the paper.

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