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Transarterial embolization/chemoembolization therapy for hepatocellular carcinoma fed by adrenal artery

Preliminary results

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Abstract

To assess the value of transarterial embolization/chemoembolization (TAE/TACE) therapy via adrenal artery for patients with hepatocellular carcinoma (HCC). Patients with HCC who underwent TAE/TACE therapy via adrenal artery between May 2003 and October 2015 across 4 medical centers were identified. Clinical information, procedural data, and imaging data were analyzed to assess technical success, disease control, and survival rates. A *t* test was used to compare the differences in serum alpha-fetoprotein before and after treatment. A total of 23 patients (23 men; mean age, 54.6 ± 7.5 years; range, 37–72 years) were included in this study. All tumors were located under the capsule of the liver and adjacent to the adrenal gland (median tumor diameter, 8.2 cm). Lesions fed by the adrenal artery were demonstrated during initial TAE/TACE in 7 patients and during repeat TAE/TACE in 16 patients. The superior, middle, and inferior adrenal arteries were involved in 14, 3, and 6 patients, respectively. The technical success rate was 100%. The disease control rate at 3 months was 100%, with partial tumor response seen in 16 (69.6%) patients and stable disease seen in 7 (30.4%) patients. The cumulative survival rate from the time of TAE/TACE was 100% at 1 year. There were no embolization-related complications. TAE/TACE therapy via the adrenal arteries can improve the therapeutic efficacy of TAE/TACE and reduce the incidence of HCC recurrence and/or presence of residual HCC.

Abbreviations: AFP = alpha-fetoprotein, BCLC = Barcelona Clinic Liver Cancer, CT = computed tomography, HCC = hepatocellular carcinoma, MRI = magnetic resonance imaging, TAE/TACE = transarterial embolization/chemoembolization.

Keywords: adrenal artery, hepatocellular carcinoma, transcatheter arterial chemoembolization

1. Introduction

Transarterial embolization/chemoembolization (TAE/TACE) has been widely used in the treatment of unresectable hepatocellular carcinoma (HCC)[1–4]; however, the rates of posttreatment recurrence and/or residual HCC remain high with this technique.[5,6] Recent studies have shown that an extrahepatic collateral pathway to the tumor may play an important role in the recurrence and/or presence of residual HCC, which can limit the effectiveness of TAE/TACE therapy.[7,8] To improve the efficacy of TAE/TACE therapy, these collaterals need to be adequately embolized.[9–16]

Adrenal arteries, including the superior, middle, and inferior adrenal artery, arise from the inferior phrenic artery, aorta, and renal artery, respectively. Although it is rare for HCC to be fed by adrenal arteries, the adrenal arteries can form a collateral pathway to HCC.[17] The value of TAE/TACE therapy via adrenal artery for HCC has not been previously reported. The purpose of this retrospective study was to assess the value of TAE/TACE therapy via adrenal artery for the treatment of HCC.

2. Materials and methods

2.1. Study design

The study was approved by all participating institutional review boards with waivers of informed consent. We performed a retrospective review of consecutive patients with HCC who underwent TAE/TACE therapy via the adrenal arteries at 4 medical centers from May 2003 to October 2015. The diagnosis of HCC was made by needle biopsy or by coincidental contrast-enhanced computed tomography (CT) scan and/or magnetic resonance imaging (MRI) in patients with a history of cirrhosis or chronic hepatitis B/C infection according to American Association for the Study of Liver Diseases guidelines.[18] All the patients with HCC who underwent TAE/TACE therapy via the adrenal arteries were included in this study. Patient demographics, clinical information, and procedural data were gathered from patients' medical records. Imaging data were gathered from the Picture Archiving and Communications System of the 4 institutions.

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2.2. TAE/TACE procedure

TAE/TACE was carried out according to the current practice guidelines.[19] The procedure was performed using a 2.7-Fr microcatheter (Progreat; Terumo, Japan), and lipiodol and polyvinyl alcohol were used as embolic agents. All patients were admitted after the TAE/TACE procedure for postprocedural supportive treatment and to be observed for potential complications. Routine management included hydration, treatment with antiemetics, pain control, and monitoring for liver function changes.

2.3. Clinical follow-up

Clinical follow-up was scheduled on the first, second, and third months after TAE/TACE treatment and every 3 months thereafter. During follow-up, contrast-enhanced CT or MRI was performed, and routine laboratory values were assessed, including complete blood count, liver enzymes, bilirubin level, and serum alpha-fetoprotein (AFP) level.

2.4. Definitions

Technical success was defined as successful catheterization and successful completion of TAE/TACE therapy. The Barcelona Clinic Liver Cancer (BCLC) staging system was used to assess tumor stage, and the modified response evaluation criteria in solid tumors was used to assess tumor response.[20] Disease control rate was defined as the percentage of patients who achieved complete response, partial response, or stable disease.[21] Survival was calculated from the date of first TAE/TACE therapy via adrenal artery for HCC to the date of death or last follow-up. Major complications related to TAE/TACE therapy as defined by the Society of Interventional Radiology[22] included admission to a hospital for therapy, higher level of care required, substantially longer hospital stay (>48 hours) required, and the occurrence of permanent adverse sequelae or death.

2.5. Statistical analysis

All statistical analyses were performed using statistical software SPSS (version 11.5) (Chicago, IL, USA). The values of serum AFP levels were recorded as mean ± SD. A *t* test was used to compare the differences in serum AFP before and after treatment. A *P* value of less than 0.05 was considered statistically significant.

3. Results

3.1. Patients

From May 2003 to October 2015, a total of 23 patients across our 4 institutions underwent TAE/TACE therapy for HCC via adrenal artery. All patients were men, with a mean age of 54.6 ± 7.5 years (range, 37–72 years). Of the 23 patients, 9 were diagnosed with HCC pathologically, and 14 were diagnosed with HCC by imaging (with a history of chronic hepatitis B infection). Seventeen of the patients overall had a history of chronic hepatitis B infection. All 23 patients had BCLC Stage B disease. In all patients, the tumors were located under the capsule of the liver and adjacent to the adrenal gland (median tumor diameter, 8.2 cm). Surgical resection was not attempted because of liver cirrhosis (n = 11) or multiple lesions (n = 12). No patients had previously undergone surgical resection of the HCC.

3.2. Treatments

Lesions fed by the adrenal artery were demonstrated during initial TAE/TACE therapy in 7 patients and during repeat TAE/TACE therapy (mean, 2.3 sessions; range, 2–5 sessions) in 16 patients. TAE/TACE via adrenal artery (right artery, 22 patients; left artery, 1 patient) was performed successfully in all patients, with a technical success rate of 100%. Lipiodol was used as an embolic agent in 20 patients (mean volume, 10.7 ± 3.2 mL; range, 6–20 mL); polyvinyl alcohol was used in the remaining 3 patients. The superior, middle, and inferior adrenal arteries were involved in 14 (60.9%), 3 (13.0%), and 6 (26.1%) patients, respectively (Figs. 1–3).

3.3. Outcomes

During 20.3 ± 7.6 months (range, 12–63 months) of follow-up, the serum AFP level was reduced significantly (from 1120.1 ± 271.1 to 71.3 ± 42.5 g/L; $P < 0.01$) 1 month after treatment in 11 patients whose AFP was higher than 400 g/L before the procedure. The disease control rate was 100% at 3 months, with partial tumor response seen in 16 (69.6%) patients and stable disease seen in 7 (30.4%) patients. The survival rate from the time of TAE/TACE therapy via the adrenal arteries was 100% at 1 year. No embolization-related complications occurred.

4. Discussion

In this study, we found that TAE/TACE via the adrenal artery was performed successfully in all patients, with a technical success rate of 100%, a disease control rate of 100% at 3 months, and a 1-year survival rate of 100%.

Although TAE/TACE is widely used in the treatment of HCC, the necrosis rate for HCC after these procedures is only 90% to 95%.[23,24] Repeat TACE has been associated with the

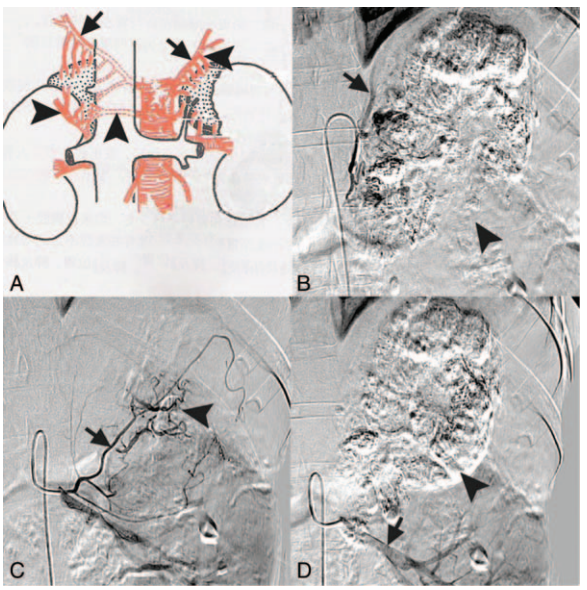

Figure 1. (A) Diagram of the adrenal arteries. The superior adrenal artery (arrowhead) arises from the inferior phrenic artery (arrow), the middle adrenal artery (arrowhead) arises from the aorta, and the inferior adrenal artery (arrowhead) arises from the renal artery. (B) A 49-year-old man presented with a huge hepatocellular carcinoma located in the left lobe of the liver. Defective lipiodol deposition of the tumor (arrowhead) was demonstrated after transarterial chemoembolization (TACE) via the left inferior phrenic artery (arrow). (C) Tumor staining (arrowhead) was demonstrated by inferior adrenal arteriography (arrow). (D) Lipiodol deposition of the whole tumor was identified after TACE via the inferior adrenal artery (arrowhead). Renal arteriography demonstrated that the inferior adrenal artery was occluded after TACE (arrow).

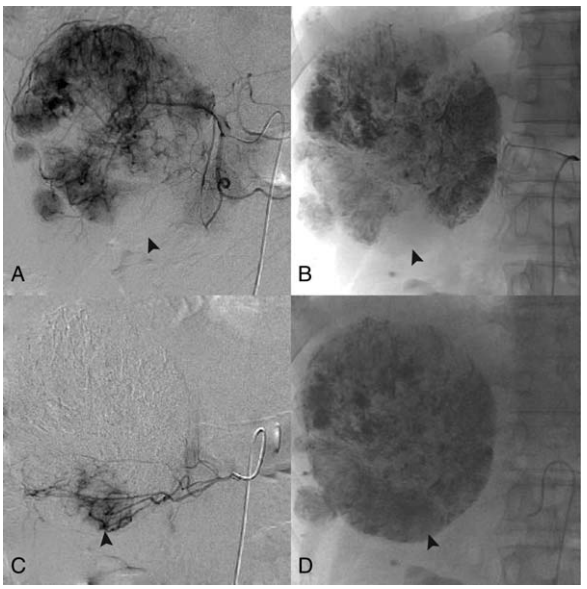

Figure 2. (A) A 57-year-old man presented with a huge hepatocellular carcinoma in the right lobe of the liver. Partial tumor staining was absent during hepatic arteriography (arrowhead). (B) Partial defective lipiodol deposition of the tumor was seen after transarterial chemoembolization (TACE) via the hepatic artery (arrowhead). (C) Tumor staining was demonstrated by middle adrenal arteriography (arrowhead). (D) Lipiodol deposition in the whole tumor was identified after TACE via the middle adrenal arteries (arrowhead).

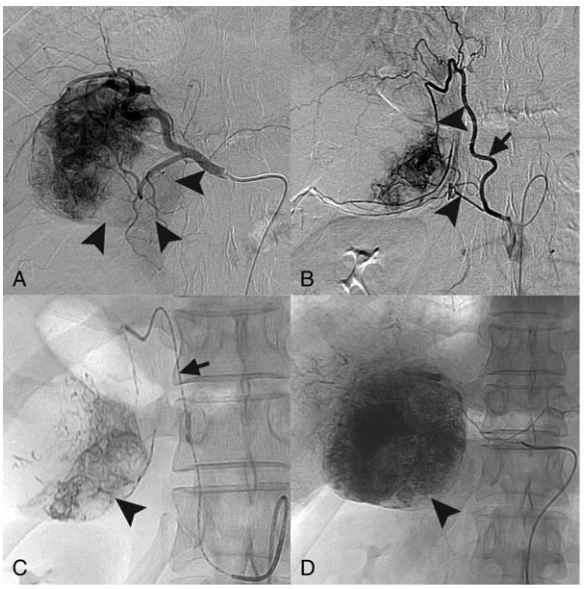

Figure 3. (A) A 67-year-old man presented with an hepatocellular carcinoma in the right lobe. Partial tumor staining was absent during hepatic arteriography (arrowheads). (B) Tumor staining was demonstrated during inferior phrenic arteriography. The superior adrenal artery (arrowheads) arose from the inferior phrenic artery (arrow). (C and D) Superselective transarterial chemoembolization via the superior adrenal artery was performed, and lipiodol deposition in the whole tumor was identified (arrowheads).

development of extrahepatic collateral supplies to the tumor, especially in patients with a tumor located at the margin of the liver.[8] These extrahepatic collateral supplies to the tumor play an important role in the recurrence and/or persistence of HCC and limit the efficacy of TACE.[7,17,25,26]

Various collateral pathways to HCC have been described.[7,17,25,26] Among these, the adrenal artery is known to be an extrahepatic collateral feeder of HCC.[17] In the present study, the right adrenal artery was more commonly involved than the left adrenal artery because of the close anatomic relationship between the right adrenal artery and the HCC. The most common extrahepatic collateral was the superior adrenal artery, which arose in all cases from the inferior phrenic artery.

The risk factors for the development of extrahepatic collateral arteries to the tumor are largely unknown. Research has suggested that these arteries usually develop after interruption of the hepatic artery by surgical ligation and/or arterial injury induced by repeat TAE/TACE procedures.[27] The development of extrahepatic arteries has also been linked with the anatomic location of the tumor for cases in which the hepatic arterial supply remains intact.[10–13,17,26] Adhesion between the liver and other organs exaggerates the degree to which extrahepatic collaterals develop.[10,17,28] In the present study, extrahepatic adrenal arteries were observed during initial TAE/TACE treatment in 7 patients and during repeat TAE/TACE treatment in 16 patients. All of the tumors were located under the capsule of the liver and adjacent to the adrenal gland, which may have induced the formation of these adrenal arteries supplying the tumor.

Superselective catheterization is critical for delivering chemotherapeutic agents to the target tumor and avoiding complications. Remarkable advances have been made in coaxial catheter systems, and the technical success rate of superselective collateral catheterization has also improved. In such cases, once the adrenal artery is selected, further selection of the tumor feeding artery is not difficult with a 2.7-Fr microcatheter and soft-tipped 0.014/0.018-inch guide wire.[29] It is also important to place the catheter into the most distal portion of the tumor feeding branch to avoid nontarget embolization; otherwise, complications can occur. In our study, the adrenal arteries all underwent superselective catheterization and embolization with a 2.7-Fr microcatheter, and there were no embolization-related complications.

In this study, the serum AFP level was significantly reduced 1 month after TAE/TACE therapy, and the disease control rate at 3 months was 100%, with partial tumor response reported in 69.6% of patients and stable disease reported in 30.4% of patients. However, prospective randomized clinical trials with large sample sizes and long-term follow-up are needed to validate these results.

The major limitation of this retrospective study was its retrospective nature. In addition, risk factors for the development of extrahepatic collateral arteries to the tumor could not be analyzed in this study because of the small patient population. The observation time was short, and all of the patients included in this study were men, which may have biased the results. Furthermore, there was no direct comparison between patients with and those without a collateral feeding adrenal artery.

Considering the results of this study and previous research, we offer several recommendations. First, several findings should prompt the performance of a selective extrahepatic collateral arteriogram, including a hypertrophied adrenal artery that runs toward the region of the tumor, defective or missing staining of the tumor on hepatic arteriogram, and defective iodized oil retention or progression of the peripheral portion of the tumor after TAE/TACE therapy. Second, adrenal artery angiography should be performed for tumors located in the ventral hepatic

areas directly adjacent to the adrenal gland, especially in patients who have undergone TACE and/or meet the conditions described above. Finally, to reduce the risk of missing an adrenal artery collateral, the operator should carefully inspect the findings from CT/MRI and angiograms in patients with a large tumor that is located at the liver surface and adjacent to the adrenal gland.

In conclusion, TAE/TACE therapy via adrenal arteries can improve the therapeutic efficacy of TAE/TACE and reduce the incidence of HCC recurrence and/or presence of residual HCC.

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