TACE plus percutaneous chemotherapy-lipiodol treatment of unresectable pedunculated hepatocellular carcinoma

Dexiao Huang, MD<sup>a,b</sup>, Yong Chen, MD<sup>b</sup>, Shuo Chen, MD<sup>a</sup>, Qingle Zeng, MD<sup>b</sup>, Jianbo Zhao, MD<sup>b</sup>, Renhua Wu, MD<sup>a,b</sup>, Yanhao Li, MD<sup>b</sup>

Abstract
Pedunculated hepatocellular carcinoma (P-HCC) is rare type of HCC. The study aimed to evaluate the clinical features and outcomes of unresectable P-HCC treated with transcatheter arterial chemoembolization (TACE) and percutaneous chemotherapeutic agents lipiodol emulsion (CALE) injection. The clinical features and outcomes of 25 patients with unresectable P-HCC treated with TACE plus percutaneous CALE injection were retrospectively reviewed, and factors associated with outcomes were analyzed. Comparison with nonpedunculated unresectable HCC was also performed. Patients underwent a median of 4 TACE sessions and received a median of 2 percutaneous CALE injections. The 1-, 2-, 3-, and 5-year actuarial survival rates were 78.9%, 52.6%, 42.1%, and 12.0%, respectively, for patients with P-HCC, and median survival was 27 months (95% confidence interval, 22.6–43.2 months). Patients with P-HCC had better overall survival than those with nonpedunculated HCC (NP-HCC) (P = .002). Vascular invasion and abdominal lymph node metastasis were poor prognostic factors for overall survival in patients with P-HCC. TACE plus percutaneous CALE injection is a safe and effective treatment for unresectable P-HCC. Patients with unresectable P-HCC might have better overall survival than those with NP-HCC after TACE plus percutaneous CALE injection. However, their prognosis remains poor.

Abbreviations: AFP = α-fetoprotein, CALE = chemotherapeutic agents lipiodol emulsion, CT = computed tomography, HBsAg = hepatitis B surface antigen, HCC = hepatocellular carcinoma, KPS = Karnofsky performance score, LP = lipiodol, MRI = magnetic resonance imaging, NP-HCC = nonpedunculated HCC, PEI = percutaneous ethanol injection, PET-CT = positron emission tomography with computed tomography, P-HCC = pedunculated hepatocellular carcinoma, RFA = radiofrequency ablation, TACE = transcatheter arterial chemoembolization, TAI = transcatheter arterial infusion.

Keywords: hepatocellular carcinoma, pedunculated hepatocellular carcinoma, percutaneous intratumoral injection, prognosis, transcatheter arterial chemoembolization

1. Introduction
Pedunculated hepatocellular carcinoma (P-HCC) is rare type of HCC, first described by Roux<sup>1</sup> in 1897. P-HCC is defined as carcinoma protruding from the liver, with or without pedicle, and with low risk of liver invasion.<sup>2</sup> In 1983, Horie et al<sup>3</sup> reported that in Japan, only 0.24% to 3.00% of all HCCs were P-HCC, and to our knowledge, not more than 200 cases have been reported in the literature.<sup>4–6</sup> Most cases of P-HCC are treated surgically with higher operability rates and better survival than nonpedunculated (NP) HCC (NP-HCC), thanks to its unique growth pattern, tumor capsule formation, and lower level of vascular invasion.<sup>6–9</sup> However, up to 39.4% of P-HCC patients cannot be treated surgically.<sup>7</sup> Therefore, palliative treatments may play a central role in the treatment of unresectable P-HCC. Such treatments include transcatheter arterial chemoembolization (TACE), transcatheter arterial infusion (TAI), and oral sorafenib.<sup>8</sup> TACE is the most widely used locoregional therapy for patients with intermediate HCC, who cannot be treated surgically.<sup>9–11</sup> Moreover, a combination of TACE with local ablation has often been used to improve locoregional therapy for patients with unresectable HCC.<sup>12–15</sup> Whether TACE in combination with local ablation achieve more favorable prognoses for P-HCC than NP unresectable HCC has not yet been reported.

The aim of the present study was to retrospectively evaluate the clinical features and outcomes of 25 unresectable P-HCC cases...
treated with TACE plus percutaneous chemotherapeutic agents lipiodol emulsion (CALE) injection. We have previously demonstrated that percutaneous intratumoral injection with CALE can effectively induce necrosis of implanted VX2 tumors in rabbits,\(^{16}\) and also reported its feasibility and efficacy in local ablation of sacral chordoma and conventional unresectable HCC.\(^{17,18}\)

2. Materials and methods

2.1. Ethics statement

All examinations and treatments were performed in accordance with the Declaration of Helsinki, and were approved by the Ethics Committee of our hospital. Written informed consent was obtained from all patients to perform a retrospective study of prospectively collected data.

2.2. Patients

From 2003 to 2014, 31 patients, with histologically proven P-HCC out of a total of 832 patients with HCC, were treated in the Department of Interventional Radiology. Among them, 25 P-HCC patients, who were treated with TACE plus percutaneous CALE injection and had completed follow-up records, were included in this study. The remaining 6 patients were excluded from the study because they only underwent TACE and their records were incomplete. Tumors were defined as unresectable if they were extensive, exhibiting major vascular invasion, or were associated with symptoms that precluded surgical resection. The inclusion criteria for the study were as follows: age $\geq 18$ years; Karnofsky performance score (KPS) $\geq 80$; an initial diagnosis of primary HCC based on biopsy and/or imaging techniques; hepatic function by Child–Pugh classification A and B; unresectable tumor status; and a leukocyte count $\geq 3000$/mL, absolute neutrophil count $\geq 1500$/mL, hemoglobin level $\geq 90$/g/L, platelets $\geq 80 \times 10^9$/L, aspartate and alanine aminotransferase levels $< 2.5$ times the upper normal limit, bilirubin levels $< 2$ times the upper normal limit, and a prothrombin time-international normalized ratio $< 1.5$ in patients not taking oral anticoagulants. Exclusion criteria were: KPS of $< 80$, hepatic function by Child–Pugh classification C, vascular tumor thrombus, extrahepatic metastases (not including regional lymph node involvement), and other previous treatments for tumor. Sixty patients with NP unresectable HCC treated during the same time window with TACE plus percutaneous CALE injection were enrolled as a control (NP-HCC group). The demographics, symptomatology, physical examination, laboratory data, associated cirrhosis, Child–Pugh classification, $\alpha$-fetoprotein (AFP) levels, tumor size, tumor-node-metastasis (TNM) stages, vascular invasion, number of procedures, and long-term survival of each group were compared. Overall actuarial survival for the patients in the P-HCC group were compared, and stratified by Child–Pugh classification, tumor size $> 5$ cm, vascular invasion, abdominal lymph node metastasis, intrahepatic metastasis, invasion of surrounding organs, and liver cirrhosis.

2.3. TACE procedure

TACE was performed using the Seldinger technique followed by arterial embolization. After introducing a 4F or 5F catheter through the femoral artery, hepatic arteriography and superior mesenteric arteriography were initially performed to localize the tumors and evaluate portal vein flow. When portal vein flow was adequate, a microcatheter was placed in the arteries that fed the HCC. An emulsion, consisting of 30 to 50 mg epirubicin (Phmarmorubicin; Pfizer, Rome, Italy), 50 to 150 mg oxaliplatin (Elotra; Sanofi-Aventis, Paris, France), 5 to 20 mg mitomycin (Mitomycin-C; Kyowa Hakko Kogyo Co., Ltd, Tokyo, Japan), 6 to 20 mL lipiodol (LP; Laboratory Guerbet, Villepinte, France), and appropriate doses of contrast medium (iopamilon 300; Schering, Berlin, Germany) (contrast medium:LP = 1:1), was injected into the segmental artery supplying blood to the tumor, followed by embolization with 1-mm-diameter gelatin sponge particles (Gelfoam; Pfizer, Tokyo, Japan) until arterial flow stasis was achieved.\(^{19-11}\) After embolization, angiography was performed again to determine the extent of vascular occlusion and to assess blood flow in other arterial vessels.\(^{19}\)

2.4. Percutaneous CALE injection procedure

Within 2 months after TACE, percutaneous CALE injection was performed, under C-arm fluoroscopy (Axiom-Artis-dTA Angiographic System; Siemens Medical Systems, Erlangen, Germany) or computed tomography (CT) guidance, to provide local ablation and supplementary therapy. Criteria for CALE treatment were: CT scan or fluoroscopy revealed defects of LP in tumor lesions, angiography during the TACE procedure suggested that the blood supply was complicated, and injection of CALE could not be administered completely using an arterial approach.\(^{18}\)

Technically, the puncture approach used was determined by preoperative CT or magnetic resonance imaging (MRI) images. The procedure was performed using a 15 cm, 21-ga needle with a closed conical tip, and 3 terminal side holes (Hakko, Tokyo, Japan). After local anesthesia (5 mL of 2% lidocaine), the needle was introduced into the target area (defined as the area with LP defects in the tumor) under C-arm fluoroscopy or CT guidance. If the needle tip was confirmed in the target area, percutaneous injection with CALE was performed. The amount of emulsion was maintained at less than 40 mL per session to avoid liver failure and myelosuppression, and was also evaluated and controlled by real-time fluoroscopy or CT monitoring during the injection. CALE was manually injected slowly under simultaneous fluoroscopy or immediate CT scan until venous drainage was achieved. Then, the needle was retracted by 1 to 2 cm, or the direction of the needle was adjusted. After the needle tip was confirmed to remain within in the target area, injection with CALE was continued until the CALE was distributed throughout the tumor.\(^{18}\) If the target area was too large to be ablated in 1 session, an additional injection was performed 5 to 7 days later, when liver function permitted, with Child–Pugh classification A or B.

2.5. Postoperative management

After the procedure, the entry point of the skin was closely monitored for femoral artery hemorrhage and hematoma for 48 hours. Vital signs were monitored in all patients. Parameters including body temperature, adverse drug reactions, and evidence of embolism syndrome were monitored, and if present and severe, patients were treated with appropriate medications.

2.6. Follow-up

Follow-up examination with CT or MRI was carried out at 1, 3, and 6 months and 1 year after the procedure, and every 6 months thereafter. In addition, positron emission tomography with CT scan was also used to assess the therapeutic outcome where
possible. If residual or recurrent lesions were recognized during imaging, or new intrahepatic lesions were found, repeated TACE and percutaneous injection with CALE was performed sequentially when the patient’s KPS exceeded 80 and hepatic function reached Child–Pugh classification A or B. Patients were followed until loss to follow-up, death, or May 31, 2016. During the follow-up period, some patients with distant metastasis received additional treatments such as systemic chemotherapy, TACE, TAI, and isotope therapy.

2.7. Statistical analysis
All data are presented as the percent of patients or the mean±SD. Data were compared by independent 2-sample Student t tests and Pearson chi-square tests as appropriate. Survival was calculated by construction of Kaplan–Meier plots and compared by log-rank test. A Cox proportional hazards regression model was used to assess the prognostic factors for overall survival in patients with P-HCC. Meanwhile, variables included in the multiple Cox regression analysis were from the results of univariate analysis (P < .1). All statistical analyses were performed using SPSS version 17.0 (Shantou, Guangdong, PR China). We considered P < .05 as significant.

3. Results
3.1. Demographics
The P-HCC group included 23 men and 2 women with a mean age of 50.3±12.3 years (range, 19–70 years), and the NP-HCC group included 56 men and 5 women with a mean age of 48.0±13.8 years (range, 17–71 years). The demographic characteristics of these groups did not differ significantly (Table 1).

3.2. Symptomatology, physical findings, hepatitis status, associated liver conditions
The clinical presentations and physical characteristics of each group were similar (Table 1). The hepatitis B surface antigen (HBsAg) status of 85 patients was recorded, and 80 were HBsAg positive (94.1%). The percentage of patients with liver cirrhosis, and patient Child–Pugh classification also did not differ significantly between these 2 groups (Table 1).

3.3. Laboratory data
The biochemical characteristics, AFP, and liver function of patients in each group 1 day before treatment did not differ significantly (Table 2).

3.4. Imaging findings, procedures, and treatments for distant metastasis
A similar fraction of patients in each group were categorized as TNM II and stage III, 56.0% and 44% in P-HCC group, respectively, and 65.0% and 35.0% in NP-HCC group, respectively (P > .05). Patients in the P-HCC group had larger tumors, and more tumors of size >5 cm than patients in the NP-HCC group (both P < .05). Furthermore, the liver tumors in P-HCC patients (36.0%) exhibited less vascular invasion than those in the NP-HCC group (68.3%, P < .05; Table 3).

TACE plus percutaneous CALE injection was performed in all patients (Figs. 1–5). In the P-HCC group, the median number of treatments was 4 TACE sessions (range, 2–9) and 2 percutaneous CALE injection sessions (range, 1–3). For the NP-HCC group,
the median number of treatments was 4 TACE sessions (range, 1–8) and 2 percutaneous CALE injection sessions (range, 1–3) (Table 3). The median number of TACE treatments in the P-HCC group exceeded that in the NP-HCC group, but the median number of percutaneous CALE injections did not differ significantly between these 2 groups. Thirty-one cases had distant metastasis, primarily pulmonary metastasis, adrenal metastasis, and bone metastasis (9 cases in the P-HCC group and 22 cases in the NP-HCC group). All patients with metastatic disease received corresponding treatments, such as systemic chemotherapy, TAI, TACE, and isotope therapy.

### 3.5. Long-term survival and complications

All 85 patients received repeated TACE and percutaneous injections and were closely monitored at regular intervals until

---

**Figure 1.** Images of a 30-year-old man with unresectable pedunculated hepatocellular carcinoma who received transcatheter arterial chemoembolization (TACE) plus percutaneous chemotherapeutic agents lipiodol emulsion (CALE) injection. (A) Angiography before TACE demonstrated an extrahepatic tumor growth in the porta hepatitis, taking blood from the right hepatic artery, and gastroduodenal artery. (B) The radiograph obtained immediately after the first TACE, showing deposition of CALE. (C) Follow-up computed tomography (CT) image obtained 1 month after TACE, showing poor lipiodol (LP) deposition in the tumor lesion. (D) CT image obtained after the second TACE and 1 session of percutaneous CALE injection, showing good deposition of CALE. (E) Follow-up CT scan obtained at 5 months showed nearly complete shrinkage of the mass, with good LP deposition, after undergoing 4 TACE sessions and 2 percutaneous CALE injection sessions.

**Figure 2.** A 70-year-old woman with unresectable pedunculated hepatocellular carcinoma underwent transcatheter arterial chemoembolization (TACE) plus percutaneous chemotherapeutic agents lipiodol-emulsion (CALE) injection. (A) Follow computed tomography (CT) scan obtained at 3 months after undergoing 2 TACE sessions, revealing poor deposition of lipiodol in the tumor. (B) CT scan obtained immediately after the third TACE and additional percutaneous CALE injection, showing that CALE deposited well within all tumor lesions.
death or the end of the follow-up period (2–87 months, median 15 months). The overall actuarial survivals for the P-HCC and NP-HCC groups are shown in Fig. 6. The 1-, 2-, 3-, and 5-year actuarial survival rates of patients in the P-HCC group were 78.9%, 52.6%, 42.1%, and 12.0%, respectively. Those for patients in the NP-HCC group were 60.6%, 24.5%, 9.9%, and 0.0%, respectively. Patients in the P-HCC group had a median survival of 27 months (95% confidence interval [CI], 22.6–43.2 months) and had higher overall survival ($P = .002$) than the NP-HCC group (median: 15 months, 95% CI, 15.2–20.3 months; Table 4). The limited number of patients in the P-HCC group were stratified by Child–Pugh classification, tumor size $>5\text{cm}$, vascular invasion, abdominal lymph node metastasis, intrahepatic metastasis, invasion of surrounding organs, and liver

Figure 3. A 53-year-old man presented with an extrahepatic tumor growth in the right diaphragmatic surface, and similarly received combined transcatheter arterial chemoembolization (TACE) plus percutaneous chemotherapeutic agents lipiodol emulsion (CALE) injection. (A) Positron emission tomography with computed tomography (PET-CT) scan carried out at 3 months after undergoing 3 sessions of TACE and 1 session of percutaneous injection showed a radiologic concentration that was still found in the periphery of lesion, indicating active residual tumor tissue (red arrow). (B) Complete ablation was achieved 3 months after additional percutaneous CALE injection, as shown by follow-up PET-CT examination.

Figure 4. Percutaneous chemotherapeutic agents lipiodol emulsion (CALE) injections were performed under computed tomography (CT) guidance. Point, direction, depth, and pathway for needling were determined based on CT scan. (A) and (C) Follow-up CT scans showed defects of CALE in tumor lesions after repeated transcatheter arterial chemoembolization. (B) and (D) CT scan obtained immediately after CALE injection and showed emulsion distributed throughout the entire target area. (B) Leakage of CALE into abdominal wall along the needle pathway.
cirrhosis, and comparison of overall actuarial survival of these groups revealed that vascular invasion, abdominal lymph node metastasis, intrahepatic metastasis, and invasion of surrounding organs were predictors of poor overall survival ($P < .05$) (Table 5). However, multivariate analysis revealed that only vascular invasion and abdominal lymph node metastasis were independent predictors of survival for unresectable P-HCC (Table 6).

Common adverse effects of TACE and percutaneous CALE injection were fever, pain, vomiting, and increased serum alanine aminotransferase or aspartate aminotransferase levels. No serious complications were observed after TACE and percutaneous CALE injection treatment. Minor complications subsided after symptomatic therapy. After treatment, all complications were alleviated and resolved.

4. Discussion

P-HCC is primarily treated with surgical resection because, in comparison NP-HCC, a wider resection margin can be obtained, and the relatively high rate of capsule formation around the tumor limits vascular invasion. Early stage P-HCC is often asymptomatic and rapid tumor growth is accompanied by intrahepatic metastasis and invasion of neighboring visceral organs. Therefore, a diagnosis of up to 39.4% of P-HCC patients cannot be treated surgically. If the patients can tolerate the procedure, TACE is the first option for the treatment of unresectable HCC including intermediate and advanced stages. In this study, P-HCC was also found to have a rich blood supply. Thus, TACE should be also used as the primary treatment for patients with unresectable P-HCC if liver function permits. As P-HCC is a hypervascular tumor, embolization of the feeding artery may cause ischemic necrosis of tumor tissue and create a window for subsequent local ablative therapies. Moreover, with TACE, intrahepatic lesions that cannot be localized via conventional imaging techniques can be treated and marked (by the LP deposition) for further monitoring and treatment after TACE. However, TACE treatment has obvious limitations for tumor control. On one hand, the blood supply of P-HCC is rather complicated and arises not only from hepatic arteries, but also from parasitic blood vessels. The anatomical features of these parasitic blood vessels make super-selective catheterization and embolization of every feeding artery practically impossible, even using a microcatheter. On the other hand, P-HCC tumor lesions share feeding arteries with neighboring organs, limiting application of arterial injection with CALE and embolization, and leading to poor or even no CALE deposition in the tumor. Therefore, TACE alone cannot achieve complete tumor necrosis,
and local ablative therapies should be subsequently employed.[12–15,22]

Clinically, local ablative therapies are usually performed under imaging guidance by means of percutaneous ethanol injection (PEI) and radiofrequency ablation (RFA). PEI can cause complete necrosis of small tumors, but is not suitable for large tumors, particularly those >5 cm, because larger tumors fibrous structures in the tumor interstitial spaces separate and limit wide diffusion of anhydrous alcohol.[23,24] In the present study, most tumor lesions were over 5 cm in diameter. Moreover, patients treated with PEI often experience intense pain during the procedure. It is also difficult to monitor whether the ethanol remains in the tumor by imaging methods, and the volume of ethanol used is typically quite arbitrary. Although only a few treatment sessions with RFA are required to achieve effective tumor necrosis, it may be difficult to perform, and is considered unsafe in some situations, including in masses that are not detected by ultrasound, and those located in the hepatic dome, in the subcapsular area, exophytic, or are surrounded by large vessels.[25] According to the unique localization and growth pattern of P-HCC, RFA is generally not suitable for treatment of P-HCC due to the rate of serious complications, such as pleural effusion, peritonitis, intestinal perforation, and tumor rupture. Also, RFA is expensive, limiting its application in developing countries.

Local ablation with high concentrations of chemotherapeutic agents may be potentially toxic to cancer tissue. However, direct injection of chemotherapeutic agents has not been practical in the past because the drug disperses rapidly into surrounding tissue and the systemic circulation shortly after injection.[26,27] In the present study, percutaneous injection with CALE was used to achieve local ablation and supplementary therapy for the treatment of unresectable P-HCC after TACE. As previous reports, the portion of tumor that retained LP was considered necrotic when necrosis observed in pathologic specimens correlated well with the necrosis rate measured on CT,[28–30] and the degree of LP accumulation after TACE was associated with improved survival in patients with unresectable HCC.[30,31] Accordingly, initial complete lipiodolization should be considered a relevant therapeutic target. We have also previously reported the feasibility and efficacy of this therapy for local ablation in the treatment of sacral chordoma and intermediate/advanced HCC when TACE alone cannot achieve complete tumor necrosis.[17,18] As a drug-carrying agent with a high viscosity, we speculate that LP accumulates in tumor lesions and cannot be easily drained into the blood. Also, CALE can be useful in tracing infiltration in tumors because the scope of its dispersion can be detected and used for image guidance. In particular, percutaneous CALE injection may be feasible for lesions that are

| Table 5 | Prognosis of pedunculated hepatocellular carcinoma in terms of risk parameters. |
|----------|---------------------------------|-----------------|---------------|-----------------|---------------|---------------|
| Parameter                                   | Overall survival, mo | No. | Mean | Median | 95% CI of mean | P (Kaplan-Meier) |
| Child–Pugh classification                   |                   | A   | 21/25| 33.9  | 28.0  | 22.8; 44.9 | .638 |
|                                             |                   | B   | 4/25 | 26.5  | 13.0  | 0.0; 55.1 | .374 |
| Tumor size >5 cm                            |                   | Yes | 23/25| 34.4  | 27.0  | 23.2; 45.5 | <.001 |
|                                             |                   | No  | 2/25 | 20.5  | 13.0  | 5.8; 35.2 | .102 |
| Vascular invasion                           |                   | Yes | 9/25 | 13.0  | 11.0  | 8.4; 17.5 | .001 |
|                                             |                   | No  | 16/25| 43.8  | 43.0  | 31.2; 56.4 | .194 |
| Abdominal lymph node metastasis             |                   | Yes | 7/25 | 14.2  | 11.0  | 9.6; 18.7 | .001 |
|                                             |                   | No  | 18/25| 39.5  | 37.0  | 27.1; 51.9 | .067 |
| Intrahepatic metastasis                     |                   | Yes | 12/25| 23.6  | 14.0  | 11.5; 35.6 | <.001 |
|                                             |                   | No  | 13/25| 43.0  | 47.0  | 27.3; 58.3 | .344 |
| Invasion of surrounding organs              |                   | Yes | 6/25 | 12.8  | 11.0  | 8.2; 17.5 | .001 |
|                                             |                   | No  | 19/25| 39.8  | 37.0  | 27.6; 52.0 | .194 |
| Liver cirrhosis                             |                   | Yes | 18/25| 37.0  | 37.0  | 23.8; 50.1 | .194 |
|                                             |                   | No  | 7/25 | 22.7  | 14.0  | 10.1; 35.2 | .344 |

95% CI = confidence interval.

| Table 6 | Cox regression analysis of prognostic factors for overall survival in patients with unresectable pedunculated hepatocellular carcinoma. |
|----------|----------------------------------------------------------------------------------------------------------------------------------|
| Feature                          | Coefficient | SE     | Wald statistics | Hazard ratio | 95% CI for hazard ratio | P     |
| ---------------------------------|-------------|--------|----------------|--------------|------------------------|-------|
| Vascular invasion                | 3.111       | 0.969  | 10.302         | 22.454       | 3.358; 150.127         | .001  |
| Abdominal lymph node metastasis  | 2.097       | 0.885  | 5.611          | 8.144        | 1.436; 46.178          | .018  |
| Intrahepatic metastasis          | 0.136       | 0.829  | 0.027          | 1.146        | 0.226; 5.821           | .870  |
| Invasion of surrounding organs   | 1.564       | 0.958  | 2.667          | 4.776        | 0.731; 31.198          | .102  |

95% CI = confidence interval. SE = standard error.
accurate punctures are required for each procedure, and percutaneous injection must be performed under image guidance. We suggest that fluoroscopy should be preferably used to guide injection because it allows simultaneous observation of the distribution of CALE after injection. Although a CT scan can accurately guide the puncture, it must be repeatedly carried out to decrease the risk of leakage of CALE. In the present study, CT scans were conducted to observe the distribution of CALE after each 2 mL of CALE was injected into the tumor. Moreover, the amount of CALE should be determined and controlled by real-time fluoroscopy or CT monitoring during injection.

During percutaneous CALE injection, CALE can leak into healthy tissues, such as the bile duct, draining veins, peritoneal tissue, liver capsule, and abdominal cavity. However, these drugs are naturally excluded from healthy tissues and thus do not cause significant damage, as shown in our previous reports.

Despite the small sample size of this study, our results indicate that percutaneous CALE injection can be used for local ablation and supplementary therapy following TACE can improve survival of patients with unresectable P-HCC. The 1- and 2-year actuarial survival rates of 25 patients with unresectable P-HCC were 78.9% and 52.6%, respectively. In contrast, Horie et al. reported poor 1- and 2-year survival rates of 21 cases of P-HCC treated with TACE or TAI in Japan (55.0% and 19.0%, respectively). Our results suggest that TACE plus percutaneous CALE injection for P-HCC achieves greater survival than TACE or TAI alone.

Patients with P-HCC had larger tumors and a higher percentage of tumors >5 cm than those with NP-HCC. Although previous studies demonstrated that large tumors, particularly those >5 cm, were associated with poor prognosis and survival,

12 found the overall survival was longer for the P-HCC than NP-HCC group, as was previously described for surgical treatment. The reason for this might be that P-HCC typically exhibits less vascular invasion than NP-HCC. Yeh et al also reported that P-HCC is more often well-encapsulated with less vascular invasion than NP-HCC. In addition, patients with P-HCC required a higher median number of treatments than NP-HCC patients. During therapy, the hepatic reserve might be better in patients with P-HCC, enabling them to tolerate repeated TACE.

Regarding the treatment and prognosis of P-HCC, surgical treatment of P-HCC may provide a more favorable prognosis than NP HCC. However, Horie et al. reported that at least 42% of the 163 P-HCC patients died within 1 year. Furthermore, Moritz et al. reported that surgically treated patients with P-HCC usually died of metastatic disease. Therefore, timely treatment is essential to improve overall survival. In the present study, 9 patients had distant metastasis, primarily pulmonary metastases, adrenal metastases, and bone metastases, during the course of therapy. All received timely corresponding treatments, such as systemic chemotherapy, TAI, TACE, and isotope therapy.

Our conclusions are, however, limited by the scope of this retrospective study. As P-HCC is rare type of HCC, and more centers could not be involved, the sample size was relatively small. As the study was conducted over several years, the choice of equipment and materials was limited in the early cases. TACE for P-HCC requires a microcatheter for super-selective catheterization as tumor-feeding branches that arise from the extrahepatic collaterals are difficult to catheterize due to branching. These branches are usually of small caliber and form acute angles. However, in the early cases, a microcatheter was not used to perform super-selective catheterization, which may have reduced the curative effect. As we report treatment at a single institution, our results may not necessarily be applicable to other institutions. The retrospective design and small population size may have resulted in unforeseen bias. Therefore, our results should be validated in a larger prospective study.

In conclusion, we presented the clinical features and outcomes of 25 patients with unresectable P-HCC and treated with TACE plus percutaneous CALE injection. We found that TACE plus percutaneous CALE injection was safe and effective for palliative treatment of unresectable P-HCC. The overall survival rate of patients with unresectable P-HCC was better than that of those with NP-HCC after treatment with TACE plus percutaneous CALE injection, but the prognosis remained poor due to the aggressive nature of the tumor.

References

[1] Roux C. Un cas de cancer primitif du foie avec pericholecystite calculeuse, perforation intestinale; hemostase hepatique. Rev Med Suisse Romande 1897;17:114–9.
[2] Eggel H. Uber das primare Carcinom der Leber. Beitr Pathol Anat Allg Pathol 1901;30:106–604.
[3] Horie Y, Katoh S, Yoshida H, et al. Pedunculated hepatocellular carcinoma. Report of three cases and review of literature. Cancer 1983;51:746–51.
[4] Horie Y, Shigoku A, Tanaka H, et al. Prognosis for pedunculated hepatocellular carcinoma. Oncology 1999;57:23–8.
[5] Moritz MW, Soto J, Sgrad G, et al. Surgical therapy in two patients with pedunculated hepatocellular carcinoma. Arch Surg 1988;123: 772–4.
[6] Yeh CN, Lee WC, Jeng LB, et al. Pedunculated hepatocellular carcinoma: clinicopathological study of 18 surgically resected cases. World J Surg 2002;26:1133–8.
[7] Anthony PP, James K. Pedunculated hepatocellular carcinoma. Is it an entity? Histopathology 1987;11:403–14.
[8] Lencioni R, Chen XP, Dagher L, et al. Treatment of intermediate/advanced hepatocellular carcinoma in the clinic: how can outcomes be improved? Oncologist 2010;15(suppl 4):42–52.
[9] Llovet JM, Real MI, Montanà X, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. Lancet 2002;359:1734–9.
[10] Lo CM, Ngan H, Tso WK, et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. Hepatology 2002;35:1164–71.
[11] Lopez PM, Villanueva A, Llovet JM. Systematic review: evidence-based management of hepatocellular carcinoma—an updated analysis of randomized controlled trials. Aliment Pharmacol Ther 2006;23:1335–47.
[12] Becker G, Sozzig T, Obschewsky M, et al. Combined TACE and PET for palliative treatment of unresectable hepatocellular carcinoma. World J Gastroenterol 2005;11:6104–9.
[13] Grégoire A, Llovet JM, Bruix J. Hepatocellular carcinoma. Lancet 2012;379:1245–55.
[14] Takaki H, Yamakado K, Uraki J, et al. Radiofrequency ablation combined with chemoembolization for the treatment of hepatocellular carcinomas larger than 5 cm. J Vasc Interv Radiol 2009;20:217–24.
[15] Wang ZJ, Wang MQ, Duan F, et al. Transcatheter arterial chemoembolization followed by immediate radiofrequency ablation for large
solitary hepatocellular carcinomas. World J Gastroenterol 2013;19: 4192–9.

[16] Song JW, Li YH, Chen Y, et al. Effect of percutaneous intratumoral injection of lipiodol emulsion of chemotherapeutic agents on implanted VX2 tumor in rabbits. Nan Fang Yi Ke Da Xue Xue Bao 2010;30: 2526–9.

[17] Chen Y, Li YH, Zeng QL, et al. Percutaneous intratumoral injection of lipiodol and chemotherapeutic agents emulsion for primary liver cancer. Chin J Gen Surg 2009;24:992–5.

[18] Huang D, Chen Y, Zeng Q, et al. Image-guided percutaneous lipiodol-pengyangmycin suspension injection therapy for sacral chordoma. Korean J Radiol 2013;14:823–8.

[19] Nishizaki T, Matsumata T, Adachi E, et al. Percutaneous intratumoral injection of lipiodol and chemotherapeutic agents emulsion for implanted VX2 tumor in rabbits. Nan Fang Yi Ke Da Xue Xue Bao 2010;30: 2526–9.

[20] Chen Y, Li YH, Zeng QL, et al. Percutaneous intratumoral injection of lipiodol and chemotherapeutic agents emulsion for primary liver cancer. Chin J Gen Surg 2009;24:992–5.

[21] Huang D, Chen Y, Zeng Q, et al. Image-guided percutaneous lipiodol-pengyangmycin suspension injection therapy for sacral chordoma. Korean J Radiol 2013;14:823–8.

[22] Chung GE, Lee JH, Kim HY, et al. Transarterial chemoembolization can be safely performed in patients with hepatocellular carcinoma invading the main portal vein and may improve the overall survival. Radiology 2011;258:627–34.

[23] Narvaez-Lugo J, Caceres WW, Toro DH, et al. Transcatheter arterial chemoembolization and percutaneous ethanol injection for Hepatocellular carcinoma: a retrospective review of the Veterans Affairs Caribbean Healthcare System. Cancer Control 2008;15:80–5.

[24] Miyayama S, Yamashiro M, Okuda M, et al. Chemoembolization for the treatment of large hepatocellular carcinoma. J Vasc Interv Radiol 2010;21:1226–34.

[25] Bouza C, López-Cuadrado T, Alcázar R, et al. Meta-analysis of percutaneous radiofrequency ablation versus ethanol injection in hepatocellular carcinoma. BMC Gastroenterol 2009;9:2296–9.

[26] Taniguchi M, Kim SR, Imoto S, et al. Long-term outcome of percutaneous ethanol injection therapy for minimum-sized hepatocellular carcinoma. World J Gastroenterol 2008;14:1997–2002.

[27] Kong WT, Zhang WW, Qiu YD, et al. Major complications after radiofrequency ablation for liver tumors: analysis of 235 patients. World J Gastroenterol 2009;15:2651–6.

[28] Begg AC, Bartelink H, Stewart FA, et al. Improvement of differential toxicity between tumor and normal tissues using intratumoral injection with or without a slow-drug-release matrix system. NCI Monogr 1988;133–6.

[29] Duncan JC, Fourie PA, Alberts AS. Direct percutaneous intratumoral bleomycin injection for palliative treatment of impending quadriplegia. AJNR Am J Neuroradiol 2004;25:1121–3.

[30] Monsky WL, Kim I, Loh S, et al. Semiautomatic segmentation for volumetric analysis of intratumoral ethiodol uptake and subsequent tumor necrosis after chemoembolization. AJR Am J Roentgenol 2010;195:1220–30.

[31] Takayasu K, Arri S, Matsuoka N, et al. Comparison of CT findings with resected specimens after chemoembolization with iodized oil for hepatocellular carcinoma. AJR Am J Roentgenol 2000;175:699–704.

[32] Yang P, Zeng ZC, Wang BL, et al. The degree of lipiodol accumulation can be an indicator of successful treatment for unresectable hepatocellular carcinoma (HCC) patients—in the case of transcatheter arterial chemoembolization (TACE) and external beam radiotherapy (EBRT). J Cancer 2016;7:1413–20.

[33] Kim DY, Ryu HJ, Choi JY, et al. Radiological response predicts survival following transcatheter chemoembolisation in patients with unresectable hepatocellular carcinoma. Aliment Pharmacol Ther 2012;35:1343–50.