Abstract. Pedunculated hepatocellular carcinoma (P-HCC) is a rare type of HCC, defined as a carcinoma protruding from the liver with or without a pedicle with a low degree of liver invasion. The present study aimed to evaluate the characteristics of blood supply of P-HCC prior to and following transcatheter arterial chemoembolization (TACE) treatment. Angiographic findings prior to and following TACE treatment in 39 patients with P-HCC were analyzed retrospectively. Angiography performed at the first TACE session revealed 70 tumor-feeding arteries collectively in all patients, including 31/70 (44.0%) extrahepatic parasitic arteries in 23/39 patients (59.0%). The intrahepatic arteries served as the main blood supply to P-HCC in all patients. Extrahepatic collateral blood supplies to P-HCCs were significantly associated with larger tumor diameter ($\chi^2=164.000$, $P<0.001$), but not tumor location ($\chi^2=7.358$, $P=0.061$). Following repeated TACE treatment, all angiographies revealed a total of 131 tumor feeding arteries collectively in all patients, including intrahepatic arteries (54/131) and extrahepatic collateral arteries (78/131) in 31 patients (79.5%). Compared with angiographies performed at the initial TACE treatment, these results also demonstrated an increase in the number of extrahepatic collateral arteries, which produced 47 new blood vessels ($\chi^2=4.278$, $P=0.039$). P-HCC tumor lesions readily acquired a parasitic blood supply from adjacent vessels following repeated TACE. Intrahepatic arteries functioned as the main blood supply for P-HCC, whereas extrahepatic collateral arteries were complementary to P-HCC, regardless of whether the patient was pre- or post-TACE. Extrahepatic collateral supplies to P-HCCs that originated from adjacent vessels were rich, were closely associated with tumor size, and were prone to be newly established following repeated TACE.

Introduction

Pedunculated hepatocellular carcinoma (P-HCC) is a rare type of HCC, which is defined as a carcinoma protruding from the liver with or without a pedicle, and with a low degree of liver invasion (1). P-HCC was first described by Roux in 1897 (2), and represents 0.24‑3.00% of all cases of HCC in Japan (3,4). Additionally, to the best of our knowledge, <200 cases have been reported in previous studies (4‑6).

The majority of P-HCC cases are treated surgically, with higher operability rates and better survival than conventional HCC, which may be due to its unique growth pattern, high rate of tumor capsule formation and lower vascular invasion (4‑6). However, up to 39.4% of patients with P-HCC are unable to undergo surgical resection (7). Therefore, palliative treatments may serve a central function in the treatment of unresectable P-HCC. Transcatheter arterial chemoembolization (TACE) is the most widely used locoregional therapy for patients with intermediate HCC, who cannot be treated surgically (8‑11). However, the blood supply to P-HCC is complicated, arising from hepatic arteries and extrahepatic collateral vessels (3). P-HCC tumor lesions protruding from the liver may receive an extrahepatic blood supply from adjacent vessels, despite the presence of a patent hepatic artery. In addition, repeated TACE results in the attenuation of hepatic arterial circulation and causes the development of extrahepatic collaterals (12). Therefore, the characteristics of the blood supply of P-HCC may aid the improvement of the therapeutic effect of transcatheter
management and determine the selection of subsequent treatment schemes for patients with P-HCC following TACE. The aim of the present study was to retrospectively analyze angiographic findings in 39 patients with P-HCC treated with TACE, and to evaluate the blood supply characteristics of P-HCC prior to and following TACE treatment.

Patients and methods

Patients. Between January 2003 and February 2016, 39 patients (male, 37; female, 2; mean age, 49 years; age range, 19 to 70 years) with histologically proven P-HCC, out of a total of 1,238 patients with HCC, were treated in the Department of Interventional Radiology, from the Nanfang Hospital of Southern Medical University and The Second Affiliated Hospital of Shantou University Medical College (Guangdong, China). Exclusion criteria were as follows: i) Karnofsky performance score of <80; ii) hepatic function analyzed using the Child-Pugh classification C (8); iii) vascular tumor thrombus; iv) extrahepatic metastases (not including regional lymph node involvement); v) received previous treatment for this type of tumor. P-HCC was defined, using computed tomography (CT) scanning or magnetic resonance imaging (MRI), as HCC with tumor lesions protruding from the liver with or without a pedicle. A total of 39 patients with P-HCC were treated with TACE (between 2 and 9 sessions) in the present study. The P-HCC tumor lesions ranged between 4.2 and 22.1 cm (mean, 10.2 cm) in diameter, including <5 cm, n=2; 5-10 cm, n=19; and >10 cm, n=18, and were localized within the right diaphragmatic surface (n=2), the right visceral surface (n=20), the left diaphragmatic surface (n=2) and the left visceral surface (n=15) (Table I).

CT scanning or MRI examination and laboratory tests, including quantification of routine blood test, liver function, coagulation function and α-fetoprotein (AFP) levels, were regularly performed prior to angiography. Written informed consent was obtained from all patients prior to treatment.

Angiography. Angiographies were performed using the Seldinger technique (13). Subsequent to introducing a 4- or 5-F catheter through the femoral artery, arteriograms of the celiac, common hepatic and superior mesenteric arteries were initially performed in all patients to localize lesions and identify blood vessels feeding the tumor. During selected catheterization, the catheter must be placed at the arterial orifice; however, it cannot be entered too deeply into the arteries orifice as this may omit extrahepatic collateral supplies. A microcatheter was used for highly selective catheterization when the tumor-feeding vessel was small and twisted. Extrahepatic collateral pathways were sought when a tumor stain not corresponding to P-HCC, as depicted by imaging modalities including contrast-enhanced CT and MRI, was not identified on angiograms of these arteries. CT and MRI results obtained prior to the TACE procedure, which can depict the tumor and guide the TACE procedure. The individual vessels, which may feed HCC, depending on the tumor location, were selected to determine whether collateral supply to the tumor was present. Aortography aided the location of the individual vessels arising from the aorta, if required.

Statistical analysis. All data were presented as the percentage of patients or the mean ± standard deviation. Data were compared using Pearson’s χ² tests when appropriate. P<0.05 was considered to indicate a statistically significant difference. All statistical analyses were performed using SPSS software (version 17.0; SPSS, Inc., Chicago, IL, USA).

Results

Angiographic results prior to TACE. Angiographies at the first TACE session revealed 70 tumor-feeding arteries in the 39 patients, including 39 (56.0%) intrahepatic arteries and 31 (44.0%) extrahepatic collateral vessels in 23 cases (23/39), which consisted of 14 cases with a tumor >10 cm in size (5/14 had two extrahepatic collateral arteries) and 9 cases with a tumor 5-10 cm in size (3/9 had two extrahepatic collateral arteries) (Figs. 1-4). All extrahepatic arteries served as the main blood supply for the P-HCC in all patients. Extrahepatic collateral vessels originated from the gastro-duodenal arteries (11/31), left gastric arteries (6/31), superior mesenteric arteries (5/31), pancreateocduodenal arteries (4/31), inferior phrenic artery (3/31) and right adrenal arteries (2/31) (Table II). Extrahepatic collateral blood supply to the P-HCC were significantly associated with a larger tumor size (χ²=164.000, P<0.001); however, no significant association was identified with regards to the tumor location (χ²=7.358, P=0.061) (Table I), which demonstrated that the larger the P-HCC tumor size, the greater the number of extrahepatic collateral supplies.

Angiographic results subsequent to repeated TACE. Following repeated TACE (2-9 sessions), angiography revealed a total of 131 tumor-feeding arteries in all patients, with 54 (41.2%) intrahepatic arteries adding new intrahepatic collateral vessels (14/54) (Fig. 3), and 78 (58.8%) extrahepatic collateral vessels from 31 cases (79.5%); these vessels arose from gastroduodenal arteries (23/78), left gastric arteries (13/78), inferior phrenic artery (11/78), superior mesenteric arteries (10/78), pancreateocduodenal arteries (8/78), right adrenal arteries (8/78), right gastric arteries (2/78), lumbar arteries (2/78) and the intercostal artery (1/78). Compared with angiographies at the initial TACE, 47 new extrahepatic blood vessels were added. These results reveal that the number of extrahepatic collateral vessels significantly increased following TACE (χ²=4.278, P=0.039; Table II).

All angiographies revealed that the intrahepatic arteries served as the main blood supply for P-HCC, whereas the extrahepatic collateral arteries served complementary functions in P-HCC, regardless of whether the patient was pre- or post-TACE (Figs. 1-4). Additionally, P-HCC tumor lesions were prone to acquire parasitic blood supplies from adjacent vessels following repeated TACE (Figs. 2 and 5).

Discussion

P-HCC is characterized by a rich blood supply, similar to HCC. All angiographies conducted in the present study revealed that the intrahepatic arteries function as the main blood supply, with the extrahepatic collateral arteries supplying a complementary blood supply for P-HCC, regardless of whether the patient is
pre- or post-TACE. Extrahepatic collateral supplies to P-HCC are rich, and are significantly associated with tumor size; these blood supplies often arise from the feeding arteries of the organs adjoining tumor lesion and are readily established following repeated TACE (14). Extrahepatic collateral supplies to P-HCC are established under various conditions (15-17). These collateral

Table I. Blood supply, tumor size, and tumor location in 39 patients with pedunculated hepatocellular carcinoma prior to transcatheter arterial chemoembolization.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Only from intrahepatic arteries(^a), n</th>
<th>Coupling with extrahepatic collateral arteries(^a), n</th>
<th>(\chi^2)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor size, cm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5</td>
<td>2</td>
<td>0</td>
<td>164.000</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>5-10</td>
<td>19</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;10</td>
<td>18</td>
<td>18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor location</td>
<td></td>
<td></td>
<td>7.358</td>
<td>0.061</td>
</tr>
<tr>
<td>Right diaphragmatic surface</td>
<td>2</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right visceral surface</td>
<td>20</td>
<td>13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left diaphragmatic surface</td>
<td>2</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left visceral surface</td>
<td>15</td>
<td>10</td>
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\(^a\)n=39. \(^\text{n}=23.\)
supplies may develop following the interruption of the hepatic artery by surgical ligation, arterial injury induced by repeated TACE or the placement of a catheter (15-17). Adhesions between tumors protruding from the liver and adjacent organs can exaggerate the degree of extrahepatic collateral blood supplies, although the hepatic arterial supply remains intact (3,15,18-22).

In the present study, extrahepatic collateral blood supplies to P-HCC commonly arose from gastroduodenal arteries, left gastric arteries, phrenic arteries, superior mesenteric arteries, pancreaticoduodenal arteries and right adrenal arteries. In patients with P-HCC, various extrahepatic collateral vessels develop and supply the tumor (3,18-29). Compared with those observed via angiographies at the initial TACE, up to 79.5% of the patients in the present study had extrahepatic collateral supplies following subsequent TACE; the results also revealed an increasing trend in the number of extrahepatic collateral vessels as the number of TACE treatments increased. Therefore, it was hypothesized that the main cause of the development of extrahepatic collaterals was attenuation of the hepatic arterial circulation by TACE (18-28).

Technically, angiographies of blood supplies to the liver, including the celiac, common hepatic and superior mesenteric arteries, should be initially performed during TACE in all patients with P-HCC, as the intrahepatic arteries manifest as the main blood supply to P-HCC (14). An arteriogram of the inferior phrenic artery, which is a major source of diaphragmatic blood supply to the liver (12,19,22-26,29), is routinely performed in patients who have an interrupted hepatic arterial circulation owing to previous treatment, or in patients with tumors located near the diaphragm, which may be identified in the initial angiography.

Extrahepatic collateral blood supplies are sought when a tumor stain that corresponds to P-HCC, identified using imaging modalities in terms of the location and size of the tumor, is not present on the angiograms of these arteries. Extrahepatic collateral blood supplies are obtained through nearby blood vessels attributed to P-HCC protruding from the liver, exaggerating the degree of extrahepatic collateral blood supply sourced from adjacent organs (18-22). In practice, the catheter must be placed at the arterial orifice to avoid omitting the origin of the extrahepatic collateral blood supply during the selective catheterization. Use of a microcatheter is required for highly selective catheterization when tumor-feeding branches that arise from the extrahepatic collaterals are difficult to catheterize, owing to their branching phenotype (23). These branches are usually of small caliber and branch at acute angles, giving a twisted appearance.

P-HCC is primarily treated by surgical resection, as a wider resection margin may be obtained, and patients have a higher
Figure 3. Angiography of a 46-year-old man with P-HCC. (A) Extrahepatic tumor growth on the left visceral surface. (B) A hepatic arteriogram reveals that the left hepatic artery is the tumor-feeding artery. (C) The catheter is advanced into the left hepatic artery, followed by arterial embolization. The radiograph obtained immediately following TACE reveals a solid chemotherapeutic agents lipiodol emulsion deposition. (D) Angiography at the third TACE revealing a new intrahepatic collateral vessel supplying blood to the P-HCC. P-HCC, pedunculated hepatocellular carcinoma; TACE, transcatheter arterial chemoembolization.

Figure 4. Images from a 30-year-old man with pedunculated hepatocellular carcinoma who received 4 TACE sessions. (A) Angiography prior to TACE demonstrates an extrahepatic tumor growth in the porta hepatitis, taking blood from the right hepatic artery, as the main blood supply, and the gastroduodenal artery. (B) Angiographies taken subsequent to 2 sessions of TACE, revealing that the right hepatic artery functions as the main blood supply, whereas the gastroduodenal artery is complementary. (C) Angiographies taken subsequent to 4 sessions of TACE, demonstrating the same phenomenon as observed in (B), with a nearly complete shrinking of the mass. TACE, transcatheter arterial chemoembolization.
percentage of capsule formation around the tumor, resulting in less vascular invasion than in conventional HCC (5). No symptoms present themselves in patients with early-stage P-HCC; however, once diagnosed, rapid tumor growth ensues, accompanied by intrahepatic metastasis and invasion of neighboring visceral organs (30). Therefore, up to 39.4% of patients with P-HCC cannot undergo surgical resection (7). If the patients are able to tolerate the procedure, TACE is the first option for the treatment of unresectable HCC, including for patients with intermediate- and advanced-stage disease (8-11,31). The results of the present study demonstrated that the supply of blood to P-HCC is complicated and arises from hepatic arteries and extrahepatic collateral supplies (3). Extrahepatic collateral blood supplies may prohibit effective treatment by TACE. For the transcatheter management of P-HCC to be effective, these collateral blood supplies must be adequately embolized (18-28).

TACE treatment has clear limitations for P-HCC tumor control. On one hand, the anatomical features of the extrahepatic collateral vessels, vessels that are often tiny and twisted, make highly selective catheterization and embolization of every feeding artery practically impossible, even when using a microcatheter (23). Additionally, P-HCC tumor lesions adjoin neighboring organs and share feeding arteries (i.e., the origin of extrahepatic collateral supply), which limit arterial injection with chemotherapeutic agents lipiodol emulsion (CALE) and embolization, resulting in poor or no CALE deposition in the tumor (14). Furthermore, a tumor fed by extrahepatic collateral blood supplies may have multiple feeding arteries, as the extrahepatic collateral vessel connects with the hepatic artery and other extrahepatic collateral blood supplies (12,18). Finally, not all extrahepatic collateral supplies are present on the angiographies and so will not receive the chemoembolization. Therefore, TACE alone cannot result in complete tumor necrosis in patients with P-HCC, and a combination of other therapies, including local ablation and oral sorafenib therapy, should be subsequently utilized (32).

The present study had a number of limitations worth noting. Firstly, there were no patients with conventional HCC enrolled.
as a control for comparison in this retrospective study. Secondly, a microcatheter was not used in highly selective catheterization, particularly in earlier cases, resulting in the omission of a number of extrahepatic collateral supplies. Thirdly, the data only consisted of intermediate or advanced P-HCC, which cannot be treated surgically, unlike early-stage P-HCC. These unobservable cases of P-HCC may form adhesions between the tumor and adjacent organs more readily, which could exaggerate the degree of extrahepatic collateral blood supplies.

The intrahepatic arteries serve as the main blood supply for P-HCC, whereas the extrahepatic collateral arteries are complementary, regardless of whether patients are pre- or post-TACE. The extrahepatic collateral blood supplies to P-HCC that arises from adjacent vessels are rich, closely associated with tumor size, and are frequently newly established following repeated TACE. As the present study reports treatment at a single institution, the results may not necessarily be applicable to other institutions. The retrospective design and small population size may have resulted in unconfounded bias. Therefore, the results should be validated in a larger prospective study in the future.

Acknowledgements

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References