REVIEW

EXTRAHEPATIC BLOOD SUPPLY TO HEPATOCELLULAR CARCINOMA – A PICTORIAL ESSAY

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ABSTRACT

Transarterial chemoembolization is a standard locoregional therapy for intermediate stage hepatocellular carcinoma. The tumour is typically supplied by the hepatic arteries; however, extrahepatic collateral arteries may significantly contribute parasitic blood supply to the tumour. Large and exophytic tumour, subcapsular location, direct invasion and adhesion to adjacent organs, hepatic artery dissection, stenosis and occlusion resulting from multiple embolizations are risk factors of extrahepatic collateral arteries. Understanding the prevalence and prediction of these parasitic supplies on pre-procedural imaging is of utmost importance for optimizing technical and clinical outcomes.

Keywords: transarterial chemoembolization, parasitic supply, extrahepatic collateral.

RéSUMÉ

La vascularisation extra-hépatique du carcinome hépatocellulaire – un essai illustré

La chimio-embolisation trans-artérielle conventionnelle est le traitement standard et locorégional du carcinome hépatocellulaire dans les stades intermédiaires. La vascularisation du carcinome hépatocellulaire est presque exclusivement artérielle, l’artère hépatique; mais des artères à destinée extra-hépatique peuvent participer à la vascularisation de certains carcinomes hépatocellulaires. Les facteurs de risque des artères collatérales extra-hépatiques sont une large tumeur exophytique; une location sous-cap- sulaire; un envahissement et une adhésion aux organes adjacents; l’artère hépatique disquante, râtrée, obstruée par de multiples embolisations précédentes. L’objectif de cet article est de décrire les différentes artères nourrissant la tumeur. Ces artères collatérales doivent être recherchées; comprendre la prévalence et la prédiction de ces artères collatérales

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most frequent malignancy and the third leading cause of cancer mortality, contributing to 11% of cancer-related death worldwide\(^1\). According to the Barcelona Clinic Liver Cancer staging system, trans-arterial chemoembolization (TACE) is the standard local-regional therapy for a large group of HCC patients of the intermediate stage who are not candidates for curative treatment\(^2\). Moreover, TACE can be indicated in patients with early-stage HCC, in whom the recommended treatments are not feasible or have failed and used as a bridging therapy or downstaging for pending liver transplant or resection\(^2\). TACE is based on the principle of intra-arterial injection of an antineoplastic agent, followed by occlusion of the tumour feeding arteries. The aim of TACE is to produce tumour ischemia and concentrate the antineoplastic agent in the tumour, reducing its systemic toxicity\(^3,7\).

Familiarity with variations in the hepatic arterial anatomy is of the utmost importance when performing TACE. Classically, HCC is mainly vascularized by the hepatic arteries (HA), however, numerous extrahepatic collateral (EHC) arteries may also provide parasitic blood supply to the tumour in certain circumstances and even when the HA is patent\(^9,10\). Generally, HCCs in contact with the liver capsule and large size have an overall likelihood of being supplied by EHC arteries\(^3,11\). The estimated prevalence of EHC arteries supplying HCC ranges between 17\% and 30.8\%\(^4,11\), and EHC development can be responsible for local tumour recurrence\(^3,11\). Moreover, EHC arteries can be the source of bleeding in the spontaneous rupture of an HCC\(^13\). TACE of HCC through HA and EHC arteries is therefore essential for achieving optimal therapeutic outcomes\(^1\). Gwon et al found that origins of the IPA are the celiac axis (39.7\%), aorta (38.6\%), renal artery (15.4\%), left gastric artery (3.7\%), hepatic artery (2.1\%), superior mesenteric artery (0.3\%) and contralateral IPA (3\%)\(^5\). The RIPA can anastomose with intrahepatic arteries at the caudate lobe and the posterior segment while the LIPA can communicate with those in the lateral segment\(^8\). In addition, the IPA can communicate with other adjacent arteries, such as RIMA, LIMA, LGA and RSRA, and facilitates an EHC blood supply to hepatic lesions located in the liver segment VII or those contact with the

PREVALENCE OF EHC

Various EHC arteries can potentially supply an HCC. Nonetheless, the presence of parasitic blood supply to HCC can be predicted based on tumour location, tumour characteristics (exophytic growth, extra capsular invasion), hypertrophy of a potential EHC artery, a peripheral defect in the tumour blush that smaller than expected tumour size at pre-procedural imaging, and marked attenuation of the HA on conventional angiography\(^8,9\). The prevalence of EHC arteries varies among studies, in which the inferior phrenic artery (IPA) and the omental artery (OMA) remain the most common\(^4,5\). Moustafa et al reported the frequency of EHC arteries as follows: right IPA (RIPA 70-83\%), left inferior phrenic artery (LIPA 12\%), OMA 13\%, right internal mammary artery (RIMA 8\%), left internal mammary artery (LIMA 1\%), right suprarenal artery (RSRA 9-11\%), right renal artery (RRA 12\%), intercostal artery (ICA 6-8\%), cystic artery (4\%), right and left gastric artery (RGA, LGA 3-4\%), lumbar artery (2\%), superior mesentery artery (SMA 1.5\%)\(^3,4,9,14\).

EHC arteries can be divided into 2 groups based on their origins: the upper abdomen group (IPA, OMA, RSRA, renal artery, cystic artery, gastric arteries, SMA, gastroduodenal artery and lumbar artery) and lower thorax group (IMA, ICA)\(^3\).

Upper Abdominal Extrahepatic Collateral Arteries

Inferior Phrenic Arteries (IPA)

The right IPA (Figure 1) is the most common source of EHC blood supply for HCC and frequently supplies HCCs located in the bare area of the liver\(^17\). Gwon et al found that origins of the IPA are the celiac axis (39.7\%), aorta (38.6\%), renal artery (15.4\%), left gastric artery (3.7\%), hepatic artery (2.1\%), superior mesenteric artery (0.3\%) and contralateral IPA (3\%)\(^5\). The RIPA can anastomose with intrahepatic arteries at the caudate lobe and the posterior segment while the LIPA can communicate with those in the lateral segment\(^8\). In addition, the IPA can communicate with other adjacent arteries, such as RIMA, LIMA, RICA, LGA and RSRA, and facilitates an EHC blood supply to hepatic lesions located in the liver segment VII or those contact with the
right hemidiaphragm\textsuperscript{4,13}. It is the main EHC artery which may contribute up to 50\% of EHC arteries\textsuperscript{4}. Notably, attenuation of the IPA can result in the augmentation or exaggeration of another adjacent EHC supply to HCC\textsuperscript{13}. The RIPA is highly suspected when (i) the lesion locates in the liver dome or caudate lobe (88\% of EHC arterial blood supply) and (ii) there is an asymmetry between the RIPA and LIPA seen on pre-procedural CT due to hypertrophied RIPA. The LIPA should be taken into consideration when the lesion abuts the left hemidiaphragm or locates in segments II and III of the left hepatic lobe\textsuperscript{4,17}. IPA embolization is usually feasible and safe. Complications may include hiccups, shoulder pain, lung consolidation, pleural effusion, esophagitis, gastritis, and gastric ulceration\textsuperscript{3,4,9}. Diaphragmatic weakness is radiologically evident in 40\% of the cases, yet mostly asymptomatic\textsuperscript{8}.

**Omental artery (OMA)**

This is the second most common EHC artery (Figure 2) which can provide parasitic supply to hepatic lesions located at the segment IV\textsuperscript{4,8}. However, due to the high mobility of the omentum, this EHC artery can supply HCC of any segment\textsuperscript{3,8}. Multiple omental branches usually originate from the gastroepiploic artery or the dorsal pancreatic artery\textsuperscript{8}. The OMA is usually hypertrophied to be detectable on CT when supplying an HCC\textsuperscript{3}. The embolization of the OMA is generally safe with several reported complications such as omental infarction and fat necrosis\textsuperscript{3,4,8}.

**Cystic Artery**

The cystic artery, a branch of the right HA, can provide parasitic feeders to HCC located adjacent to the gallbladder fossa\textsuperscript{4,9}. It can also provide an EHC arterial supply to HCC located in other portions of the right hepatic lobe and in the medial segment of the left hepatic lobe (Figure 3). This occurs more frequently when the HA is attenuated owing to prior TACE procedures. Selective catheterization is strongly recommended to avoid non-target embolization. Ischemic cholecystitis and gallbladder infarction are reported complications\textsuperscript{4,9}.

**Suprarenal arteries**

Suprarenal arteries consist of 3 sources (superior, middle, and inferior) that supply the adrenal gland\textsuperscript{8}. The right suprarenal arteries may provide parasitic supply to HCC which grows inferomedial and contacts the adrenal gland\textsuperscript{3}. TACE through the suprarenal arteries is generally safe, given the rich blood supply to the adrenal gland, though adrenal insufficiency and infarction have been encountered\textsuperscript{4,8}.
Figure 3. Extrahepatic parasitic supply from the cystic artery. (A) Celiac angiogram showed a tumour staining at the segment V, partially supplied from the cystic artery. (B) Super selective cystic arteriogram showed tumour network. (C) Dense Lipiodol uptake after chemoembolization.

Figure 4. Parasitic supply from the right suprarenal artery. (A) Tumour staining was evident on suprarenal arteriogram. Note a connection with bilateral inferior phrenic artery (arrow). (B) Super selection of the right suprarenal artery before embolization. (C) Lipiodol uptake.

Figure 5. Multiple hepatic and extrahepatic parasitic supplies to a multifocal HCC. (A) Celiac angiogram of the 4th TACE showed tumour staining at the posterior segment and multiple Lipiodol uptake from previous TACE. (B) Selective embolization of the posterior segment branch. (C): Tumour staining from the adrenal artery injection. (D) Selective embolization of the right renal capsular artery. (E) Multiple tumour staining from the lumbar artery.

Figure 6. Marginal recurrence of an HCC after left lobectomy. (A) Celiac angiogram demonstrated a tumour staining at the segment V (arrow), supplied by the right hepatic artery and the left gastric artery. (B) Super selective chemoembolization of the left gastric artery. (C) Lipiodol uptake.
Right renal artery
The right renal arteries may provide parasitic blood supply to HCC at segments VI and VIII [8]. The superior capsular artery is also reported to have an important role in providing these feeders (Figure 5). Detection of an EHC arterial supply from the right renal artery on pre-TACE CT scans is limited and accounts for about 5% of cases of EHC arteries supplying HCC. The embolization of these feeders has a wide range of technical success and is generally safe without documented complications4.

Gastric Arteries
The right and left gastric arteries may provide blood flow to hepatic lesions in close contact with the lesser curvature of the stomach (segment I, II, III). Again, super-selective embolization is necessary to avoid gastric ischemia4,18 (Figure 6).

Superior Mesenteric Artery (SMA)
Exophytic HCC at the inferior tip of the liver (segments V and VI) or in close contact with adjacent bowel loop may receive an EHC arterial supply from the right colic branch or even the ileocolic branch of the SMA8 (Figure 7). Detection of parasitic feeders from the terminal branches of the SMA with CT is limited, therefore, tumour location is usually the clue for prediction4. Distal embolization is recommended to avoid bowel ischemia4.

Figure 7. A 57-year-old man with a huge exophytic HCC. Common hepatic arteriogram shows tumour staining at the posterior segment (A). Parasitic supplies from the right colic branch (B) and the ileocolic branch (C) of the superior mesenteric artery, and from the superior adrenal branch of the right inferior phrenic artery (D).

Figure 8. Repeat TACE for a residual HCC supplied by the gastroduodenal artery (GDA). (B) Super selective embolization of the GDA. (C) Full Lipiodol uptake on spot image.

Figure 9. A 56-year-old with multifocal HCC undergoing multisession TACE. (A) Follow-up CT scan shows incomplete Lipiodol uptake and a viable exophytic tumour (asterisk) at the dome area after previous embolization of the RIPA. (B) Selective angiogram of the right lumbar artery reveals a tumour staining (arrow). (C,D) Dense Lipiodol uptake on final angiogram and follow-up CT.
Gastroduodenal Artery (GDA)

HCC at the medial aspect of the segments V and VI or in close contact with the duodenum may receive an EHC arterial supply from the gastroduodenal artery or its branches (Figure 8). Post hepatectomy is another favorable factor of EHC development due to neovascularization and stimulation of vascular endothelial growth factor. Acute pancreatitis, upper gastrointestinal inflammation, ulceration, and even perforations are possible complications of non-targeted embolization of GDA branches.

Lumbar Arteries

The lumbar arteries can Anastomose with the lower ICAs and may provide a parasitic arterial blood supply to HCC lesions located at segment VI (Figure 9). The technical success of TACE of lumbar arteries supplying HCC is limited (40%) owing to the various anastomoses between the lumbar and spinal arteries. Identifying this communication on angiography is crucial to decide if TACE is indicated.

Lower Thoracic Extrahepatic Collateral Arteries

Internal mammary artery (IMA)

The right IMA accounts for 8% of EHC arterial supply to an HCC (Figure 10). Small branches from the superior epigastric artery, one of a terminal branch of the IMA, extend into the falciform ligament and communicate with the HA. Parasitic supply from IMA is suspected when the vessel is hypertrophied and there is a large HCC abutting the ventral aspect of the diaphragm or locating in the segment II, III, IV, and VIII. Though complications of IMA embolization are usually mild and self-limiting, TACE should be performed super-selectively to avoid any non-targeted embolization of the anterior chest wall cutaneous branches. Chest wall pain, skin rash, pleural effusion, basal atelectasis, and even skin necrosis have been reported.

Intercostal Arteries (ICA)

Generally, large HCCs in the subcapsular region of the segment VI and VII and in contact with the anterior abdominal wall are prone to recruit a blood supply from an ICA, though this is not a common parasitic supply (Figure 11). Up to 83%
of HCCs supplied by an ICA are found in patients who have a history of TACE through the IPA. This could be explained by the anastomosis between the lower posterior ICAs and the IPA at the diaphragmatic insertion. The right 8th – 11th ICAs are the most common sources of EHC supplies to hepatic tumours. Suggestive CT findings were large HCC (10 cm), subcapsular location, defect in Lipiodol retention, HCC abutting abdominal wall, and hypertrophy. Technically, a microcatheter should be advanced further to the ascending vertical limb of the ICA before embolization to prevent regurgitation, otherwise, TACE is contraindicated due to the risk of spinal cord ischemia. Complications may include shoulder pain, pruritus, erythema, and skin necrosis.

**HOW TO PREDICT AN EHC**

Generally, the main cause of EHC development was considered HA occlusion by surgical ligation, mechanical injury or multiple TACE procedures. Recent studies have reported interruption or dissection of the HA by multiple TACE procedures to be the principal cause of the formation of EHC vessels. Patient age, atherosclerosis, patency of the HA, tumour size, anatomic location, direct invasion or adhesions to adjacent organs and previous treatment (surgical resection, ligation, TACE) are considered the causative factors of EHC formation. According to previous studies, tumour size is a consistent predictor of EHC development. A positive correlation between tumour location, tumour size (> 5 cm) and number of previous TACE and presence of parasitic blood supply to HCC has been observed. Peripheral tumours and tumours at the bare area of the liver, even small in size, have been found to have a higher incidence of EHC arterial supply. On the other hand, patients who have never undergone TACE or who have a patent HA may also have EHC arterial supplies. Tumour hypervascularity is another important factor in the development of EHC arteries. Another study investigated that the non-intact pseudo-capsule group had a higher incidence of ectopic blood supply than the intact pseudo-capsule group. Kim et al suggested EHC vessels when (1) a tumour grows exophytic or invades adjacent organs, (2) a tumour was in contact with the ligaments and bare area of the liver, (3) a hypertrophied EHC vessel is seen on a computed tomographic (CT) scan, (4) a peripheral defect of iodized oil retention within a tumour is seen during chemoembolization or on a follow-up CT scan, (5) a local recurrence develops at the peripheral portion of the treated tumour during follow-up, or (6) a sustained elevation in serum alpha-fetoprotein level is noted despite adequate embolization of the HA. Additionally, several arteries close to the liver, which are initially non-hepatic in nature, can be recruited by the tumour for its vascular supply.

**CONCLUSION**

Parasitic supply from EHC arteries is common in clinical practice. Detection and embolization of these vessels are essential to optimize treatment outcomes. Tumour size, location, vessel hypertrophy,
attenuated HA and multiple embolizations are suggestive of EHC pathway. Careful review of pre-procedural CT is strongly recommended before any procedure. Super-selective embolization where possible and understanding any vascular communication and anastomoses are crucial for a safe and effective TACE.

Author Contributions:
T.N.H.H.H. conceived the original draft preparation. T.B.L. and T.K.L. were responsible for conception and design of the review. T.B.L., A.D.H., D.H.N., H.P. and H.C.T. were responsible for the data acquisition. T.N.H.H.H. and T.B.L. were responsible for the collection and assembly of the articles/published data, and their inclusion and interpretation in this review. All authors contributed to the critical revision of the manuscript for valuable intellectual content. All authors have read and agreed with the final version of the manuscript.

Compliance with Ethics Requirements:
“The authors declare no conflict of interest regarding this article”

“The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study”

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