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REVIEW / *Cardiovascular imaging*

Hepatocellular carcinoma vascularization: From the most common to the lesser known arteries

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Abstract Hepatocellular carcinoma is the sixth most common cancer throughout the world. It is almost exclusively arterially vascularized, unlike the vascularization of the liver, which has a dual supply with a portal component of 75 to 80% and an arterial component of 20 to 25%. The reference treatment for intermediary stages of the Barcelona (B) classification is hepatic artery chemoembolization. The aim of chemoembolization is to inject the tumor chemotherapy into the artery and then to embolize the artery (or arteries), which supply the tumor. For this, knowledge of the anatomy of the hepatic artery is essential. Approximately 55% of the patients belong to the modal distribution, although numerous anatomical variants exist and must be recognized. In addition, primarily non-hepatic arteries may contribute to the vascularization of some hepatocellular carcinomas. Furthermore, new arterial supplies can be recruited by tumors after surgical or chemoembolization treatments. The aim of this article is to describe the different arteries, which may vascularize hepatocellular carcinomas. These arteries must be looked for, recognized, and reported by the radiologist on cross-section examinations in the pre-treatment assessment.

Hepatocellular carcinoma is the sixth most common cancer throughout the world [1]. It is the third leading cause of cancer deaths in the world after colorectal and lung cancers [2]. The incidence of hepatocellular carcinoma in France increased by 4.8% in men and by 3.4% in women during the period from 1980 to 2005 [3].

Hepatocellular carcinoma typically (75 to 80% of the cases) develops on a background of cirrhosis, although it may also occur in non-cirrhotic chronic liver disease and occasionally in a healthy liver [4].

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The Barcelona Clinic Liver Cancer (BCLC) classification takes account of the tumor features, liver function and the patient's general health. The BCLC algorithm proposes optimal treatment strategies based on the different stages of the disease: its use is currently recommended by the main European (EASL) and American (AASLD) learned societies for the treatment of patients suffering from hepatocellular carcinoma [1].

In the intermediary stages, which make up approximately one third of the cases at the time of diagnosis, the recommended treatment is chemoembolization [1]. This can also be used as an expectant treatment pending liver transplantation or surgical resection. Chemoembolization is based on the principle of intra-arterial injection of an antineoplastic agent, followed by occlusion of the artery or arteries, which supplies the tumor(s). Hepatocellular carcinomas are almost exclusively vascularized by the hepatic artery, whereas liver, which does not contain tumor, has a dual theoretical vascularization (a portal component of 75 to 80% and an arterial component of approximately 20 to 25%). The aim of chemoembolization is to produce tumor ischemia and concentrate the antineoplastic agent in the tumor, reducing its systemic toxicity.

In order for the treatment to be effective, it is essential that it is injected into the artery or arteries, which supply the tumor(s). These arteries must be identified by imaging in the pre-treatment assessment. Firstly, it is essential to understand the common hepatic arterial anatomy and its variants, and then, to identify any extra-hepatic branches which have vascularized the tumor, and whether these have been recruited spontaneously by the tumor or have been recruited after treatment (particularly surgical resection or previous chemoembolization).

The aim of this review is to describe the different arteries, which may vascularize hepatocellular carcinomas. These arteries must be looked for, recognized and reported by the radiologist on sectional imaging in the pre-treatment assessment and catheterized during chemoembolization.

Hepatic arterial anatomy

Approximately 55% of the patients fall within the modal distribution. Anatomical variants of the hepatic artery were reported by Michelsin in 1953 after cadaver dissections [5]. This classification was revisited by Hiatt et al. from surgical liver findings in 1000 patients [6] and then extended as a result of improved modern imaging techniques [7]. There are numerous variants, particularly of the right and left hepatic arteries, which may be present in isolation or associated with the hepatic artery per se.

Hepatocellular carcinomas may be vascularized by one or more branches arising from arteries supplying the liver. Selective catheterization of the different supplying artery or arteries can target injection of the treatment into the tumor and achieve maximum sparing of liver, which is not involved by the tumor.

Modal distribution

The modal distribution of hepatic arterial vascularization is a single hepatic artery (the so-called proper hepatic artery or middle hepatic artery), which supplies all of the liver. The celiac trunk, which arises from the anterior aspect of the aorta at the level of the T12 vertebra, divides into three branches: the splenic artery, the left gastric artery and the common hepatic artery. The common hepatic artery becomes the proper hepatic artery after the origin of the gastro-duodenal artery. The proper hepatic artery divides into the right and left branches of the hepatic artery (Fig. 1).

The vascular supply to segments I and IV is variable. In most people, the arterial branches which supply segment I arise from the right and left branches (Fig. 2), whereas the branch for segment IV usually arises from the left branch of the hepatic artery (in approximately 50% of the people) although it also frequently arises from the right branch (approximately 40% of the people) (Fig. 3).

Right hepatic artery

The right hepatic artery is, by definition, an artery arising from the superior mesenteric artery and is present in approximately 12% of the population [7]. It is classically the first branch arising from the right edge of the superior mesenteric artery (Figs. 4 and 5). It usually passes behind the portal vein and should not be confused with an early bifurcation of the hepatic artery in which the right branch of the hepatic artery arises from the lateral edge of the celiac trunk before the bifurcation into the splenic, left gastric and common hepatic artery, and runs behind the portal vein (Fig. 6). The right hepatic artery can supply either just the right side or the entire liver.

Left hepatic artery

The left hepatic artery arises from the left edge of the left gastric artery and passes through the Arantius sulcus before entering the liver (Figs. 7 and 8). It classically supplies the left lobe or the left side of the liver, but can vascularize the whole liver in under 0.5% of the people [6]. It is present in approximately 5% of the population [7].

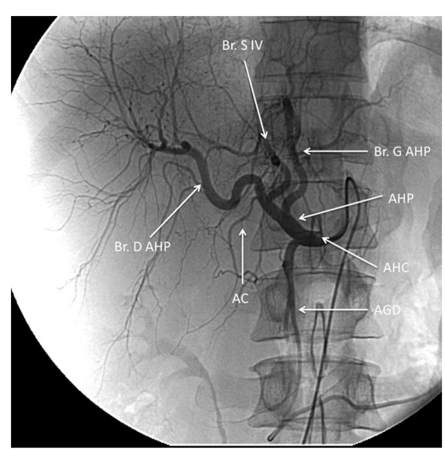

Figure 1. Arteriography. Catheterization of the common hepatic artery showing the common anatomy. CHA = common hepatic artery, PHA = proper hepatic artery, CA = cystic artery, GDA = gastro-duodenal artery, R Br. PHA = right branch of proper hepatic artery, L Br. PHA = left branch of proper hepatic artery, S IV Br. = segment IV branch.

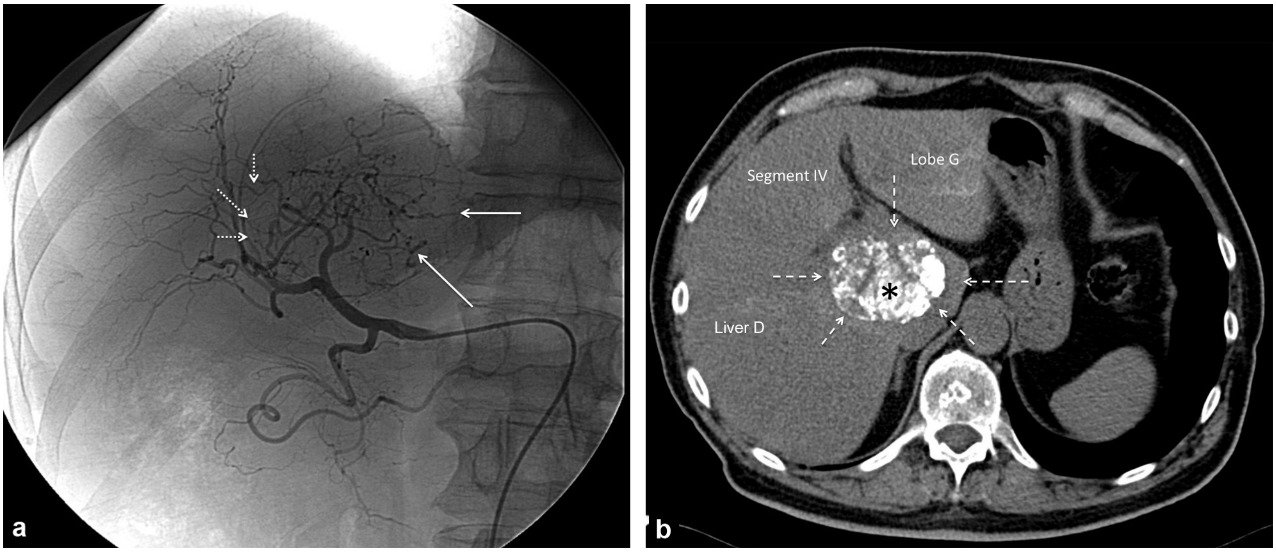

Figure 2. Vascularization of a segment I hepatocellular carcinoma in a 68-year-old man. Arteriography showing the arterial branches supplying the nodule, arising from the left branch (white arrows) and right branch (dotted arrows) of the proper hepatic artery. Axial CT without iodinated contrast enhancement performed a month after chemoembolization, with lipiodol (b) shows lipiodol uptake in the nodule (*) of segment I (shown by the dashed arrows), with no uptake in the left lobe, segment IV or right lobe of the liver.

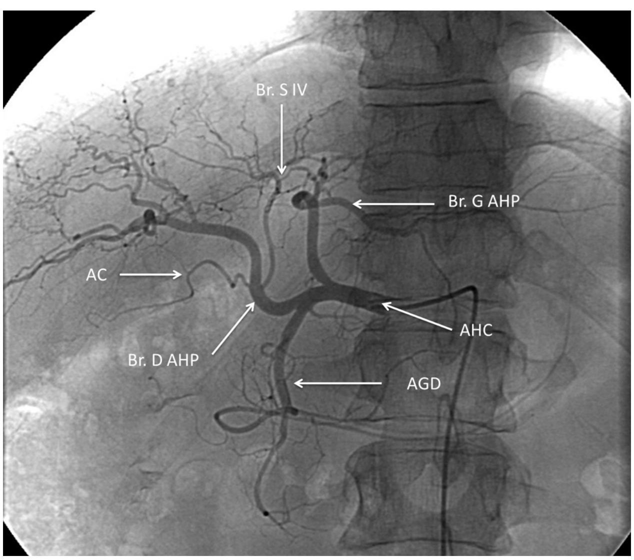

Figure 3. Arteriography showing the branch supplying segment IV arising from the right branch of the proper hepatic artery. PHA = proper hepatic artery, CA = cystic artery, GDA = gastroduodenal artery, R Br. PHA = right branch of proper hepatic artery, L Br. PHA = left branch of the proper hepatic artery, S IV Br. = segment IV branch.

Cystic artery

The cystic artery is classically the first branch arising from the right branch of the hepatic artery. In some people, particularly if the hepatocellular carcinoma is located on either side of the gall-bladder fossa (segments IV and V), the cystic artery may partially or exclusively vascularize the tumor. The cystic artery supplies 9% of the hepatocellular carcinomas, which are vascularized by extra-hepatic arteries [8].

Chemoembolization of the cystic artery is possible and has been described as being safe and technically possible

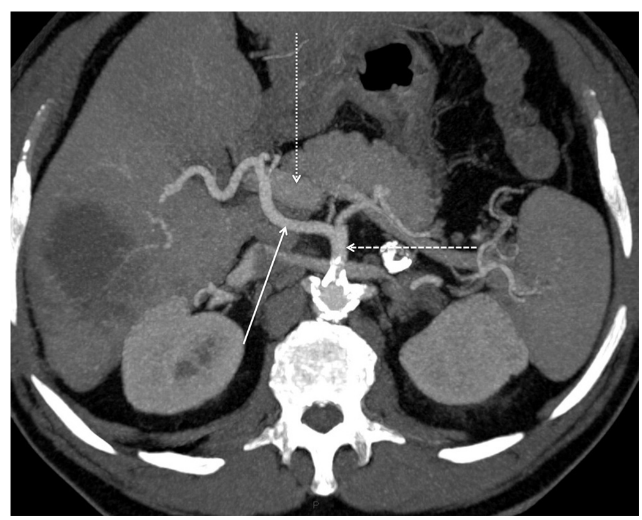

Figure 4. Axial CT with MIP. The right hepatic artery (arrow) arises from the superior mesenteric artery (dashed arrow) and passes behind the portal trunk (dotted arrow): retro-portal course.

in 67% of the cases in a series of 25 patients [9]. It may, however, cause ischemic cholecystitis and for this reason supraselective catheterization is recommended to preserve the vascularization of the gall-bladder [10].

Hepato-mesenteric (splenic) trunk

A single, common trunk may be present in under 0.5% of the cases, from which the celiac trunk and mesenteric artery arise. This is easy to recognize on sagittal CT sections (even without contrast enhancement), as a single, large artery is seen arising from the anterior aspect of the abdominal aorta before dividing into four separate arteries (splenic, common hepatic, left gastric and superior mesenteric arteries). The hepatic artery arises from the superior mesenteric artery

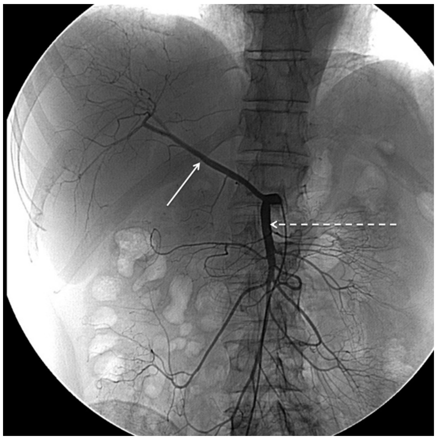

Figure 5. Selective arteriography of the superior mesenteric artery. The right hepatic artery (arrow), which is present in approximately 12% of the population, is the first branch arising from the right edge of the superior mesenteric artery (dashed arrow). This runs upwards and to the right, behind the portal vein.

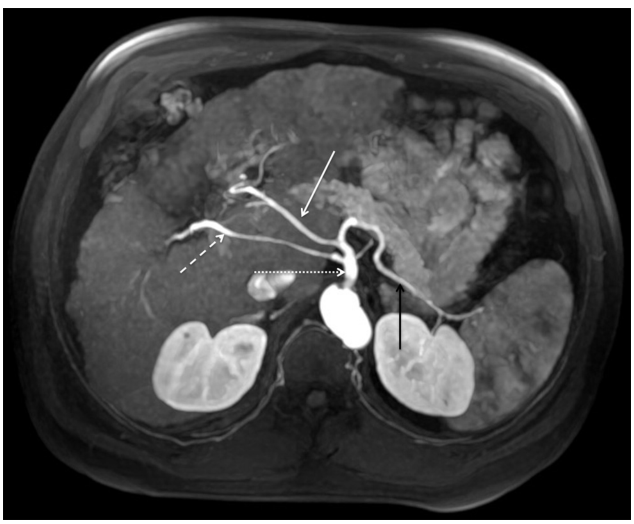

Figure 6. Axial MIP MRI showing the early origin of the right branch of the hepatic artery. The celiac trunk (dotted arrow) divides into the splenic artery (black arrow) and the common hepatic artery (white arrow). The right branch of the hepatic artery (dashed arrow) arises early from the right edge of the celiac trunk and there is no proper hepatic artery.

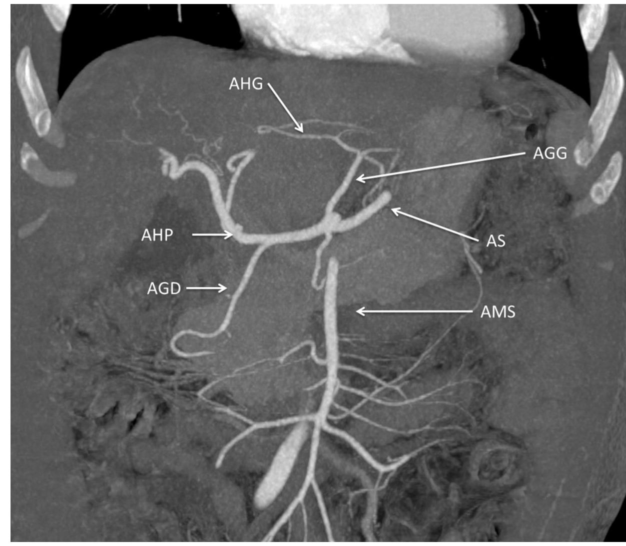

Figure 7. Hepatic artery CT angiogram. Coronal MIP reconstruction showing a left hepatic artery (LHA) arising from the left gastric artery (LGA). SA = splenic artery, SMA = superior mesenteric artery, GDA = gastro-duodenal artery, PHA = proper hepatic artery.

(hepato-mesenteric trunk) in approximately 0.5% to 1% of the people, whereas the splenic artery and left gastric artery arise above and instead of the celiac trunk (Fig. 9). Once these variants have been identified, endovascular guiding is then identical to that which is performed with the common hepatic artery and its branches.

Duodenal pancreatic arcades

Hemodynamic changes may develop as a result of stenosis or occlusion of the celiac trunk due to an arcuate ligament or atheromatous disease. The arterial supply to the liver is then provided by the duodenal pancreatic arcades, which arise from the superior mesenteric artery and run to the gastro-duodenal artery (in which the flow is countercurrent) and then the proper hepatic artery [11]. Chemoembolization may be performed by catheterizing these various arteries, usually with a microcatheter (Fig. 10).

Extra-hepatic arteries

Although most hepatocellular carcinomas are vascularized by the hepatic artery or its branches, they may receive their arterial supply from extra-hepatic arteries. Patients must be checked for ''parasitic'' collateral vascularization to ensure that chemoembolization is both effective and safe [10].

Several arteries close to the liver, which are initially ''non-hepatic'' in destination, may be ''recruited'' by the tumor for its vascular supply. There are two reasons for this: the site of the tumor (subcapsular, subdiaphragmatic, pedunculated, etc) and some previous treatments, which lead to changes in tumor vascularization (development of neovascularization after surgical division of an artery, redistribution of arterial flow after obstruction of some arteries by chemoembolization).

Hepatocellular carcinomas in contact with the liver capsule have an overall likelihood of 17% of being supplied by extra-hepatic arteries [12]. This likelihood depends on tumor size [13]: 63% of tumors over 6 cm in size and 3% of tumors under 4 cm in size are vascularized by extra-hepatic arteries [12].

The main extra-hepatic arteries, which may supply hepatocellular carcinomas, are the right inferior phrenic, omental, intercostal, right internal mammary, right renal, adrenal and lumbar arteries.

Right inferior phrenic artery

The phrenic arteries usually arise from the aorta but may originate from the celiac trunk (in 41% of the cases) [14], or more occasionally from the ipsilateral renal artery. The right inferior phrenic artery is the main extra-hepatic artery, which may supply hepatocellular carcinoma (Fig. 11) and is

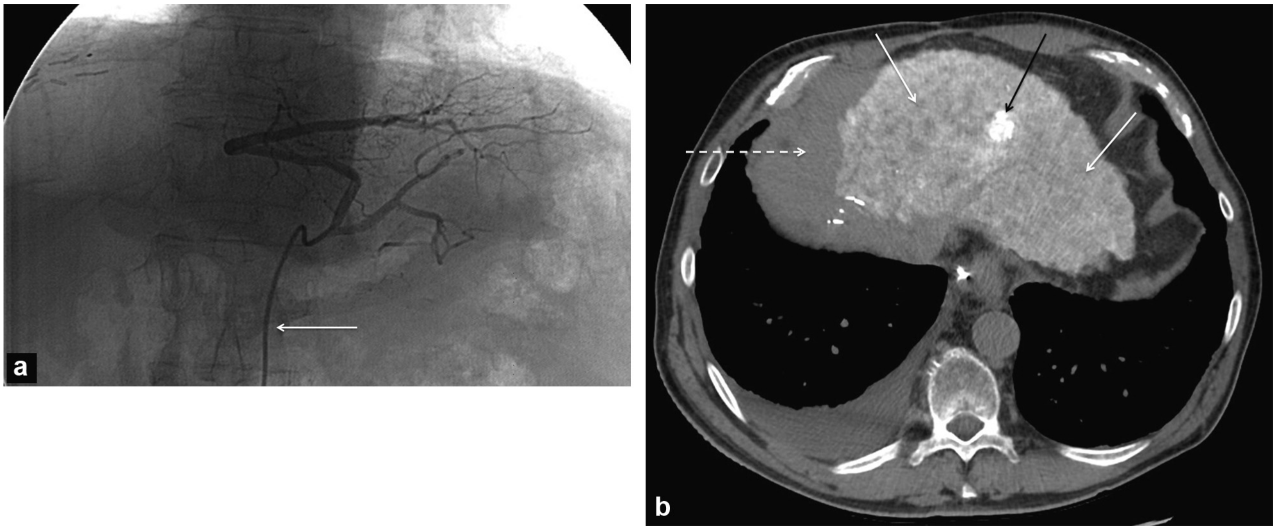

Figure 8. 68-year-old male patient with left lobe hepatocellular carcinoma and the left hepatic artery. Selective angiography of the left hepatic artery (a): the white arrow shows the catheter in the left hepatic artery. CT scan (b) a few hours after lipiodol chemoembolization of the left hepatic artery, showing uptake in the nodule (black arrow), with diffuse distribution of lipiodol in the left lobe and segment IV (white arrow) and no lipiodol in the right lobe of the liver (dashed arrow).

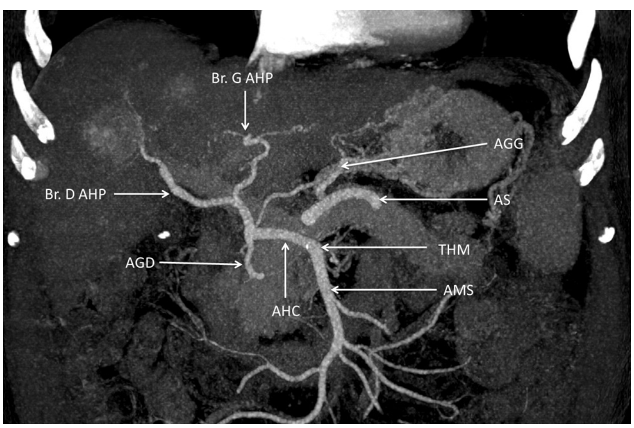

Figure 9. Selective arteriography showing a hepato-mesenteric trunk (HMT). The common hepatic artery (CHA) arises from the superior mesenteric artery (SMA) before dividing into the gastroduodenal artery (GDA) and its right (R Br. PHA) and left (L Br. PHA) branches; whereas the splenic artery (SA) and left gastric artery (LGA) arise from a common ''gastro-splenic'' trunk.

found in up to 50% of the ''parasitic'' extra-hepatic arteries [8]. The right inferior phrenic artery may, in particular, vascularize hepatocellular carcinomas located in segment VII [13,15], the right postero-superior (de-peritonealized) region of the liver (area nuda) and also segment I [15].

Chemoembolization via the right inferior phrenic artery is generally well tolerated although right shoulder pain, pleural effusion, atelectasis and diaphragmatic paralysis have been described [10].

Omental arteries

The omental arteries are the second most common extra-hepatic arteries, which may vascularize hepatocellular carcinoma and have been described in 15% of the cases of extra-hepatic vascularization [8]. The omental arteries supply the greater omentum and arise from the right and left gastro-epiploic arteries, which in turn arise from the gastroduodenal artery and the distal portion of the splenic artery.

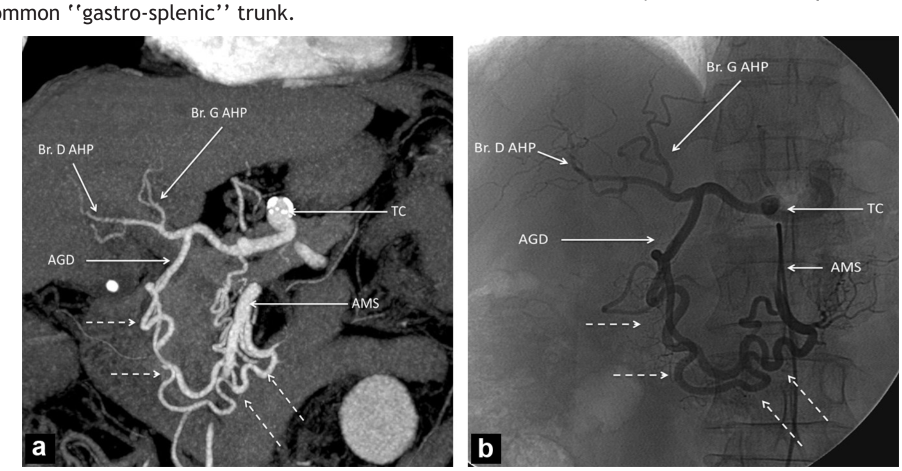

Figure 10. Coronal abdominal CT with MIP reconstruction (a) and correspondence with selective arteriography of the superior mesenteric artery (b) showing dilated, tortuous duodeno-pancreatic arcades (dashed arrow). The liver is vascularized by these arcades, blood circulating from the mesenteric artery (MSA) to the gastro-duodenal artery (GDA), before entering its right (R Br. PHA) and left (L Br. PHA) branches of the proper hepatic artery. CA = celiac trunk.

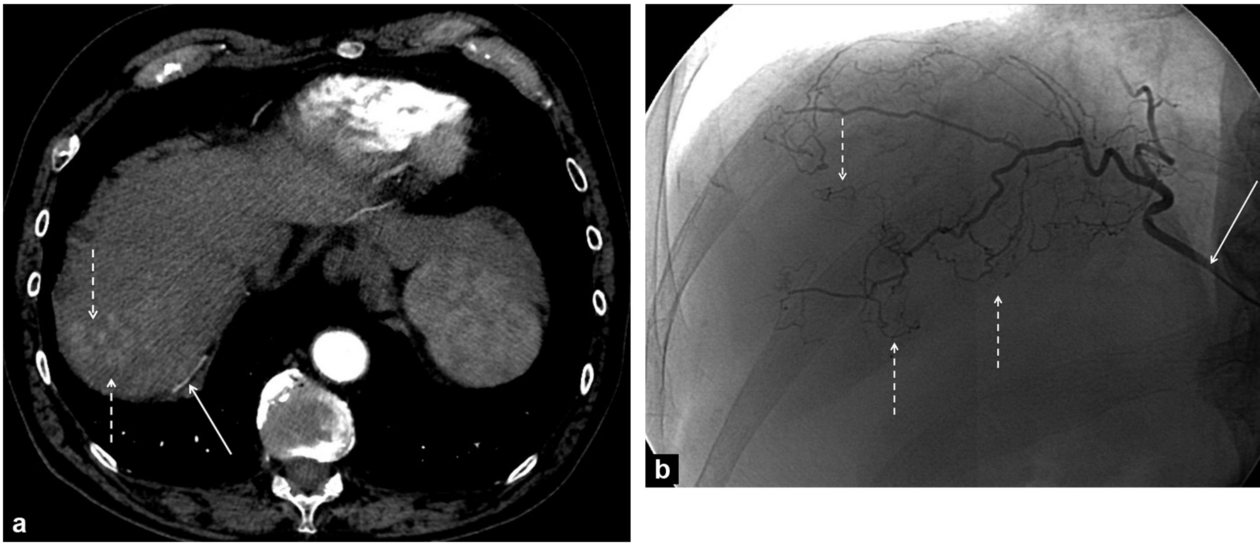

Figure 11. Axial abdominal CT scan (a) showing several hypervascular nodules of carcinoma in liver segment VII (dashed arrow) and a large diameter right inferior phrenic artery (arrow). Selective arteriography of the right inferior phrenic artery (arrow) showing tortuous dilated vessels (dashed arrows) in the dome of the liver (b).

Hepatocellular carcinomas, which are vascularized by the omental arteries, are those in contact with the surface of the liver [16] but because of the mobility of the greater omentum, they may be found in any region of the surface of the liver (Fig. 12) [10].

In a recent study, omental arteries supplying a hepatocellular carcinoma were found to arise from branches of the splenic artery in 0.6% of the cases (34/5413 patients). This ''parasitic'' vascularization was visible angiographically in 85% of the cases and on the pre-embolization CT scan in 79% of the cases [17].

Chemoembolization via the omental arteries is described as being safe and effective. No severe complications (omental or gastro-intestinal ischemia) were reported in a series of 21 patients, and overall survival was 81% at 6 months and 68% at 12 months [16]. In the series reported by Choi et al., a partial or complete response was obtained in 21 (62%) of the 34 patients treated [17].

Intercostal arteries

Hepatocellular carcinomas can be vascularized by the intercostal arteries. These are generally large hepatocellular carcinomas in the subcapsular region, in contact with the anterior abdominal wall, with or without abdominal wall invasion (Fig. 13). The intercostal arteries responsible are generally hypertrophied and arise from levels T8 to T11 on the right [18].

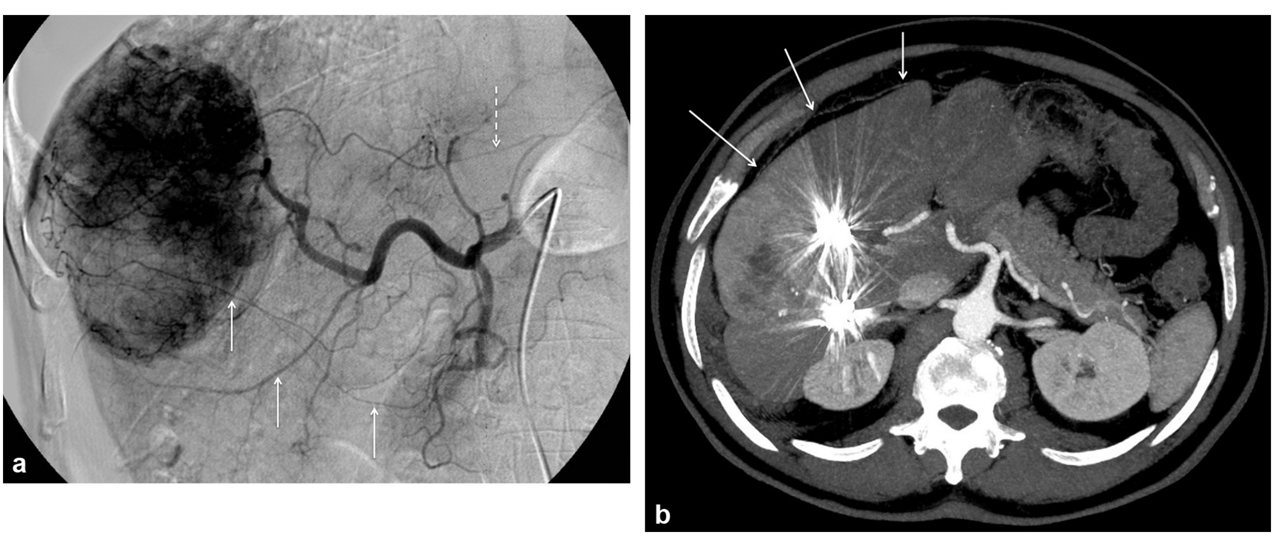

Figure 12. Celiac trunk arteriography (a) showing several omental arteries arising from the gastro-duodenal artery (arrows) and the left gastric artery (dashed arrow), contributing to the vascular supply of a large subcapsular hepatocellular carcinoma in the right lobe of the liver. These arteries are visible (arrows) on the axial section MIP abdominal CT scan (b) after a lipiodol chemoembolization ''sequence'' followed by right portal embolization before right hepatectomy. Note, coils in the branches of the right anterior and posterior portal sector branches (after right portal embolization).

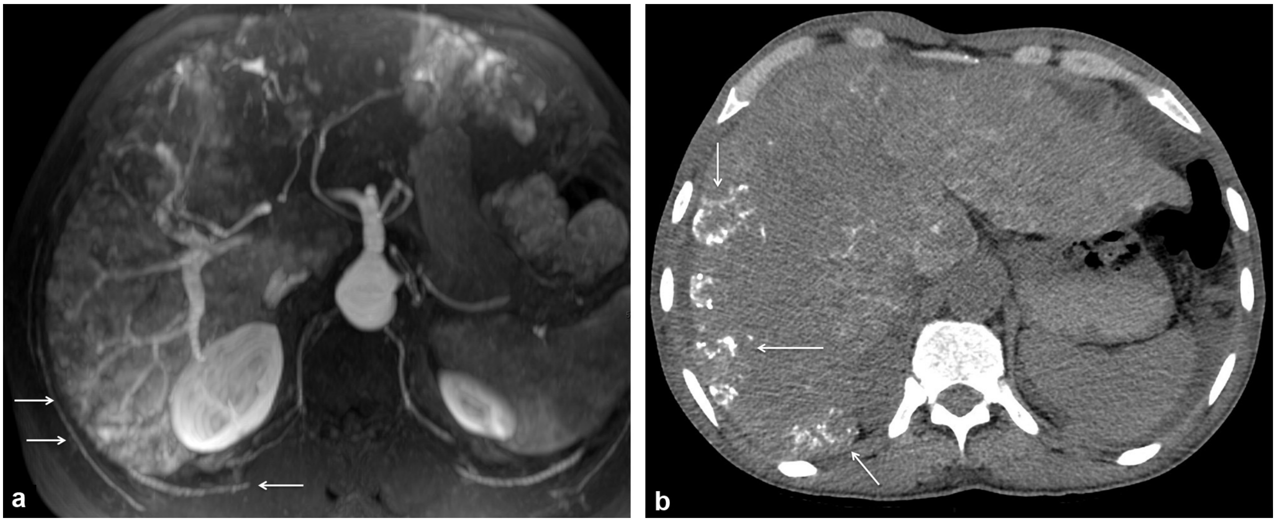

Figure 13. 73-year-old man with multifocal hepatocellular carcinoma. The most peripheral carcinoma nodules are partly supplied by intercostal arteries. Two intercostal arteries are seen on the axial abdominal MRI with MIP reconstruction (a). different areas of lipiodol uptake (arrows) in the peripheral subcapsular nodules on the abdominal scan without enhancement, after selective chemoembolization of the intercostal arteries (b).

Intercostal arteries, supplying hepatocellular carcinomas, can be seen in approximately 50% of the people by multi-detector CT compared to rotational scanning (C-Arm CT) using a flat sensor when angiography is performed [19] and in approximately 54% of the cases compared to arteriography [20]. Most studies consistently report that visualization of an intercostal artery on the CT scan is an important diagnostic feature of ''parasitic'' vascularization of hepatocellular carcinoma, particularly when the diameter of the hepatic artery is reduced [20].

Chemoembolization is possible but may cause complications, involving shoulder pain, pruritus, erythema and skin necrosis [18].

Internal mammary artery (or internal thoracic artery)

The internal mammary artery can also be recruited by hepatocellular carcinomas, in approximately 2.3% of the cases [8]. It arises from the interior aspect of the ipsilateral subclavian artery, descends vertically along the anterior chest wall and stems into the phrenic and intercostal branches. The right internal mammary artery can supply tumors in segments VIII and IV of the liver (Fig. 14) in hepatocellular carcinomas located on the ventral aspect of the liver whereas the left internal mammary artery can supply left lobe tumors.

In one study, 38 out of the 2815 patients that had chemoembolization, had at east partial vascularization of their hepatocellular carcinoma by an internal mammary artery on angiography (which is considered to be the ''reference'' investigation) [21]. A supplying artery was seen on the pre-treatment CT scan in 30 of these 38 patients (79% of the cases). The two criteria in this study [21] supporting vascularization of a hepatocellular carcinoma by the internal mammary artery were a supplying artery, which was

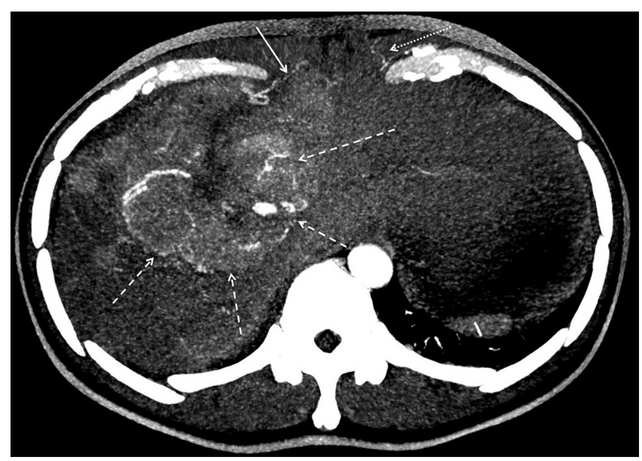

Figure 14. Axial abdominal CT with MIP reconstruction showing a large centro-hepatic hepatocellular carcinoma (dashed arrows). The anterior peripheral subcapsular portion is partly vascularized from the right internal mammary artery (arrow), which is dilated compared to the left internal mammary artery (dotted arrow).

clearly visible on CT scanning ($P = 0.002$) and a large tumor over 5 cm in size ($P = 0.025$).

Right renal artery

Tumors, which develop in the postero-inferior part of the right lobe of the liver, can be vascularized by a superior renal capsular branch in up to 2.2% of the cases [8]. The superior renal capsular artery arises from the inferior adrenal artery and therefore, it is sometimes difficult to distinguish these arteries from each other in multifocal hepatocellular carcinoma. This neovascularization has been described secondary to surgery, despite the hepatic artery being patent [22].

Lumbar arteries

Very occasionally, the lumbar arteries can provide extra-hepatic ''parasitic'' vascularization to a hepatocellular carcinoma (from 0.1% to 2%) [8,23]. This vascularization often occurs at a late stage in the progression of the malignancy as it has been shown to occur after vascularization (and then treatment) [23] by the right inferior phrenic artery.

Atypical post-treatment vascularization

Post-surgical neovascularization (branches of the GDA)

Surgery, either resection or hepatectomy, generally divides the hepatic parietal and capsular arteries. Healing results in neovascularization with stimulation of VEGF growth factors, which is greater following laparotomy than after laparoscopy in small animals [24]. As a result, arteries, which are not initially destined for the liver, can supply some hepatocellular carcinomas, particularly recurrences at the hepatectomy margin (Fig. 15) or after liver resection [25]. The arteries involved may be branches of the gastro-duodenal artery, the superior mesenteric and the right inferior phrenic artery.

Changes to pre-existing arteries after chemoembolization [26]

Chemoembolization may also result in vascular redistribution. It reduces or even stops, arterial blood flow to the tumor, in particular using loaded beads, which can embolize irreversibly unlike temporary embolization with resorbable haemostatic gelatin particles, which are used in lipiodol chemoembolization. Complete occlusion of the hepatic artery was only achieved in 4% of the cases in which extra-hepatic vascularization was found and it is possible that distal peripheral hepatic infarctions secondary to chemoembolization may result in omental or peritoneal adhesions and therefore lead to new vascularization via these adhesions [8]. In relapsed disease, the tumor is usually vascularized by the hepatic artery and its branches, but may occasionally be supplied by arteries not destined for the liver. It is important to check on follow-up imaging sections that chemoembolization has not altered the diameter of the hepatic arteries (stenosis, obstruction, dissection, etc.) or that of the extra-hepatic arteries (increase in diameter as a result of recruitment) (Fig. 16).

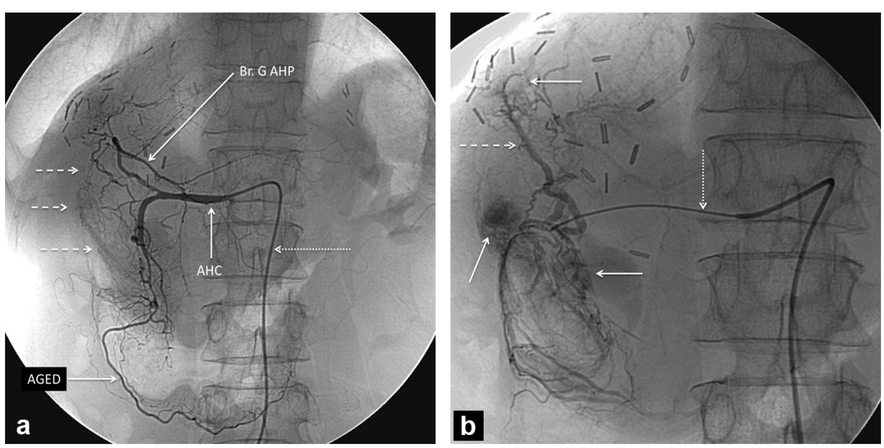

Figure 15. 58-year-old woman with hepatocellular carcinoma in a healthy liver. A right hepatectomy was performed 1 year before trifocal relapse at the hepatectomy margin. Several anarchic new arteries have developed in contact with the liver resection margin supplying the nodules of hepatocellular carcinoma. (a) Arteriography of the common hepatic artery showing the catheter (dotted arrow) in the common hepatic artery (CHA), dividing into the left branch of the proper hepatic artery (L Br. PHA) and the gastro-duodenal artery, which continues into the right gastro-epiploic artery (RGEA). Many small anarchic new vessels (dashed arrows) arise from these arteries and intertwine, supplying the liver resection margin. (b) Selective arteriography of a branch of the gastro-duodenal artery. The microcatheter (dotted arrow) is located in a horizontal dividing branch of the gastro-duodenal artery. The three tumor blushes are shown by the white arrows. The ''anastomotic'' (dashed arrow) artery is dilated.

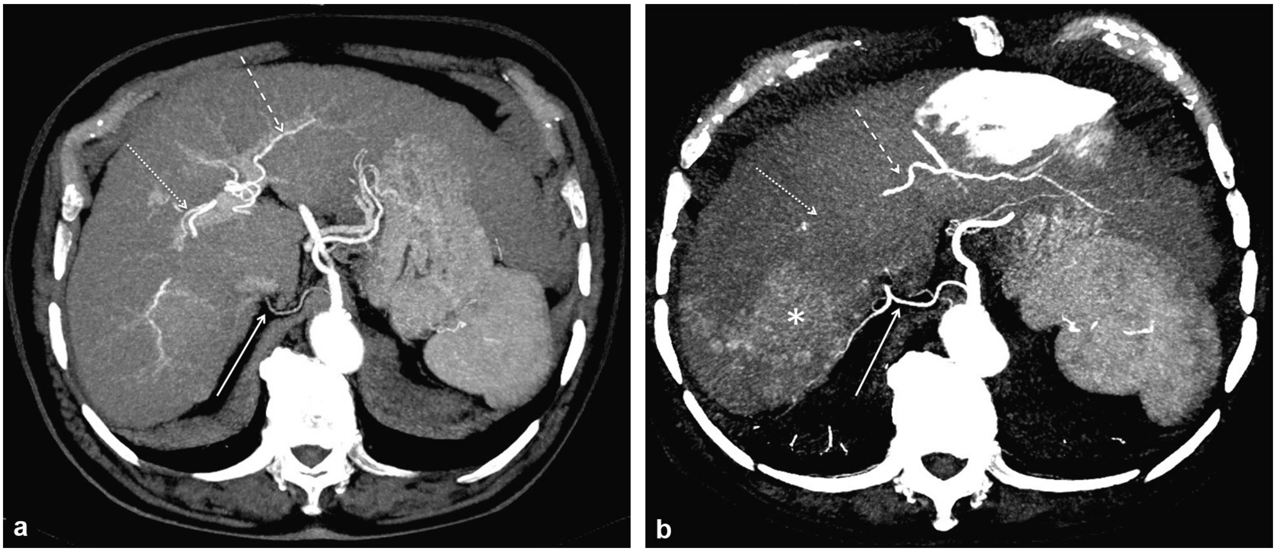

Figure 16. 73-year-old male patient with hepatocellular carcinoma in the right lobe of the liver treated by chemoembolization using non-resorbable loaded particles (with doxorubicin). (a) Axial abdominal CT with MIP reconstruction performed before chemoembolization showing a phrenic artery of normal diameter (arrow); the right and left branches of the hepatic artery are patent and of the same diameter. (b) Axial abdominal CT with MIP after chemoembolization, showing recurrence of tumor in segment VII of the liver, and a phrenic artery which is increased in diameter (arrow) compared to the pre-treatment CT scan, with occlusion of the right branch of the hepatic artery and moderate hypertrophy of the left branch of the hepatic artery compared to the pre-treatment scan.

Conclusion

The great majority of hepatocellular carcinomas are vascularized from the hepatic artery and its branches. Before chemoembolization, the hepatic arterial anatomy must be checked and it is vital that its major variants are recognised on the pre-treatment CT scan or arteriography.

These tumors may, however, acquire atypical ''parasitic'' vascularization from extra-hepatic arteries recruited by the tumor. There are some recognized risk factors, which must be looked for: a past history of resection, hepatectomy or repeated chemoembolization and large peripheral, subcapsular, exophytic tumors. In addition, finding a large diameter extra-hepatic artery running towards the liver or a vascular pedicle belonging to the tumor itself on the pre-treatment CT scan is evidence that the tumor has acquired ''parasitic'' vascular supply.

All of these findings should be noted on the CT or MRI report in the assessment of a hepatocellular carcinoma and must be taken into account by the interventional radiologist during chemoembolization.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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