Intra- and Extrahepatic Collaterals: Pitfalls and Pathways for Locoregional Therapy

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Intra-arterial interventions are increasingly performed for several other primary and metastatic liver tumors including hepatocellular carcinoma (HCC), cholangiocarcinoma, neuroendocrine tumor, colorectal cancer, uveal melanoma, and other less common entities.^{1–4} Understanding common patterns of extrahepatic collateral supply to metastases is vital in patients with bulky disease, especially following multiple treatment sessions with resulting arteriopathy with tumors in anatomically relevant locations. With the advent of radioembolization and the recognized risk of radiation-induced ulcer, insight into other intrahepatic pathways is also valuable to identify less common sources of tumor supply and to avoid nontarget infusion of the stomach or skin via accessory supply to the right gastric or falciform arteries, respectively. In this review, we describe common patterns originating from outside the liver or from the hepatic arteries.

Inferior Phrenic Artery

The right inferior phrenic artery (IPA) is the most common extrahepatic vessel that supplies HCC (→Fig. 1), while the left IPA is the sixth most common.⁵ The right and left IPAs most often arise as independent branches off the aorta (61.6%) or the celiac trunk (28.2%). Less common origins include the renal 4.3%; (→Fig. 2), left gastric (2.9%), and middle adrenal arteries (2.9%).⁶ Multidetector computed tomography (CT) can be used to identify the origin of the IPA and abdominal angiography can be used to confirm and treat. The right and left IPAs diverge from each other across the crura of the diaphragm and course superiorly and laterally along its undersurface. The IPA provides for most of the blood supply of the diaphragm and anastomoses with adjacent arteries, including the internal mammary, intercostal, and adrenal arteries.⁵

The presence of an extrahepatic collateral supplying HCC from the IPA may be present at initial diagnosis. Chung et al reported that out of a study of 50 patients with IPA collat-

erals, 37 showed evidence of a parasitic blood supply at the time of the initial TACE.⁷ Collateral supply of HCC by the IPA should be considered primarily based on the stage and anatomic location of the tumor. If the tumor is adjacent to the bare area of the liver and suspensory ligaments, the presence of a collateral supply from the right IPA is more likely. On the other hand, if the tumor is located adjacent to the left hemidiaphragm, a collateral supply from the left IPA may be considered.^{5,7}

The best predictor of favorable tumor response with IPA TACE is if blood supply to the tumor is exclusively through the IPA.⁸ The most common complication resulting from the TACE procedure is shoulder pain that occurs during or immediately after the procedure but typically subsides within a few days. Other notable complications include transient pleural effusion, basal atelectasis, and diaphragmatic weakness with an associated decrease in vital capacity.⁸ The diaphragmatic weakness results from ischemia, but the severity of the condition is varied as the diaphragm may survive through collateral flow through anastomoses of the IPA. Lee et al reported that the most important determinant factor for the development of diaphragmatic weakness is the extent of embolization of the IPA.⁹ The development of skin necrosis after IPA TACE is rare, but Brennan et al discussed the role the hepatic fetal artery, a variable remnant of the hepatic arterial system, may play in its development.¹⁰ Complications are best prevented by superselective embolization of only the tumor feeding vessels.⁹

Internal Mammary Artery

The IMA arises from the subclavian artery near its origin and courses inferiorly on the inside of the ribcage approximately a centimeter lateral to the sternum. During its descent, the IMA gives off the pericardiophrenic artery and anterior intercostal arteries, as well as numerous small branches to the anterior abdominal wall and diaphragm. After traversing

Fig. 1 This patient had a hepatocellular carcinoma at the dome of segment 2 (arrow, **a**), which extended far into his left upper quadrant. Initial selective chemoembolization was performed via segment 2 (**b**, **c**). Residual tumor was identified at imaging and at the next visit; inadvertent reflux into the left inferior phrenic artery (**d**) identified supply to the mass (arrow). This was embolized (**e**, **f**) while sparing some of the phrenic branches (**g**). Follow-up imaging demonstrated complete necrosis (**h**).

the sixth intercostal space, the IMA divides into the musculophrenic and inferior epigastric arteries. The musculophrenic artery runs obliquely inferiorly and laterally, roughly following the costal margin. The superior epigastric crosses the diaphragm and courses inferiorly, eventually anastomosing with the inferior epigastric artery at the umbilicus. The right superior epigastric artery runs through the falciform ligament and ligament teres, anastomosing with the hepatic falciform artery (FA), a terminal branch of the hepatic artery.¹¹

HCCs supplied by the right IMA are more common than those supplied by the left primarily because the right hepatic lobe is larger than the left lobe in most patients (►**Fig. 3**).¹² The IMA more frequently supplies tumors in patients who have survived for an extended period and those who have undergone multiple TACE procedures. However, the possibility of the IMA as an extrahepatic collateral should be kept in mind at initial diagnosis. Kim et al reported the presence of an IMA supply in 16% of patients at initial TACE.¹³ The IMA should be considered as a feeding artery if the tumor is in the ventral part of the liver abutting the diaphragm and anterior abdominal wall.¹⁴ Out of all HCCs supplied by the IMA, about two-third of tumors are supplied by the pericardiophrenic

artery and about one-third by the musculophrenic artery. The superior epigastric artery rarely supplies HCC.⁵ Tumors located in Couinaud segments IV and VIII have a higher chance of being supplied by the RIMA, whereas tumors in segments II and III have a higher chance of being supplied through the LIMA.¹²

As with other extrahepatic collaterals, the best positive predictor of a successful tumor response is whether the IMA is the exclusive blood supply of the tumor. Negative predictors include tumor size, multiplicity, and the presence of portal vein thrombosis.^{12,13} The most well-known complication of IMA embolization is the development of a precordial skin rash and ulceration likely caused by insufficient distal catheterization or unintentional regurgitation of embolizing material into other arteries.^{13–15} The rash typically resolves on its own over a period of weeks to months. Use of topical silver sulfadiazine does not seem to accelerate healing; however, antibiotics and analgesics can be used to control the progression of further complications.^{16,17} The most reliable way to decrease the incidence of dermatological complications after TACE is to catheterize the finest feeder of the tumor and perform chemoembolization only in catheterized tumor feeders.¹²

Fig. 2 This patient had a large hepatocellular carcinoma in the right liver, which extended cephalad as an exophytic mass (a) with portal vein invasion (arrow, b). Given the size of the mass, we planned on multiple sessions of treatment. The initial right lobar TACE was well tolerated (c). At the second visit, we performed an aortogram to look for accessory supply and the phrenic branch was identified arising from the right renal artery (arrow, d). This was selected (e) confirming tumor supply and embolized with particles (f).

Intercostal Artery

The lower nine pairs of posterior ICAs originate from the dorsal surface of the thoracic aorta. The posterior ICAs course in the intercostal space, running in between the internal intercostal and the innermost intercostal muscles. After giving off the dorsal, collateral intercostal, and muscular branches, the posterior ICA anastomoses with the anterior intercostal branches that come off the internal mammary artery or the musculophrenic artery. The lowermost posterior ICAs anastomose with the lateral branches of the IPA at the insertion site of the diaphragm on the lateral and posterior thoracic wall.¹⁸

ICA collateral supply of tumors is relatively uncommon. In a trial focused on HCC, Park et al reported that ICA collaterals occur at a frequency of 1.3% of all patients¹⁸ (►Fig. 4). ICA collateral supply also occurs late after multiple sessions of TACE when the native hepatic arteries fail to recanalize. HCCs that are abutting the inferolateral aspect of the diaphragm or those invading the abdominal wall are those that are more frequently supplied by the ICA. Tumors supplied by ICA collaterals are almost always located in Couinaud segments VI and/or VII.¹⁸ ICA collaterals that supply HCC all originate on the right side of the body and always pass the insertion site of the diaphragm to the thoracic cage, making a sharp

turn upward near the costochondral junction. The most common levels of the ICAs that supply HCC are T10, T9, and T11, in order of frequency.¹⁸ Multidetector CT can potentially be used to visualize ICA tumor feeders which become hypertrophied and appear as an enhancing dot in the upper intercostal space.¹⁹

Recanalization or further development of ICA collaterals often occurs after ICA TACE. Park et al reported that because ICA collateral supply is usually discovered in the advanced stage or after multiple sessions of TACE, it is difficult to measure the therapeutic efficacy of the procedure.¹⁸ Common complications are similar to those seen with other extrahepatic collaterals and include shoulder pain, itching sensation, erythema of the skin, and necrosis of the skin.²⁰ A rare but serious complication that can emerge after ICA TACE is spinal cord infarction leading to paraplegia (►Fig. 5). Spinal cord vasculature is complex and highly variable. The artery of Adamkiewicz can originate from the right ICAs and its occlusion can lead to anterior spinal artery syndrome.²¹ To minimize complications while performing ICA TACE, the microcatheter should be advanced beyond the diaphragmatic insertion to the thoracic cage, where a sharp upward turn near the costochondral junction is seen. If it is not possible to advance a microcatheter to this point, the

Fig. 3 This patient had two neuroendocrine tumor metastases. The first was exophytic off the posterior liver at the level of the hepatic vein confluence (thick arrow, **a**) and the second was perihepatic, extending anteriorly and cephalad from the level of the first tumor (thin arrows, **a**, **b**). At angiography, there was no intrahepatic supply. Injection of the right internal mammary artery clearly outlined the anterior mass (arrow, **c**) and c-arm CT also demonstrated supply to the posterior mass, which was also supplied by the phrenic artery (**d**, **e**). We treated the internal mammary artery first using 100- μ m particles after coil embolizing the terminal branches (**f**). The phrenic artery was also occluded during internal mammary artery embolization (**g**). Despite this, ischemic skin changes were identified following the procedure (**h**). These healed at follow-up examination with minimal residual (**i**).

potential risk of possible skin necrosis and spinal infarction must be strongly considered.¹⁸

Watershed Regions

Watershed tumors bridge two or more segments of the liver and are often supplied by two or more segmental

arteries (**►Fig. 6**). Intra-arterial therapy is rarely performed to more than 50% of the liver in one session. Therefore, the watershed zone between the left and right hepatic lobes (segment IV of left lobe and segments V/VIII of right lobe) is particularly important for interventional radiologists, as tumors in this location can be supplied by primary or accessory branches of the left or right left

Fig. 4 This patient had recurrent hepatocellular carcinoma with a large tumor near the dome (a). Flush angiography demonstrated tumor blush potentially supplied by extrahepatic branches (b). The inferior phrenic artery was selected (c) and embolized with particles (d). The right 12th intercostal artery also supplied the tumor (e). This was successfully embolized with particles as well (f).

Fig. 5 This patient had undergone multiple previous hepatic arterial treatments for metastatic uveal melanoma and had supply identified from a low intercostal artery. During the embolization, filling of the artery of Adamkiewicz was identified (arrow, a). This vessel was not visible earlier in the procedure. Embolization was terminated at this point. Unfortunately, the patient developed lower extremity weakness and MR confirmed injury to the spinal cord (arrow, b).

Fig. 6 Multiphase CT demonstrates arterial phase enhancement (a, arrow) and washout (b, arrow) of hepatocellular carcinoma. At treatment, celiac artery injection (c) outlines lateral segment branches arising off of the native left hepatic artery (thin arrows) and an accessory left hepatic branch arises from the left gastric artery (thick arrow). Native left hepatic artery digital subtraction angiography with supply to the lateral segment tumor identified (d). The lateral segment artery was chemoembolized and noncontrast injection c-arm CT performed which revealed partial coverage of the tumor with lipiodol and a central area that had not yet been treated (e). The accessory branch to the tumor in the lateral segment was then treated (f). Follow-up MRI demonstrated complete tumor necrosis (g).

Fig. 7 Contrast-enhanced CT (a) outlines a hypervascular mass (arrow) in the center of the liver in this patient with a history of nonalcoholic fatty liver disease. At initial angiography (b), the mass appears to potentially have supply from both hepatic artery branches. Right chemoembolization was performed. Restaging was done following the procedure and on noncontrast CT (c) a defect in the left margin of lipiodol uptake (arrow) that filled in with contrast (arrow, d) on arterial phase imaging. The defect was similarly identified at the beginning of the second session of chemoembolization.

Fig. 8 MRI demonstrates a segment 4 hepatocellular carcinoma (a). Celiac DSA (b) outlines the left hepatic artery supply to the tumor and absence of the right hepatic artery, which arose from the SMA. A prominent falciform artery was identified arising from the left hepatic artery (arrow, c). Given the straightforward course, it was catheterized (d) and coil embolized (e) to avoid nontarget embolization.

Fig. 9 CT demonstrates a large segment 4 hepatocellular carcinoma (a). At left hepatic angiography (b), a falciform artery was identified (arrow). In the same projection, the location of the artery was marked (c) using the surgical clips as a guide and a bag of ice placed on the patient's skin (d) allowing safe treatment without cutaneous complications.

Fig. 10 Left hepatic angiography at Y90 mapping prior to treatment for colorectal cancer metastases. Curvilinear, tortuous vessels typical of an accessory gastric artery are identified (arrows, a). Review of the preprocedure MR (b) demonstrates the liver margin medial to the midclavicular line. The concerning vessel was catheterized (c) and redistribution was attempted with coil embolization (d). Unfortunately, at the day of treatment, collateralization around the coils had occurred (e).

Fig. 11 Patient with intermediate-grade neuroendocrine malignancy presents for Y90 mapping in the setting of bilobar metastases (a). The celiac arteriogram (b) demonstrates the right hepatic artery arising directly from the celiac origin (thick arrow). The medial and lateral segmental branches have separate origins as well (thin arrows), both in close proximity to the gastroduodenal artery. DSA of the lateral segment branch (c) outlines the most cephalad vessel with curvilinear supply suggesting gastric collateralization (arrow). This suspicion was confirmed at c-arm CT as supply to the medial stomach was definitively identified (arrow, d). The concerning branch was catheterized distally (e) and embolized with small particle embolics and coils with stasis achieved (f). The vessel remained occluded at the day of therapy.

Fig. 12 This patient had undergone multiple right chemoembolizations for hepatocellular carcinoma and had local progression of a dominant tumor in the inferior right lobe (arrow, a). Celiac DSA (b) revealed a prominent omental branch from the gastroduodenal branch extending to the tumor region (arrow). This was selected (c) and delayed angiography (d) showed perfusion. This branch was embolized with small particles and coils back to the GDA origin (e). At treatment, there was greater supply to the tumor from the native right hepatic artery (f) and treatment from the right artery led to complete necrosis (arrow) at follow-up (g).

hepatic artery, alone or together (►Fig. 7).^{22,23} In a study by Kothary et al looking at 155 patients with unresectable HCCs, 54% had index watershed tumors located across two segments. Half of these tumors were between segment IV and segments V/VIII.²³ Although the dominant supply for watershed HCCs may be easily identified, collateral supply from adjacent segments may be less conspicuous. Tumors in these regions are at a higher risk for incomplete response as well as shorter disease-free survival following treatment. Cone-beam CT to identify cross-over and/or dual supplies prior to treatment may improve outcomes, while others have recommended prophylactic bilateral embolization of segmental arteries that “book-end” the tumor.^{22,23} In all cases, vigilant follow-up is recommended.

Falciform Artery

The falciform artery (FA) originates as a small terminal branch off the left or middle hepatic artery and courses through the falciform ligament, supplying the anterior abdominal wall between the xyphoid process and umbilicus. Visualization of the FA has been reported to be between 2 and 25% in angiographic studies and up to 67% in cadaveric studies.^{24,25} The presence of a patent FA on angiography has been linked to posttreatment supraumbilical skin rash, and in severe cases, fat/dermal necrosis and ulceration. Although prophylactic coil embolization of the FA prior to radioembolization to prevent cutaneous complications is well-accepted practice (►Fig. 8), there is currently no consensus on prophylactic embolization of the FA prior to

Fig. 13 This patient with hepatocellular carcinoma had occlusion of his hepatic arteries following treatment at an outside hospital. Initial flush angiography (a) did not demonstrate native hepatic artery supply. The inferior phrenic artery (b) was selected and treated (c) with particle embolization. In another visit, left lobe tumors (arrows) were treated via the internal mammary arteries (d, e).

chemoembolization due to low reported rates of complications.²⁵ In cases where the FA cannot be visualized due to diminutive size or tortuosity, prophylactic topical application of ice packs to vasoconstrict superficial arterial branches before and during radioembolization or chemoembolization may decrease risk of postprocedural cutaneous complications²⁴ (►Fig. 9).

Accessory Gastric Artery Branches

The right gastric artery (RGA) most commonly arises off the proper hepatic or left hepatic artery and runs along the lesser curvature of the stomach before anastomosing with the left gastric artery. Other origins of the RGA include the common hepatic, right hepatic, middle hepatic, and gastroduodenal (GDA) arteries. In addition to its variable origin, the RGA is small, usually less than 2 mm in diameter, and often sharply angulated, making it potentially difficult to select with a catheter.²⁶

In current practice, prophylactic coil embolization of RGA branches prior to radioembolization has been deemed unnecessary. Incidence rates of nontarget embolization without prophylactic coil embolization of either the GDA or RGA have been reported to be as low as 1% when using glass microspheres in conjunction with careful catheter placement in patients with good hepatic antegrade flow.²⁷ One situation where embolization is absolutely required is in the setting of

aberrant gastric supply from the left hepatic artery. This variant was identified in 3.3% of cadavers in one study.²⁸ Embolization in this scenario is essential to prevent nontarget gastric embolization. Embolization performed as distally as possible may result in better long-term occlusion and allow use of Y90²⁹ (►Fig. 10). Our current practice is to use medium size particles distally and coil back to the origin of the variant arterial branch (►Fig. 11).

Omental Collateral

A less common collateral pathway following multiple treatments is hypertrophy of omental branches via the GDA/gastroepiploic branches (►Fig. 12). We treat these lesions similarly with accessory right gastric branches with distal particle embolization followed by coil embolization of the main vessel back to the GDA artery.

Multiple Collaterals

In patients who have undergone multiple rounds of therapy, the presence of multiple collateral vessels supplying hepatic tumors needs to be considered (►Figs. 13 and 14). Our investigation algorithm includes the IPA for tumors at the dome, the IMA for anterior tumors, and the ICA for posterior and lateral neoplasms.

Fig. 14 In the setting of multiple treatments, multiple collaterals may develop. This patient with neuroendocrine tumor and carcinoid symptoms underwent 10 embolizations over 15 years. Flush angiography demonstrates threadlike remnants of his native right hepatic vasculature (a). The replaced left lateral segment branch was the last native branch remaining (b, c). The right inferior phrenic artery was embolized multiple times (d, e) and eventually was diminutive. As residual vessels diminished (f), the internal mammary artery was investigated and embolized (g). Finally, with persistent symptoms and threadlike collaterals through the liver (h), the gastroduodenal artery was coil embolized (i) and the right liver and segment 4 embolized from the distal common hepatic artery (j).

Conclusion

Collateral extrahepatic vascular supply is common and should be investigated as early as the first therapeutic procedure if tumor enhancement is incomplete at digital subtraction angiography or cone-beam computed tomography. Residual enhancement following treatment in appropriate locations can provide additional clues. At the time of treatment, it is also crucial to critically evaluate the diagnostic arteriography to identify potential nontarget collaterals that could lead to cutaneous injury or gastrointestinal ulceration.

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