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Extrahepatic collateral blood supply of hepatocellular carcinoma : Prevalence and success rate of chemoembolization in King Chulalongkorn Memorial Hospital

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Background : Extrahepatic collaterals that supply hepatocellular carcinoma (HCC) were frequently encountered. Transarterial chemoembolization (TACE) of these vessels increased the efficiency control of tumor. Impact of these collaterals in term of prevalence, success rate of TACE and complication were described.

Objective : To find the prevalence of each extrahepatic collateral that supplied HCC and clarify technical success rates and postprocedural complications following TACE of these vessels.

Design : Retrospective descriptive study.

Materials and Methods : We retrospectively reviewed angiograms and angiographic reports of 1,351 TACE sessions from 602 HCC patients between 2008 - 2010. Patients with tumor supply from extrahepatic collaterals were included. Then patient demographics, prevalence of the each extrahepatic collateral, technical success rates of TACE and post-TACE complications were recorded.

- Results** : *From the total of 141 cases of HCC, 119 men and 22 women with their median age 58 years old were found extrahepatic arterial supplies to the tumor on angiogram. Most patients had chronic viral hepatitis or liver cirrhosis. The right inferior phrenic artery was the most common extrahepatic collateral vessel, followed by the right intercostal artery and the right gastroepiploic artery. There were high technical success rates of TACE via the right adrenal artery (100%), cystic artery (100%), right intercostal artery (96.3%), left inferior phrenic artery (94.7%) and right inferior phrenic artery (92.86%). TACE via the gastroduodenal artery (64.7%), superior mesenteric artery (65%) and right renal artery (66.7%) showed less technical success rates. Of the total 195 extrahepatic vessels that we embolized, only 4 patients developed complications. There was no procedure related mortality.*
- Conclusions** : *HCCs with extrahepatic arterial blood supply were frequently founded in our institute (23%). There were varying branches of extrahepatic collateral arteries, which the right inferior phrenic artery was the most common. Selective chemoembolization of these vessels was safe. Postprocedural complications were seldom observed. Therefore, extrahepatic collateral supply to HCC should be sought and treated for effective tumor control.*
- Keywords** : *Extrahepatic collateral, hepatocellular carcinoma, transarterial chemoembolization.*

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- เหตุผลของการทำวิจัย** : หลอดเลือดสำรองจากภายนอกตับซึ่งเลี้ยงมะเร็งตับชนิด *hepatocellular* สามารถพบได้บ่อย การฉีดยาเคมีบำบัดเพื่อออกันหลอดเลือดเหล่านี้ทำให้การควบคุมโรคมีประสิทธิภาพยิ่งขึ้น ผู้วิจัยได้ศึกษาถึงความชุก, อัตราการประสบความสำเร็จและภาวะแทรกซ้อนที่เกิดขึ้นจากการฉีดยาเคมีบำบัดเพื่อออกันหลอดเลือดดังกล่าว
- วัตถุประสงค์** : เพื่อค้นหาความชุกของหลอดเลือดสำรองจากภายนอกตับซึ่งเลี้ยงมะเร็งตับชนิด *hepatocellular* แต่ละชนิดและแจกแจงอัตราประสบความสำเร็จในการฉีดยาเคมีบำบัดเพื่อออกันหลอดเลือดดังกล่าว รวมถึงภาวะแทรกซ้อนที่เกิดขึ้น
- รูปแบบการวิจัย** : การศึกษาเชิงพรรณนาแบบย้อนหลัง
- ตัวอย่างและวิธีการศึกษา** : ผู้วิจัยได้ทบทวนภาพการฉีดสีหลอดเลือดและรายงานผลย้อนหลังของผู้ป่วยมะเร็งตับจำนวน 602 คนที่ผ่านการฉีดยาเคมีบำบัดเพื่อออกันหลอดเลือดทั้งหมด 1,351 ครั้งตั้งแต่พ.ศ.2551 - 2553 ประกอบด้วยผู้ป่วยที่มีมะเร็งซึ่งเลี้ยงด้วยหลอดเลือดสำรองจากภายนอกตับ โดยมีการเก็บข้อมูลประชากร, ความชุกของหลอดเลือดสำรองจากภายนอกตับแต่ละเส้น, อัตราการประสบความสำเร็จและภาวะแทรกซ้อนที่เกิดขึ้นจากการฉีดยาเคมีบำบัดเพื่อออกันหลอดเลือดดังกล่าว
- ผลการศึกษา** : จากผู้ป่วยมะเร็งตับทั้งหมด 141 คนประกอบด้วย ชาย 119 คน หญิง 22 คน อายุเฉลี่ย 58 ปีที่พบหลอดเลือดสำรองจากภายนอกตับซึ่งเลี้ยงมะเร็งตับชนิด *hepatocellular* จากการตรวจด้วยการฉีดสีหลอดเลือด โดยพบว่าผู้ป่วยส่วนใหญ่มีการติดเชื้อไวรัสตับอักเสบบีเรื้อรังหรือมีภาวะตับแข็ง หลอดเลือดแดง *inferior phrenic* ขวาเป็นหลอดเลือดสำรองจากภายนอกตับที่มาเลี้ยงมะเร็งตับที่พบบ่อยที่สุด รองลงมาคือ หลอดเลือดแดง *intercostal* ขวา และ หลอดเลือดแดง *gastroepiploic* ขวา การฉีดยาเคมีบำบัดเพื่อออกันหลอดเลือดมีอัตราประสบความสำเร็จสูงในหลอดเลือดแดง *adrenal* ขวา (100%),

หลอดเลือดแดง cystic (100%), หลอดเลือดแดง intercostal (96.30%), หลอดเลือดแดง inferior phrenic ซ้าย (94.74%), หลอดเลือดแดง inferior phrenic ขวา (92.86%) ในขณะที่การฉีดยาเคมีเพื่ออุดกั้น หลอดเลือดแดง gastroduodenal, superior mesenteric และ renal มีอัตราประสบความสำเร็จน้อยกว่า ในจำนวนหลอดเลือดสำรวจจากภายนอกทั้งหมด 195 เส้นที่ได้รับการฉีดยาเคมีเพื่ออุดกั้นหลอดเลือด พบภาวะแทรกซ้อนหลังทำเพียง 4 คน และไม่พบว่ามีผู้ป่วยเสียชีวิตจากการทำหัตถการ

สรุป : มะเร็งตับที่มีหลอดเลือดสำรวจจากภายนอกตีบมาเลี้ยงพบได้บ่อย ในสถาบันของผู้วิจัย (23%) มีที่มาจากหลายแหล่ง โดยพบเป็นหลอดเลือดแดง inferior phrenic ขวามากที่สุด การฉีดยาเคมีบำบัดเพื่ออุดกั้นหลอดเลือดดังกล่าวค่อนข้างปลอดภัยและพบภาวะแทรกซ้อนได้น้อย ดังนั้น จึงแนะนำให้ค้นหาและรักษาหลอดเลือดสำรวจจากภายนอกซึ่งเลี้ยงมะเร็งตับเพื่อให้สามารถควบคุมโรคได้

คำสำคัญ : หลอดเลือดสำรวจจากภายนอกตีบ, มะเร็งตับชนิด hepatocellular, การฉีดยาเคมีเพื่ออุดกั้นหลอดเลือดแดง.

Hepatocellular carcinoma (HCC) is one of the most common malignant tumors in East Asia. From the database of National Cancer Institute, Minister of Public Health of Thailand; malignant neoplasm of the liver and intrahepatic bile duct is a leading cause of morbidity and mortality, ranking third in men and fifth in women as the source of primary malignancy in 2008. ⁽¹⁾

Curative treatment options for HCC induced surgical removal of tumor either liver resection or transplantation and local ablative therapy are established for the best treatment for early HCC, whereas transarterial chemoembolization (TACE) plays an important role in the treatment of unresectable HCC as well as percutaneous ablation. ^(2, 3)

Most of the HCCs are supplied by the hepatic arteries. But in practice, HCCs that are supplied by the extrahepatic collateral arteries are frequently encountered. ⁽⁴⁾ Chemoembolization of these collateral vessels should be performed for the best tumor control but some collaterals are challenging to approach and resulted in technical failure. ⁽⁴⁾

When extrahepatic collaterals are embolized, there is a risk of non-target branch embolization, which can lead to a variety of complications, depending on its location, territory and magnitude of TACE. ⁽⁵⁾ For example, TACE of the inferior phrenic artery might causes pleural effusion and basal atelectasis afterward. ⁽⁵⁾ Cutaneous complications can occur as a result of TACE of the internal mammary artery and the intercostal artery. ⁽⁵⁾

Materials and Methods

This retrospective-descriptive study was

approved by the Ethics Committee of the Faculty of Medicine, Chulalongkorn university. The data collection is considered a low risk to the patient and expected benefits received, so the need to obtain informed consent was waived.

Patient selection

From January 2008 to December 2010, there are 1,351 TACE sessions performed in 602 patients. Of the total 602 patients, two patients whose pathology had been proven cholangiocarcinoma were excluded from the study. Both showed typical imaging features for hepatocellular carcinoma and underwent TACE and liver biopsy in the same admission. After the official pathologic reports were obtained, both patients were referred to the specialist for proper management. We retrospectively reviewed angiogram and reported TACE of each session to determine the prevalence of each extrahepatic collateral. Total 268 collaterals in 145 patients were found. Seven extrahepatic collaterals supply the peritoneal nodules and two extrahepatic collaterals supply the intra-abdominal lymph nodes (Figure 1) were excluded from our study. The remaining 259 collaterals in 141 patients were included from this study.

Methods

The patient's medical records, angiograms and pre- and post-procedural computed tomography (CT) images were retrospectively reviewed. The patients' demographics, underlying liver disease, angiogram findings and post-procedural complication were recorded.

Angiographic evidence of extrahepatic collaterals supplying hepatocellular carcinoma were

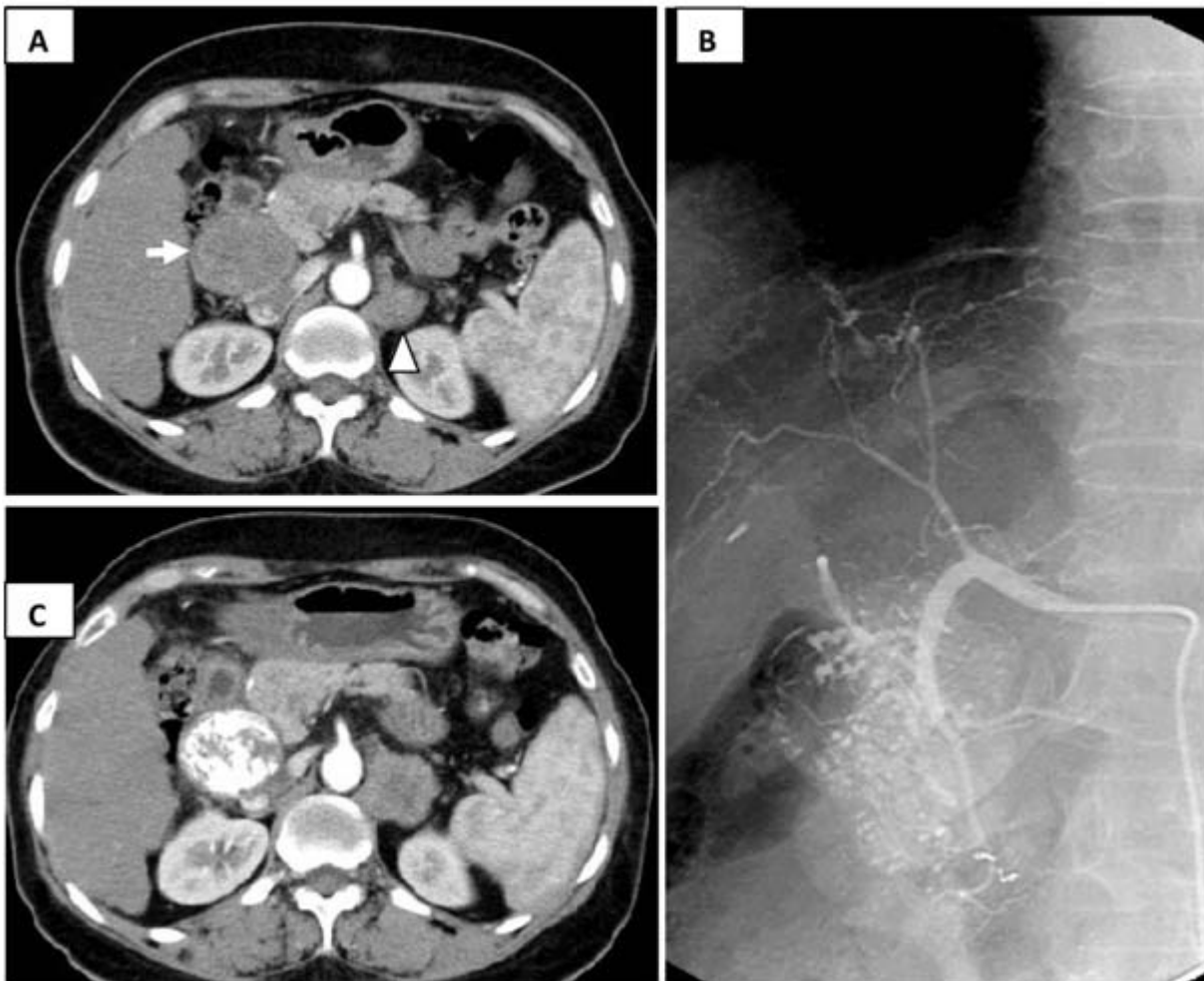


Figure 1. A) Contrast-enhanced CT scan (arterial phase) before TACE showed a 4.3 X 4.4 X 3.9 cm enlarged gastrohepatic node (arrow). A 3.2 X 3.4 X 3.6 cm enlarged left para-aortic node (arrowhead) are also seen. B) Spot radiograph obtained during TACE via inferior pancreaticoduodenal artery showed increased lipiodol staining in the mass at the inferior aspect of the liver. C) Contrast-enhanced CT scan (arterial phase) obtained 2 months after TACE showed dense lipiodol staining of the previous mentioned gastrohepatic node.

solely diagnosed by digital subtraction angiography (DSA). TACE of extrahepatic collaterals were undergone only when evidence of tumor supply on DSA were definite and we were able to place the catheter in the proper position.

Technical success was defined by successful catheter placement within the tumor-feeding branch of extrahepatic collaterals and successful administration of chemoembolic agents.

Technical success rate was calculated by a number of successfully embolized vessels divided by the number of vessels that selective catheterization was attempted. Because sometimes the amount of chemoembolic agent was not enough to embolize every single feeding vessel. In that case, the patient would be scheduled for next TACE within 4-6 weeks to complete the treatment.

If the selective embolization was not possible due to failure of selective catheterization, vascular injury or any reason, it would be recorded as technical failure.

The postprocedural complications associated with TACE of extrahepatic collateral were retrospectively reviewed from discharge summaries and outpatient records.

Results

Extrahepatic collaterals were observed in 141 patients (23.42%) from 187 sessions of TACE. The patients included 119 men and 22 women, their age was ranging from 28-84 years old (mean age 58 years old). Most patients had chronic viral hepatitis and/or liver cirrhosis. Forty nine patients had viral hepatitis B infection and liver cirrhosis. Twenty-eight patients had only viral hepatitis B infection without liver cirrhosis. Fourteen patients had cryptogenic liver cirrhosis. Ten patients had viral hepatitis C infection and liver cirrhosis. Seven patients had only viral hepatitis C infection without liver cirrhosis. Two patients had co-infection of viral hepatitis B and C. Two patients had nonalcoholic steatohepatitis with liver cirrhosis. There were 28 patients without known underlying liver disease.

Results of the prevalence, technical success of each extrahepatic collateral and postprocedural complications are summarized in Table 1.

Right inferior phrenic artery

In our study, the right inferior phrenic artery was the most common extrahepatic collateral arterial that supplied HCC, i.e. 76 patients out of 602 patients,

corresponding with 12.6% prevalence. Technical success rate of TACE via the right inferior phrenic artery was rather high (92.86%). Both failure of selective catheterization and vascular dissection were the failure causes. Two patients developed mild postprocedural complications which were right basal lung atelectasis (Figure 2) and right shoulder pain. The symptoms resolved spontaneously in both patients. Another one patient developed right pleural effusion after TACE and got worsening of other medical conditions. He was sent to the community hospital for end-of-life care.

Right intercostal artery

The right intercostal artery was the second most common collateral vessel in our study. T11 is the most common level of intercostal artery that supplies the HCC, followed by T10, T9, T12 and T8, respectively.

Overall technical success rate was 96.30 %. No associated complication followed TACE such as skin necrosis or spinal infarction was found.

Gastroepiploic artery

Blood supply from the right gastroepiploic artery to HCC was found in 28 patients, whereas the left gastroepiploic artery was found only 1 patient. TACE via the right gastroepiploic artery had fairly good technical success rate (77.27%). No postprocedural complication occurred.

The technical success rate of TACE via the left gastroepiploic artery could not be evaluated because selective catheterization was not attempted.

Table 1. Technical success rate and complications of each extrahepatic collateral vessels.

Collateral vessels	No. of vessels	Prevalence		No. of vessels that selective embolization was attempted	No. of successfully embolized vessels (Technical success rate)	Failure of selective catheterization	Vascular dissection	Complications
		By total TACE patients (N=602)	By total patient with extrahepatic collateral (n=141)					
R IPA	76	12.62%	53.90%	70	65 (92.86%)	2	3	Pleural effusion(1), Shoulder pain (1), basal lung atelectasis(1),
R ICA	29	4.82%	20.57%	27	26 (96.30%)	1	0	None
-T8	1							
-T9	7							
-T10	9							
-T11	10							
-T12	2							
R GEA	28	4.65%	19.86%	22	17 (77.27%)	4	1	None
SMA	23	3.82%	16.31%	20	13 (65.00%)	7	0	None
GDA	23	3.82%	16.31%	17	11 (64.71%)	6	0	Duodenal ulcer(1)
L IPA	20	3.32%	14.18%	19	18 (94.74%)	1	0	None
R AA	16	2.66%	11.35%	15	15 (100.00%)	0	0	None
L GA	10	1.66%	7.09%	9	8 (88.89%)	1	0	None
CA	8	1.33%	5.67%	7	7 (100.00%)	0	0	None
R RA	6	1.00%	4.26%	6	4 (66.67%)	2	0	None
R IMA	4	0.66%	2.84%	4	4 (100.00%)	0	0	None
R GA	4	0.66%	2.84%	4	1 (25.00%)	3	0	None
SA	4	0.66%	2.84%	1	1 (100.00%)	0	0	None
L IMA	3	0.50%	2.13%	3	3 (100.00%)	0	0	None
PDA	2	0.33%	1.42%	2	0 (0.00%)	2	0	None
LA	1	0.17%	0.71%	1	1 (100.00%)	0	0	None
Celiac	1	0.17%	0.71%	1	1 (100.00%)	0	0	None
L GEA	1	0.17%	0.71%	0	-	-	-	None

Abbreviations : R IPA = Right inferior phrenic artery, R ICA = Right intercostals artery, T = Thoracic level, R GEA = Right gastroepiploic artery, SMA = Superior mesenteric artery, GDA = Gastroduodenal artery, L IPA = Left inferior phrenic artery, R AA = Right adrenal artery, L GA = Left gastric artery, CA = Cystic artery, R RA = Right renal artery, R IMA = Right internal mammary artery, R GA = Right gastric artery, SA = Splenic artery, L IMA = Left internal mammary artery, PDA = Pancreaticoduodenal artery, LA = Lumbar artery, Celiac = Celiac artery, L GEA = Left gastroepiploic artery.

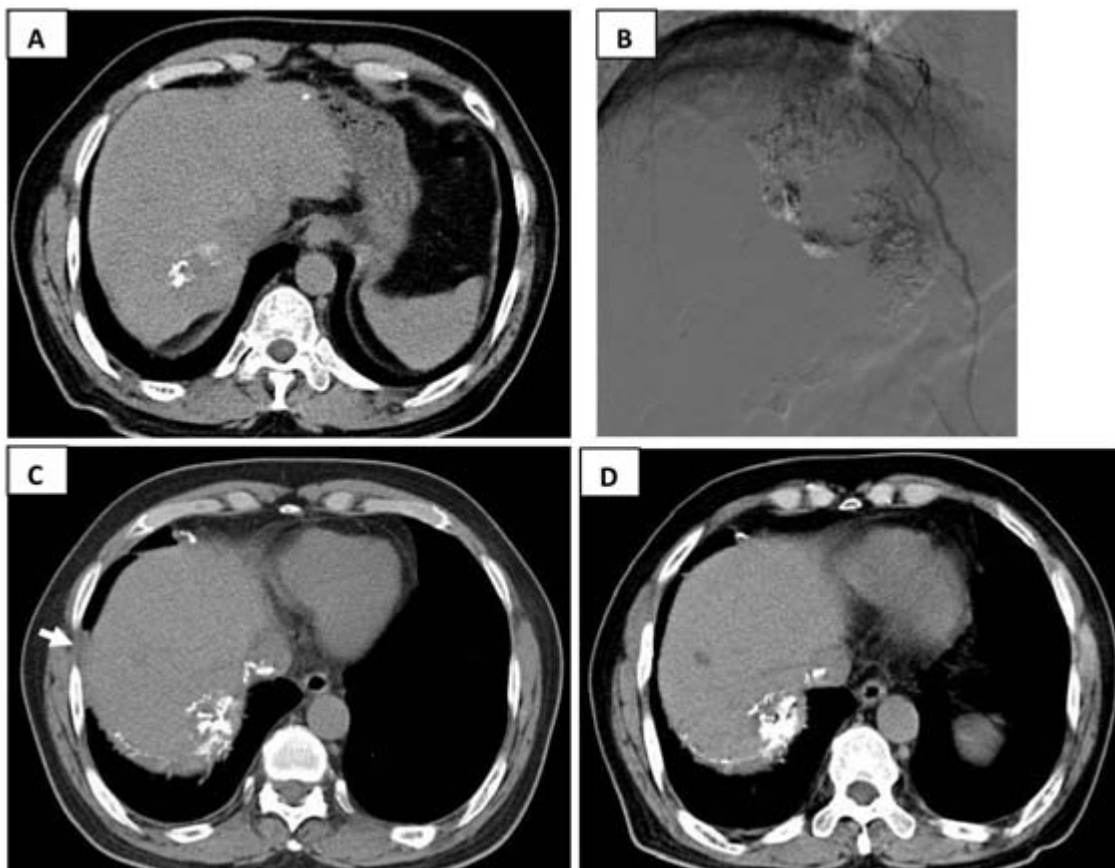


Figure 2. A) Axial plain CT scan before TACE showed partial lipiodol staining at the hepatic segment 7 with no abnormal density at the right basal lung. B) Spot radiography obtained after TACE of the right inferior phrenic artery. C) Axial plain CT scan obtained 1 month after TACE showed minimal right basal lung thickening (arrow). Interval increased lipiodol staining at the hepatic segment 7 are also seen. D) Axial plain CT scan obtained 2 months after TACE showed complete resolution of the previous right basal lung atelectasis.

Superior mesenteric artery

There were 23 collaterals from the superior mesenteric artery (SMA). Technical success rate of TACE via SMA was 65.0%. The procedures were frequently unsuccessful due to the failure of selective catheterization (Figure 3). However, when the vascular selection and embolization were successfully performed, no postprocedural complication was found.

Gastroduodenal artery

There were 33 collaterals from the gastroduodenal artery (GDA). The technical success rate was fair (64.7%). Only one patient developed one episode of upper gastrointestinal bleeding after TACE for two days. The patient underwent esophagogastrosocopy which showed gastric and duodenal ulcers at the gastric antrum and duodenal bulb. After medical treatment (proton-pump inhibitor) and supportive care, patient obtained full recovery without evidence of ongoing bleeding or recurrent bleeding.



Figure 3. Selective angiography of the superior mesenteric artery (SMA) shows small hypervascular mass at the right hepatic lobe fed by SMA. This vascular branch is too small caliber to access, resulting in technical failure.

Left inferior phrenic artery

Extrahepatic collaterals from the left inferior phrenic artery were found in 20 patients. Selective

embolization was attempted in 19 patients with 94.74% technical success rate (Figure 4). No complication associated with TACE procedure occurred.

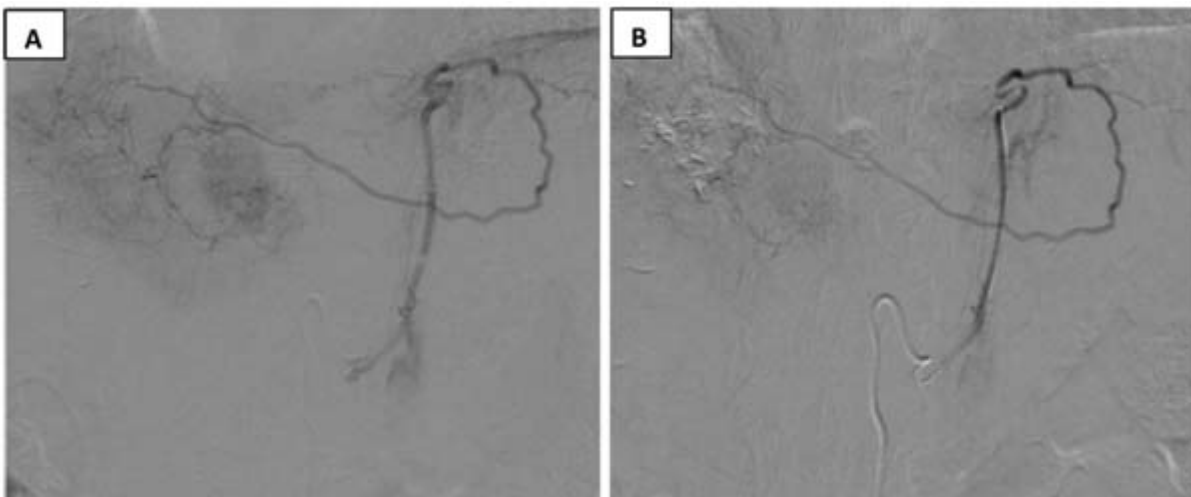


Figure 4. A) Selective angiography of the left inferior phrenic artery shows a hypervascular mass at the superior aspect of the right hepatic lobe, fed by left inferior phrenic artery. B) Spot radiography obtained after TACE showed increased lipiodol staining at the mentioned mass with decreased vascularity.

Right adrenal artery

There were 16 collaterals from the right adrenal artery. Technical success rate of TACE via the right adrenal artery was 100% and no post procedural complication occurred.

Gastric artery

Extrahepatic collaterals from the left and right gastric arteries were found about 10 and 4 vessels, respectively. Embolization of the left gastric artery was frequently success (88.89%), whereas embolization of the right gastric artery was usually failed (25.00%). No complication occurred following TACE via both vessels.

Cystic artery

The collateral arterial supply from the cystic artery was uncommon in our study. Eight collaterals were found in 602 patients, corresponding with 1.33 % prevalence. All 7 selected vessels were technical success (100%). No complication occurred following the procedure.

Miscellaneous arteries

There were other collaterals from the different branches including the right renal artery (6 vessels), right internal mammary artery (4 vessels), left internal mammary artery (3 vessels), splenic artery (4 vessels), pancreaticoduodenal artery (2 vessels), lumbar artery (1 vessel) and celiac axis (1 vessel) with their technical success rates as shown in the Table 1.

Discussions

Extrahepatic collateral arteries to HCC were frequently encountered especially in cases of tumors

of large size, subcapsular location or occlusion of hepatic artery due to previous embolization. Embolization of these vessels similar to the routine standard for hepatic vessels was attempted to obtain better tumor control. In our institute, extrahepatic collaterals have been searched in cases of tumor with suspected extrahepatic arterial supply on arterial-phase CT imaging, evidence of extrahepatic supply on previous angiogram, subcapsular location, exophytic growth, direct adjacent organ invasion, peripheral defect of previous iodized oil retention within the tumor, local recurrence developed at the peripheral portion of the treated tumor or occlusion of hepatic artery due to previous embolization.

In our study, the three most common extrahepatic collaterals were the right inferior phrenic artery, right intercostal artery and right gastroepiploic artery, respectively. The right inferior phrenic artery is the most common one. This finding is consistent with several previous studies.⁽⁴⁻⁷⁾ Unlike the previous study[6], the right intercostal artery is the second most common collateral vessel in our study. Other extrahepatic collateral branches were originated from abdominal aorta and its branches, except for the right and left internal mammary arteries.

Based upon our data, searching for extrahepatic collaterals by performing angiograms of the celiac, SMA, right inferior phrenic artery, right lower intercostal arteries and right renal artery should cover more than 90% of possible extrahepatic feeding vessels. The other possible vessels which were not included were the left inferior phrenic artery, right and left internal mammary arteries and lumbar artery. Angiogram of the left inferior phrenic artery should be performed in case of a bulky tumor in the left hepatic

lobe. If the viable tumor is dominant in the anterosuperior subcapsular location, either the right or left internal mammary arteries were suspicious.

Most of the extrahepatic collaterals showed high technical success rates especially the right adrenal artery (100%), cystic artery (100%), right intercostal artery (96.30%), left inferior phrenic artery (94.74%) and right inferior phrenic artery (92.86%).

Superselective catheterization of the gastroduodenal artery, superior mesenteric artery and right renal artery were more difficult, resulting in frequent technical failure. Upon encountering these difficult vessels, clinical judgment to pursue embolization should balance between risk and benefit either on the patient and the operator.

The uncommon branches of collaterals such as the left gastroepiploic artery, celiac axis, lumbar artery, pancreaticoduodenal artery, bilateral internal mammary arteries, splenic artery, right gastric artery were too small in number to conclude that how difficult it is to access these vessels.

In our study, TACE via the extrahepatic collateral was rather safe. Of the total 195 extrahepatic collateral vessels that we embolized, only 4 patients developed postprocedural complications. Two of them resolved spontaneously. One was UGI bleeding that was fully recovered after medical treatment. The other one developed right pleural effusion after TACE via right inferior phrenic artery and complicated by worsening of other medical conditions. There was no procedure related mortality.

Three of 4 patients were complicated after right inferior phrenic artery embolization. The reasons might be due to the fact that the right inferior phrenic artery was the most common extrahepatic vessel that

we embolized and sometimes the majority of chemoembolic agent was administered into the right inferior phrenic artery especially in the cases of hepatic artery occlusion.

They were some limitations in our study. All the angiographic data were retrospectively reviewed from PACS (Picture Archiving and Communication System) and angiographic report. Some extrahepatic collaterals (31 vessels out of 259 vessels) were found on routine angiography of the celiac axis or superior mesenteric artery without evidence of vascular selection from imaging or official report. We do not know whether superselection of these vessels was attempted or not. So we dismissed these vessels from the calculation of technical success rate. Due to the limitation of retrospective data collection, the true technical success rate of each extrahepatic collaterals may be quite different from what we report especially for the uncommon collaterals.

Some patients (13 out of 141 patients) in our study were referred from the other hospitals for TACE and then followed up at their primary hospitals. Therefore, some data regarding postprocedural complications could be missing.

Conclusion

HCCs with extrahepatic arterial blood supply were frequently encountered in our institute (23%). There were varying branches of extrahepatic collateral arteries, mostly arising from branches of the abdominal aorta. The right inferior phrenic artery was the most common one, followed by the right intercostal artery and right gastroepiploic artery. If superselective catheterization of the tumor feeding branch was achieved, TACE via extrahepatic collaterals was

almost always safe. Postprocedural complications were seldom observed and mostly responded to medical treatment or resolved spontaneously. Therefore, extrahepatic collateral arterial supply to HCC should be sought and treated with chemoembolization for the effective tumor control.

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