Analysis of Extrahepatic Collateral Arteries in Transcatheter Arterial Chemoembolization of Hepatocellular Carcinoma

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ABSTRACT
Objective: Development of extrahepatic collateral arteries (ECAs) supply to hepatocellular carcinoma (HCC) can interfere effective control of tumor by transcatheter arterial chemoembolization (TACE) treatment. The aim of this study is to analyze the prevalence and causative factors of ECAs to HCC and complications of TACE through each ECAs.
Methods: We performed a retrospective review of total 1,374 procedures from 639 patients with a diagnosis of HCC who were sent for TACE (range from 1 - 16 sessions, mean = 2.87 sessions) from January 2008 - May 2010. Prevalence, causative factors such as size and location of the tumor and previous treatment were analyzed.
Results: There are 122 (19.09%) from 639 patients that showed ECAs supplying the tumors. The prevalence of ECAs to HCC was 34.39% from right inferior phrenic artery, 30.68% from omental artery, 9.52% from left gastric artery, 5.82% from left inferior phrenic artery, 5.29% from colic branch of superior mesenteric artery (SMA) and 4.23% from intercostal artery. Statistical analysis showed that tumor size of more than 8-10 cm and location at hepatic surface, especially liver bare area were significantly associated with the presence of ECAs ($p<0.01$). The cumulative probability of ECAs formation increases with a number of the sessions of TACE.
Conclusion: Our observation indicates that the factors which could influence ECAs formation included tumor size of more than 8-10 cm and tumor location at surface area, especially liver bare area. As the number of TACE sessions increased, the cumulative probability of the presence of ECAs also increased. TACE through the ECAs is a relatively safe procedure. To recognize and get familiar with the presence of ECAs to HCC are essential to improve treatment outcome of the patients.

Keywords: Extrahepatic collateral arteries; hepatocellular carcinoma (Siriraj Med J 2018;70: 247-253)

INTRODUCTION

Hepatocellular carcinoma is the most common primary malignancy of the liver, with an annual incidence of more than 1 million worldwide.[1]

Surgical resection is the standard treatment for HCC. However, most patients with HCC were inoperable because of advanced stage at time of the presentation and would miss the optimal chance of operation.[2]

Transcatheter arterial chemoembolization (TACE) has been widely used as the effective therapeutic method or as an alternative palliative treatment. TACE is based on the fact that the normal liver receives a dual blood supply from the hepatic artery and the portal vein, but HCC is exclusively supplied by the hepatic artery.[3]

The extrahepatic collateral arteries (ECAs) to the liver are established in various conditions. The development of ECAs in HCC is certainly a situation that limits the efficacy of TACE. Chemoembolization through ECAs

Abbreviations: ECAs = extrahepatic collateral arteries, HCC = hepatocellular carcinoma, TACE = transcatheter arterial chemoembolization

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can be attempted to improve the therapeutic efficacy of TACE.

Previously, there was no study in Siriraj Hospital to analyze the prevalence and other concerns about the development of ECAs to HCC. Therefore, we retrospectively reviewed the prevalence of ECAs supplying HCC on digital subtraction angiography (DSA), causative factor and complication of TACE through each ECA in Siriraj Hospital.

MATERIALS AND METHODS

The study was approved by the Siriraj Institutional Review Board (Si.025/2553(EC1)). Between January 2008-May 2010, we retrospectively reviewed 1374 procedures (ranged from 1 - 16 sessions, mean = 2.87 sessions) from 639 consecutive patients with diagnosed HCC who were sent for TACE in Interventional Radiology (IR) Unit, Department of Radiology, Siriraj Hospital. Of the 639 patients, there were 521 males and 118 females with age ranging from 14 - 87 years (mean = 58.78 years). There were 49 patients who underwent radiofrequency ablation (RFA) before 1st TACE, and 37 patients underwent surgery before 1st TACE.

The sequence of study and intervention

General protocol of the patients who were sent to for TACE in our IR unit included dual phase enhanced CT scan of liver (64-section CT scanner: Lightspeed VCT; GE medical System) before initial TACE session. Then, initial angiogram with TACE was performed. Dual phase enhanced CT scan was done 4-5 weeks after initial TACE to evaluate residual tumor. If indicated, 2nd TACE was performed in the following week. After that, the 2nd dual phase enhanced CT was done to evaluate residual tumor in next 4-5 weeks and repeated TACE was done if indicated.

Before the TACE procedure, the anatomical imaging (CT or MRI of liver) were reviewed and planning for selecting the relevant arterial supply to the HCC mass included direct supply from hepatic artery and possible supply from extrahepatic collateral arteries as correlated with tumor characteristics that have risk of developing extrahepatic collateral arteries such as large tumor size, exophytic, extending to subcapsular areas or previous TACE procedure with hepatic artery dissection, stenosis and occlusion by repeated TACEs or evidence of previous tumor staining. The TACE procedure in IR unit, Siriraj Hospital were performed by chemo infusion using 5-FU 500 mg + Lipiodol 5 ml and Mitomycin-C 20 mg + Lipiodol 5 ml until arterial flow stasis was achieved. If the initial hepatic arterial blockade was insufficient because of a largely sized mass or arterioportal shunting, then embolization was performed with absorbable gelatin sponge particles (about 1 mm in diameter; Gelfoam; Upjohn, Kalamazoo, MI) soaked in 10 mL of nonionic contrast medium.

Statistical analysis

The angiogram and dual phase CT scan were retrospectively reviewed by an interventional radiologist who had experience in IR field for more than ten years and a 3rd-year radiology resident. Fisher's exact test for nominal variables and t-test for continuous variables were used and P values < 0.05 were considered to indicate statistical significance. SPSS statistical analysis software (SPSS Inc.) was used.

RESULTS

The mean patient's age was 58.78 years (range from 14 - 87 years) included 521 males and 118 females. There was no significant association of the patient's age and gender with the formation of ECAs.

In 122 patients (19.09%) from 639 patients, 189 ECAs were found to supply HCC. The number of ECAs per patient were one (71 patients), two (36 patients), three (11 patients), four (2 patients) and five ECAs (2 patients). The mean number of ECAs was 1.54 ECAs per patient. The prevalence of each ECA was shown in Table 1, Figs 1-4.

The tumor size and location were shown in table 2. The overall mean tumor size was 8.8 cm. The mean tumor size of first TACE was 9.6 cm. The mean tumor size of repeated TACE was 8 cm.

Univariate analysis showed that tumor size ($p < 0.01$), and location ($p < 0.01$) especially liver bare area were significantly associated with the formation of ECAs (Table 3). The cumulative probability curve (Table 4) showed that, as the number of TACE sessions increased, the probability of ECAs formation also increased.

There were 48 patients that underwent previous radiofrequency ablation (RFA) before first TACE, and all of these patients showed no ECA formation to supply HCC. There were 37 patients that underwent previous surgical resection before first TACE and 9 (24.32%) patients showed the formation of ECAs (P value = 0.536).

From 189 ECAs in 122 patients, embolization was done in 101 ECAs from 78 patients (Right inferior phrenic artery (RIPA) = 43, gastroduodenal artery (GDA) = 26, right inferior adrenal artery (RIAA) = 3, intercostal artery (ICA) = 6, left gastric artery (LGA) = 10, left inferior phrenic artery (LIPA) = 4, right renal capsular artery (RRCA) = 5, cystic artery = 1, colic branch from

TABLE 1. Prevalence of extrahepatic collateral arteries (ECAs).

Origination of ECAs	Incidence of ECAs	Percentage of ECA present (%)
Right inferior phrenic a.	65	34.39
Omental a.	58	30.68
Left gastric a.	18	9.52
Left inferior phrenic a.	11	5.82
Colic branch from SMA	10	5.29
Intercostal a.	8	4.23
Right renal capsular a.	6	3.17
Cystic a.	5	2.64
Right inferior adrenal a.	4	2.11
Right gastric a.	2	1.05
Right middle adrenal a.	1	0.52
Right superior adrenal a.	1	0.52
Total	189	100

(A) (B)

Fig 1. (A) A 50-year-old man with hepatocellular carcinoma was sent for 5th TACE. The right inferior phrenic angiogram show abnormal tumor staining at superior part of right lobe of liver supplied by dilated right inferior phrenic artery (arrow), (B) CT liver show HCC mass at right hepatic dome with partial lipiodol staining.

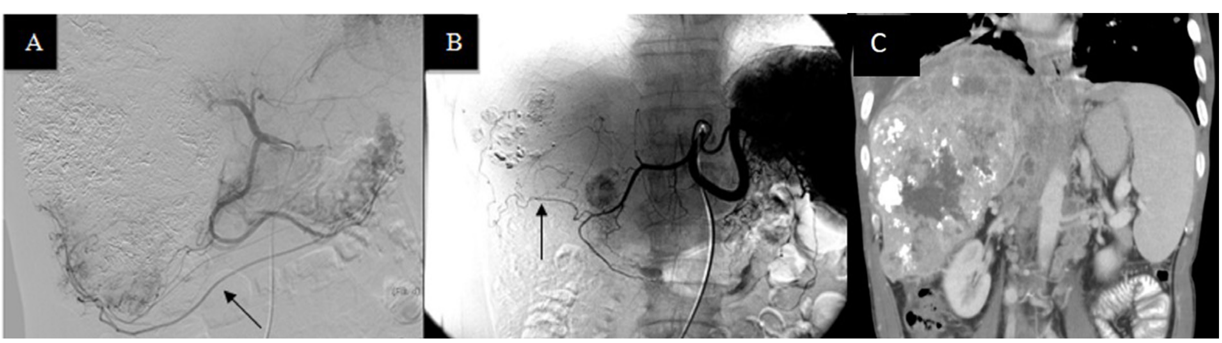


Fig 2. (A) A 40-year-old man with hepatocellular carcinoma was sent for 1st TACE. A. Gastroduodenal artery angiogram shows tumor staining at inferior part of right lobe of liver supplied by omental branch of right gastroepiploic artery (arrow). (B) TACE was performed in this ECA and showed increased lipiodol staining and decreased tumor vascularization (arrow). C. CT liver shows a large HCC at right lobe of liver with partial lipiodol staining.

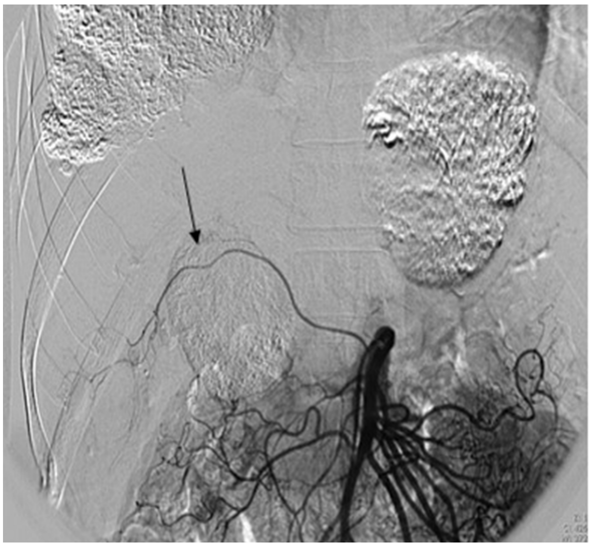
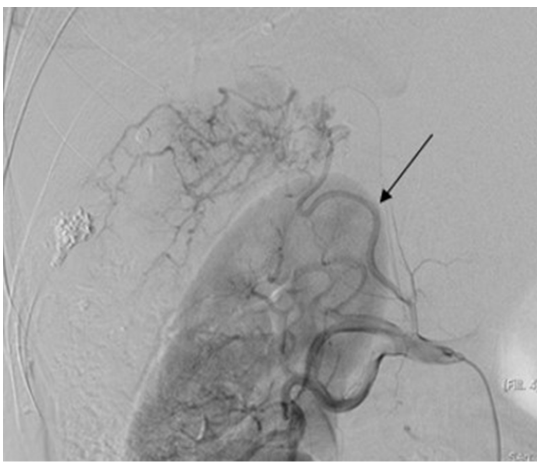
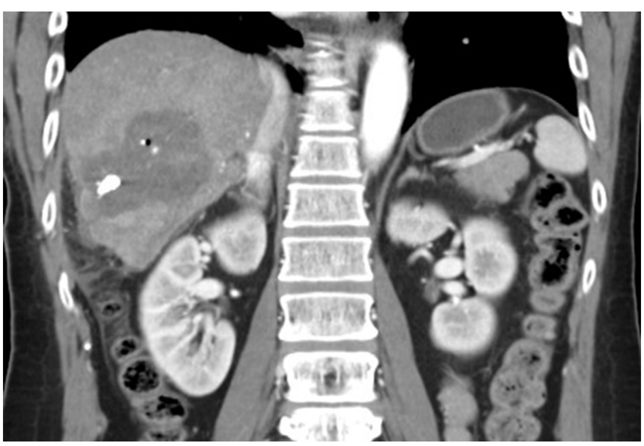


Fig 3. The same patient in fig 2 showed abnormal tumor staining at inferior part of right lobe of liver supplied by colic branch of superior mesenteric artery (arrow).



(A)



(B)

Fig 4. (A) A 50-year-old man with hepatocellular carcinoma with the right renal angiogram revealed abnormal tumor staining at inferior part of right lobe of liver supplied by right renal capsular artery (arrow) which has common origin to right inferior adrenal artery. (B) CT liver shows HCC mass at inferior part of right lobe of liver near the upper pole of right kidney.

SMA (superior mesenteric artery) = 2 and right middle adrenal artery (RMAA) = 1).

The complication occurred were described as follows, myelopathy or spinal cord infarction in 1 / 6 patients from embolization of ICA, which probably resulted from the inadvertent embolization of spinal branches arising from intercostal artery or non-target embolization; fever, abdominal pain and nausea/vomiting in 41 patients from RIPA (24 / 43 patients), ICA (1 / 4 patient), RIAA (1 / 3 patient), GDA (12 / 26 patients), LGA (3 / 10 patients); back pain from RIPA (2 / 43 patients) and hiccough from RIPA (1 / 43 patient). To prevent some serious complications especially myelopathy or spinal cord infarction, a good planning before TACE, including evaluation for a shunt and choice of the vessels used for the Lipiodol infusion prior to TACE, are very important to achieve a good overall result.

DISCUSSION

The development of ECAs in HCC is certainly a situation that limits the efficacy of TACE. There were several studies that reported the prevalence of ECAs and their concern. Wang YL et al.,[2] reported that extrahepatic blood supply tumors could be found in 43.1% patients with unresectable HCC. Okazaki et al.[4] found that one or more focuses of recurrence of HCC after hepatectomy in 38.2% patients (26/68) were fed not only by hepatic arteries but also by ECAs. Jin Wook Chung et al.,[3] showed that 82 (17%) of 479 patients showed 108 ECAs supplying tumor at initial presentation and 70 (14%) during repeated TACE sessions. They also found that the tumor size was a significant causative factor for development of these collateral vessels. Although they were differences among reported studies about incidence of ECAs, they had influenced the efficacy of chemoembolization of unresectable HCC. The prevalence and other concerns about ECAs formation have not been previously evaluated in Siriraj Hospital.

In our study, the tumor size was an important factor associated with ECAs formation (P value < 0.01) and the tumor size of > 8-10 cm, had the highest prevalence of ECAs. The larger size of tumor also have tendency to find ECAs formation as shown in Table 4., which correspond to the study of Wang YL et al.,[2] and Jin Wook Chung et al.[3] A surface tumor location, especially bare area (P value < 0.001) is a prerequisite for formation of ECAs which corresponds to the study from Jin Wook Chung et al.[3] As the number of TACE sessions increased, the cumulative probability of the presence of ECAs was also increased, corresponding with the previous study from Wang YL et al.,[2] and Jin Wook Chung et al.[3]

TABLE 2. Tumor size and correlation with presentation of extrahepatic collateral arteries (ECAs).

Tumor size	ECAs		Percentage of		
	absent	present	ECA present (%)	Total	P value
<2 cm	87	0	0	87	
2-4 cm	177	23	11.5	200	
4-6 cm	86	27	23.89	113	
6-8 cm	49	14	22.22	63	<0.01
8-10 cm	41	27	39.71	68	
>10 cm	77	31	28.7	108	
Total	517	122	19.09	639	

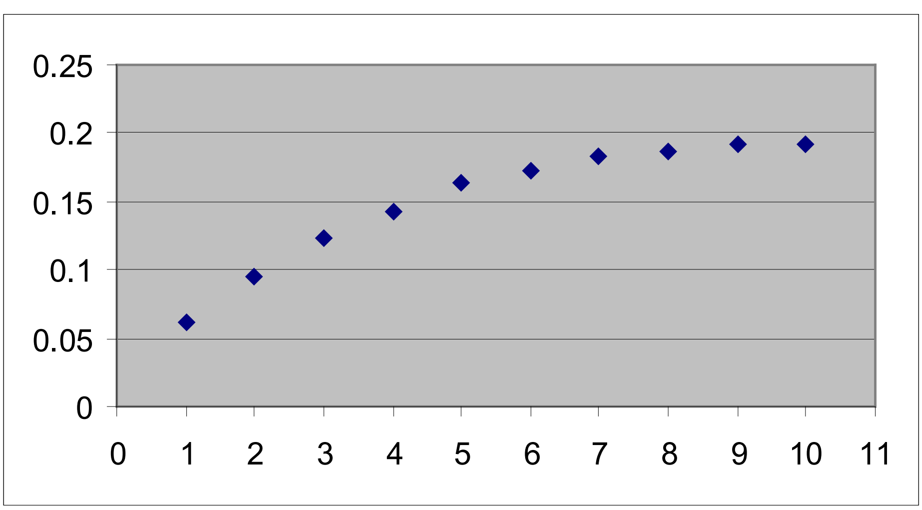
TABLE 3. Tumor size and correlation with presentation of extrahepatic collateral arteries (ECAs)

Location[1]		ECAs		Persentage of		
		Absent	Present	ECA present (%)	Total	P value
Surface	Bare area[2]	34	41	54.66	75	<0.01
	non-bare area	253	69	20.11	322	
Non-surface		230	12	5.06	242	<0.01
Total		517	122	19.09	639	

[1] If a tumor showed exophytic growth or it was observed to reach the liver margin on CT, then it was considered to have a surface location, but if it did not reach the liver margin, then it was considered to have a nonsurface location.[3]

[2] Posterior surface hepatic segment 7 and posterior half of the diaphragmatic surface of hepatic segment 8.[3]

TABLE 4. Cummulative probability curve of extrahepatic collateral artery formation of hepatocellular carcinoma.



Session (s) of TACE

Many articles have reported the prevalence of each ECAs. Shiro miyayama et al.,[5] reported incidence of RIPA (83%), cystic a. (24%) and omental a. (13%). Jin Wook Chung et al.,[3] reported incidence of RIPA (49.8%), omental a. (15.6%) and cystic a. (8.8%); Wang YL et al.,[2] showed incidence of RIPA (38.5%), SMA (23.1%) and LGA (12.8%). All mentioned studies showed that the right inferior phrenic artery was the most common ECA, corresponding to our result, (RIPA 34.3%, omental 30.6% and LGA 9.5%). The large tumor size which is located in contact with diaphragm especially bare areas is likely to be supplied from inferior phrenic artery. The tumor is probably supplied by omental branch if it located near surface of right hepatic lobe and medial segment. However, this omental branch can also supply a tumor at any location of liver due to it traverses along the greater omentum which is relatively mobile.

The procedure that causes ECAs in the literature included hepatic a. occlusion by surgical ligation, hepatic arterial interruption by repeated TACE or arterial dissection, previous abdominal operation due to postoperative omental or peritoneal adhesion and recurrent tumor at the resection margin.[6] However, ECAs supplying HCC also develop in the anatomical location of HCC, although the hepatic arterial supply remains intact.[7,8] In our study, 38 procedures from 10 patients who underwent previous surgical resection before 1st TACE developed ECAs. However, there was no significant correlation between previous treatment and development of ECAs (due to P-value=0.536 (>0.05)). We suggest that more patients who had previous surgical resection should be further evaluated for this correlation.

The patients who underwent previous RFA before TACE showed no ECA formation. Our study showed that RFA has no correlation with ECA formation, probably due to relatively small tumor size for sending to perform RFA.

Complications from chemoembolization of ECAs included cutaneous problems itching, erythema and necrosis from internal mammary, intercostal, or lumbar artery; gastrointestinal erosion, ulceration, or perforation from gastric, omental, and colic branch; paraplegia from spinal branches arising from intercostal or lumbar collateral vessels; cholecystitis or gallbladder infarction from cystic artery; shoulder pain, pleural effusion or basal atelectasis from inferior phrenic artery.[6,8-11]

The complications, which occurred in this study, included myelopathy from 1/6 patients from ICA; fever and abdominal pain with nausea/vomiting in 41 patients (24/ 43 patients from RIPA, 1/ 4 patients from ICA, 1/3 patients from RIAA, 12/26 patients from GDA, 3/10 patients from LGA; back pain 2/43 from RIPA; hiccough 1/43 patients from RIPA. The prevalence of complications from TACE through the ECAs are relatively low. Therefore, TACE through the ECAs are the relatively safe procedure.

Limitation of this study is due to retrospective analysis. We usually look for the ECAs in the patients who are suspected to have another tumor blood supply further than the hepatic artery. However, we could miss unsuspected ECAs in some patients due to many factors such as non-recognition from the interventional radiologists, or the ECAs are too small to be detected. Therefore, the prevalence of ECAs could be underestimated.

Another limitation was another treatment concerned in individual patients. The causative factors that we evaluated were only RFA and previous surgical resection before 1st TACE due to many patients who were treated by RFA and surgical resection were consulted for TACE. However, some patients had RFA or surgical resection between sessions of TACE and could be unpredictable whether this treatment would effect the formation of ECAs or not.

CONCLUSION

Our observation indicates that the factors which could influence ECAs formation include tumor size and tumor location, especially liver bare area (P value<0.01). As the number of TACE sessions increase, the cumulative probability of ECAs formation also increases. To recognize and get familiar with ECAs supplying HCC are essential to improve treatment outcome of HCC and avoid complication of TACE.

Conflict of Interest: None

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