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Hepatic arterial changes following iodized oil chemoembolization of hepatocellular carcinoma: Incidence and technical consequence

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Abstract *Objective:* To describe the nature, incidence, and therapeutic consequence of hepatic arterial changes seen following transcatheter arterial chemoembolization (TACE) for hepatocellular carcinoma (HCC).
Methods: In this retrospective study, 46 patients with HCC underwent ≥ 2 TACE treatment sessions between 2004 and 2010. All patients had hepatic angiography on days of treatment. Sequential angiographic studies were reviewed to assess for abnormalities in appearance of the hepatic vasculature. Angiographic abnormalities were graded in a binary fashion: present or absent. When present, abnormalities and effect on drug delivery were recorded.
Results: 123 (mean 2.7, range 2–5) successful lobar ($n = 34$), segmental ($n = 88$), or superselective ($n = 1$) TACE procedures were performed in 46 patients (M:F = 36:10, mean age 59 years). TACE was performed using 1:1 chemotherapy to iodized oil mixture without ($n = 102$) or with ($n = 21$) particle embolization. An abnormal angiographic appearance was identified in 21/46 (38%) patients and in 23/123 (19%) procedures, with first appearance after mean 1.5 (range 1–3) TACE sessions and mean 176 (range 27–509) days after initial TACE. Abnormalities included new vessel attenuation or stenosis ($n = 10$, 43%), slow flow ($n = 2$, 9%), and new vascular occlusions ($n = 11$, 48%). These vascular changes did not result in inability to perform repeat TACE in 16/16 (100%) cases where vascular changes were present and TACE was repeated to the same liver lobe.
Conclusion: While the hepatic vasculature is altered in many patients undergoing TACE, arterial abnormalities did not preclude therapy.Further investigation is warranted.

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Introduction

Transcatheter arterial chemoembolization (TACE) is an established liver directed intra-arterial treatment for hepatocellular carcinoma (HCC) which confers survival benefit to patients with surgically unresectable tumors.[1,2] This therapy exploits the discrepancy in blood supply between the hypervascular neoplastic tissue of HCC, which derives 90–100% of its blood flow from the hepatic artery, and non-tumorous liver parenchyma, which is predominantly perfused by the portal vein.[3] A combination of chemotherapeutic drugs and embolic agents are delivered via the hepatic artery directly to the tumor, resulting in local tumor devascularization and chemotherapy drug retention.[4,5] Because tumor response rates following TACE range from only 31–64% and time to disease progression averages 7.9 months,[6] patients with HCC often require repeated TACE therapy to treat residual, recurrent, or newly developed tumor. However, the caustic nature of chemotherapeutic agents administered during TACE may precipitate injury to the hepatic artery system,[7] potentially resulting in elimination of future arterial access to tumor and limitation of TACE therapy. Hepatic arterial damage has been reported to occur in 8–48% of patients, with loss of vascular patency in 56–81% of cases when TACE is performed to a stasis or near stasis angiographic endpoint.[8–11] This study was undertaken to assess the nature and incidence of hepatic arterial changes seen following iodized oil TACE for treatment of HCC when performed to a substasis angiographic endpoint, and to evaluate the degree of therapeutic limitation on future TACE resulting from hepatic arterial damage.

Materials and methods

This retrospective study was approved by our hospital's Institutional Review Board, and was in compliance with the Health Insurance Portability and Accountability Act. All patients provided written informed consent for procedures.

Clinical setting, patients, and tumors

Between January 2004 and March 2010, 46 patients with surgically unresectable HCC who underwent a total of 123 TACE procedures were identified among all patients undergoing TACE at a single academic university affiliated hospital situated in a large metropolitan area and were selected for study. Inclusion criteria for TACE consisted of (a) age greater than 18 years, (b) surgically unresectable HCC, (c) ability to undergo angiography and selective visceral catheterization, (d) ability to lay supine greater than 30 min, (e) ability to provide informed consent. Patients with portal vein thrombosis were included if segmental TACE was technically feasible. Patients were included for analysis in this study if they had undergone $\geq$2 TACE sessions such that sequential arteriograms could be compared. Patient who underwent only a single TACE session without angiographic follow-up were excluded from analysis. Patients who received systemic chemotherapy with sorafenib (Nexavar; Bayer, Leverkusen Germany) and who underwent drug-eluting bead TACE were also excluded from analysis. Previous percutaneous ablation therapy, surgical resection, and intra-arterial therapy using yttrium-90 microspheres prior to TACE therapy were not exclusion criteria, although patients who underwent combination TACE and percutaneous ablation (within two weeks of each other) were excluded.

The diagnosis of HCC was established by percutaneous biopsy or non-invasively based upon the presence of a hepatic mass greater than 2 cm diameter with characteristic imaging findings in the setting of liver cirrhosis and tumor marker elevation (alpha fetoprotein $\geq$ 200 ng/dL).[12] Surgical unresectability was determined by multidisciplinary consensus at tumor conference comprised of medical oncology, transplant surgery, hepatology, and interventional radiology.

Patient demographic and tumor characteristic information is presented in Table 1.

TACE

TACE procedures were performed in the interventional radiology suite using intravenous moderate sedation. Patients were prepared and draped in standard sterile fashion while supine on the angiographic procedure table, and routine arterial access was generally gained via the right common femoral artery. Initial mapping visceral angiography was then performed using a 5 French visceral catheter (cobra, Sos, or Simmons 1). Subsequent lobar or segmental angiography in the tumor vascular distribution was performed using a 4 French angled glide coated catheter (used in 8/123 procedures) or a coaxially placed 2.3–2.8 French microcatheter (used in 115/123 procedures) after vessel selection with a 0.016, 0.018, or 0.035 inch diameter guidewire. Catheter position was confirmed using DSA with iohexol (Omnipaque 300; Amersham Health, Princeton NJ) injection. After selecting the appropriate catheter position for TACE, chemoembolization was performed with a 1:1, 20 mL volume solution of chemotherapy agents and emulsifying iodized oil (Ethiodol; Savage Laboratories, Melville NY). Chemotherapy regimens followed a "CAM protocol" consisting of cisplatin 100 mg and doxorubicin 50 mg with (n = 119) or without (n = 4) mitomycin C 10 mg. The chemotherapy suspension was injected under direct fluoroscopic observation. Chemotherapy infusion was continued to a substasis angiographic endpoint. Endpoints were retrospectively graded according to the subjective angiographic chemoembolization endpoint (SACE) scale, a scheme designed to assist in reproducibly classifying angiographic TACE endpoints.[12] This scale is based on the Thrombolysis In Myocardial Infarction (TIMI) flow grade used in coronary angiography,[13] and consists of four levels[1]: (1) normal antegrade arterial flow and normal or reduced tumor blush, (2) reduced antegrade arterial flow and reduced tumor blush, (3) reduced antegrade arterial flow and no tumor blush, (4) no antegrade arterial flow and no tumor blush. Substasis embolization was defined as SACE levels 1–3, while stasis embolization was defined as SACE level 4. In 21/123 (17%) cases, TACE was concluded by injecting 100–300 μm