CLINICAL STUDY

Watershed Hepatocellular Carcinomas: The Risk of Incomplete Response following Transhepatic Arterial Chemoembolization

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ABSTRACT

Purpose: Hepatocellular carcinomas (HCCs) bridging two or more Couinaud–Bismuth segments of the liver ("watershed tumors") can recruit multiple segmental arteries. The primary hypothesis of this study was that fewer watershed tumors show complete response (CR) after chemoembolization, with shorter time to local recurrence. Secondary analysis on the impact on transplantation eligibility in the presence of progressive disease was also performed.

Materials and Methods: A total of 155 transplantation-eligible patients whose HCC met Milan criteria (watershed, n = 83; nonwatershed, n = 72) and was treated with chemoembolization were included. Cone-beam computed tomography (CT) was used for guidance and for confirmation of circumferential uptake. Local response to chemoembolization per modified Response Evaluation Criteria In Solid Tumors and local disease-free survival (DFS) for the index tumor were calculated. Differences were assessed by univariate and multivariate analyses.

Results: CR after a single of chemoembolization was observed in 55.4% of watershed tumors and in 72.2% of nonwatershed tumors ($P = .045$). Estimated DFS intervals were 151 days (95% confidence interval [CI], 93–245 d) and 336 days (95% CI, 231–747 d; $P = .040$) in the watershed and nonwatershed groups, respectively. Worse DFS was observed with a Model for End-Stage Liver Disease score > 20 ($P = .0001$), higher Child–Pugh–Turcotte score ($P = .049$), and watershed location ($P = .040$). Waiting list drop-off rates were statistically similar between groups.

Conclusions: Hepatocellular carcinomas located in the watershed region of the liver have a poorer response to chemoembolization than those located elsewhere. These tumors are associated with worse DFS and require additional treatments to maintain transplantation eligibility per Milan criteria. Cone-beam CT can identify crossover supply and confirm complete geographic drug uptake, possibly reducing (but not eliminating) the risk of incomplete response.

ABBREVIATIONS

CI = confidence interval, CR = complete response, CTP = Child–Turcotte–Pugh, DFS = disease-free survival, HCC = hepatocellular carcinoma, MELD = Model for End-Stage Liver Disease, mRECIST = modified Response Evaluation Criteria In Solid Tumors, SBRT = stereotactic body radiation therapy, SD = standard deviation

The Couinaud–Bismuth nomenclature (1,2) describes the liver anatomy as individual functional liver segments defined by the portal and hepatic venous planes. Despite widespread adoption of this nomenclature for surgical purposes (3–5), concerns exist that this approach does not account for arterial variations, including crossover arterial supply between adjacent segments (6–8).

Of particular importance to the interventional radiologist is the arterial supply to segment IV. Routinely used to define a surgical plane, it may be supplied by arteries

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arising from the left hepatic artery, the accessory or replaced left hepatic artery, the right hepatic artery, the middle hepatic artery, or a combination of any or all of these (8–10). For surgeons, the importance of identifying the origin(s) of the segment IV artery before resection and split liver transplantation is well understood (9,11–13). This variability can similarly influence the performance of transhepatic arterial chemoembolization (henceforth called simply chemoembolization) (6,9,10,14). Most commonly described for segment IV (6,10), this phenomenon can be seen with tumors that cross boundaries between any two adjacent segments. Tumors in these areas, termed watershed areas, are challenging to treat because identification of all arterial supply is difficult in the angiographic background of corkscrew vessels seen in a cirrhotic liver (9,10,14,15). In addition, by straddling two adjacent segments, these "watershed tumors" could eventually recruit tumor vessels from either or both segments (14).

The primary goal of the present study was to compare the rates of complete response (CR) as defined by modified Response Evaluation Criteria In Solid Tumors (mRECIST) (16) between watershed and nonwatershed hepatocellular carcinoma (HCC) following a single session of chemoembolization. Secondary analyses included the impact of incomplete response and subsequent disease progression on transplantation eligibility.

MATERIALS AND METHODS

This was a single-institution, retrospective study that was Health Insurance Portability and Accountability Act–compliant and had institutional review board approval.

Patient Selection

Between January 2008 and December 2012, patients with unresectable HCC that met the Milan criteria for tumor burden, ie, a single tumor ≤ 5 cm or no more than three synchronous tumors ≤ 3 cm (17), were reviewed. All patients and treatment plans were discussed at a multidisciplinary transplantation conference. Clinical, laboratory, and imaging data were reviewed for all patients.

The two cohorts created for comparison were distinguished based on the location of the index tumor on the pretreatment cross-sectional imaging study and/or procedural angiography, including C-arm cone-beam computed tomography (CT). An index tumor was classified as a watershed tumor if it visually straddled two or more segments on the portal venous phase of preprocedural cross-sectional imaging or was supplied by two distinct segmental arteries on the angiogram. In patients with two or three synchronous tumors, the largest tumor was considered the index tumor, and its location was used for stratification. These cohorts consisted only of treatment-naive patients, so patients with previous chemoembolizations or ablations were excluded even if they underwent additional chemoembolizations during the study period. Patients with parasitized extrahepatic arterial supply to the tumor were also excluded. Finally, patients without any follow-up contrast-enhanced cross-sectional imaging were excluded.

After these exclusions were applied, 155 patients, 83 with watershed tumors and 72 with index tumors located elsewhere, were included in the analyses. Age, sex, race, and underlying liver disease distribution were statistically similar between groups (**Table 1**). Child–Turcotte–Pugh (CTP) scores were lower in the watershed group (6.6 vs 7.3; $P = .025$); however, the medical Model for End-Stage Liver Disease (MELD) scores were comparable (10.7 vs 11.6; $P = .11$). Although all patients' HCC met Milan criteria, statistically, the mean index tumor diameter was greater in the watershed group (2.7 cm $\pm$ 0.86; range, 1.2–5.0 cm) than in the nonwatershed group (2.4 cm $\pm$ 0.83; range, 1.2–4.5 cm; $P = .009$).

Segmental tumor localization on imaging is listed in **Table 1**. Watershed tumors straddled segment IV and an adjoining segment in 72.3% of cases, followed by segment V/VIII (8.4%) or segment VII/VIII (7.2%). Fifty-five patients (66.3%) with watershed tumors and 48 patients (66.7%) with nonwatershed tumors had solitary tumors ($P = 1$). Among the patients with synchronous tumors, the smaller second tumor was located in a nonwatershed zone in 21 and 23 patients in the watershed and nonwatershed groups, respectively.

Technique and Follow-up

Procedures were performed in a single-plane angiography suite capable of cone-beam CT with a 30-cm × 40-cm flat-panel detector (AXIOM Artis dTA with DynaCT; Siemens, Forchheim, Germany). Digital subtraction angiograms were supplemented with a contrast-enhanced cone-beam CT acquisition to identify all arterial feeder vessels to the tumor. For watershed tumors, each segmental artery identified as a potential supplier was selectively catheterized, interrogated, and treated if confirmed to supply the tumor (**Fig 1a–1b**).

Conventional chemoembolization was performed by using 5 mg/mL doxorubicin dissolved in Iohexol 300 (GE Healthcare, Waukesha, Wisconsin) and 5 mg/mL cisplatin in Iohexol 300, emulsified at a 1:1:2 ratio (vol./vol./vol.) with ethiodized oil (Ethiodol; Savage Laboratories, Melville, New York), for a maximum dose of 50 mg doxorubicin, 50 mg cisplatin, and 20 mL Ethiodol. The remaining patients were treated with drug-eluting embolic agents (100–300-μm LC Bead; Biocompatibles/BTG, Farnham, United Kingdom; or 200–400-μm QuadraSphere; Merit Medical, South Jordan, Utah), for a maximum dose of 150 mg of doxorubicin mixed in Iohexol. Chemoembolization was performed only in a superselective fashion from segmental or subseg-