Modified Response Evaluation Criteria in Solid Tumors and European Association for the Study of the Liver Criteria Using Delayed-Phase Imaging at an Early Time Point Predict Survival in Patients with Unresectable Intrahepatic Cholangiocarcinoma following Yttrium-90 Radioembolization

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ABSTRACT

Purpose: To investigate early imaging prognostic factors in unresectable intrahepatic cholangiocarcinoma (ICC) refractory to standard chemotherapy after yttrium-90 (^{90}Y) radioembolization therapy.

Materials and Methods: In an institutional review board–approved prospective correlative study, 21 consecutive patients with ICC refractory to standard chemotherapy underwent ^{90}Y radioembolization therapy. Target and overall Response Evaluation Criteria In Solid Tumors (RECIST), modified RECIST (mRECIST), and European Association for the Study of the Liver (EASL) treatment responses were assessed. The mRECIST and EASL criteria were modified for application on delayed phases of dynamic contrast-enhanced cross-sectional imaging studies. Conventional definitions for complete and partial response were applied; these responses comprised objective response. Restaging imaging was obtained at 1- and 3-month intervals until patient death. Survival analyses by Kaplan–Meier and log-rank proportional models including application of the landmark method to avoid lead-time bias were performed from the day of treatment. Significance was set at $P < .05$.

Results: Median overall survival (OS) from the time of ^{90}Y therapy was 16.3 months (95% confidence interval, 7.2–25.4 mo). Significant differences between mRECIST and EASL versus RECIST were found when categorizing patients into responders and nonresponders ($P < .001$). Significantly prolonged OS was observed for patients with targeted objective response based on modified mRECIST and EASL criteria ($P = .005$ and $P = .001$, respectively) at 3 months. RECIST was not found to correlate with survival at 1- or 3-month follow-up.

Conclusions: Modified target mRECIST and EASL criteria that employ delayed-phase contrast enhancement at 3 months after ^{90}Y radioembolization therapy for ICC predicted OS. RECIST did not correlate with survival.

ABBREVIATIONS

CR = complete response, EASL = European Association for the Study of the Liver, ICC = intrahepatic cholangiocarcinoma, mRECIST = modified Response Evaluation Criteria In Solid Tumors, PD = progressive disease, PR = partial response, RECIST = Response Evaluation Criteria In Solid Tumors

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Intrahepatic cholangiocarcinoma (ICC) accounts for 10%–20% of all primary hepatic tumors and is the second most common primary liver malignancy originating from the epithelium of the biliary tract (1). Histologically, these tumors are adenocarcinomas with abundant fibrous stroma (2), giving rise to its classic appearance on magnetic resonance (MR) imaging, which includes irregular margins, high signal intensity on T2-weighted sequences, low signal intensity on T1-weighted acquisitions, and peripheral/centripetal enhancement on equilibrium/delayed phase after contrast medium administration (3).

The only curative treatment available for ICC is complete surgical excision (4). However, the majority of patients have unresectable disease at the time of presentation, significantly reducing overall patient survival (1) Although improved survival has been achieved with systemic chemotherapy (5–8), further studies in the field are still needed. Given these facts, intraarterial locoregional therapies including yttrium-90 (^{90}Y) radioembolization have been explored as a valid alternative and may play a significant role in the treatment of ICC (9–13).

Diagnostic imaging is a reliable prognostic marker in the assessment of tumor response and time to progression, particularly for locoregional therapies (14). Multiple imaging follow-up criteria have been developed, although few correlate with survival (14–16). It has been reported that the World Health Organization criteria tend to underestimate response (17), and previous studies have raised concerns that some disease categories may be easily achieved by chance via changes in measurements (ie, a 25% increase in the product of two measurements could occur with an approximately 11% increase in each dimension) (18). Response Evaluation Criteria In Solid Tumors (RECIST) were proposed based on tumor size. However, local intraarterial therapies behave differently than systemic agents, and, given the arterial enhancement characteristics of hepatocellular carcinoma, the American Association for the Study of Liver Disease adopted modifications to RECIST criteria (referred to as modified RECIST [mRECIST]) by acknowledging the concept of viable tumor as the arterially enhancing tissue on contrast-enhanced imaging (19). The European Association for the Study of the Liver (EASL) also supported this statement by developing independent arterial-based enhancement criteria (16).

However, as previously reported, ICC enhances on delayed acquisitions (3), and the previously mentioned criteria may not accurately assess treatment response for ICC after locoregional therapy. Hence, the objective of the present study was to investigate early imaging prognostic factors in unresectable ICC refractory to standard chemotherapy by modifying the known arterial-based enhancement criteria (mRECIST and EASL) to be applied on delayed acquisitions after ^{90}Y therapy.

MATERIALS AND METHODS

Study Cohort

Analysis of a prospective cohort was performed with institutional review board approval and Health Insurance Portability and Accountability Act compliance. The study cohort consisted of consecutive patients with unresectable mass-like ICC refractory to standard chemotherapy who received care between January 2009 and December 2012 at a single institution. Patients were eligible for inclusion if they met the following criteria: histologically proven diagnosis of ICC not eligible for surgical management (20), progressive disease (PD) while receiving standard systemic chemotherapy (gemcitabine, gemcitabine plus cisplatin, or 5-fluorouracil regimens), Eastern Cooperative Oncology Group performance status of 0–2; normal hematologic status (granulocyte count $> 1.5 \times 10^9$/L, platelet count $> 50 \times 10^9$/L), preserved renal function (creatinine level < 2.0 mg/dL), and normal hepatic function (bilirubin level < 2.0 mg/dL). Additionally, pulmonary shunt fraction was measured, and a safety cutoff point was set as less than 20% (21,22). Main portal vein tumor thrombus was a contraindication for therapy; however, branch portal vein thrombosis was allowed.

Patient Demographics

A total of 21 patients were enrolled (**Table 1**). Overall, there were 13 men (62%) and eight women (38%), ranging in age from 31.8 to 87.5 years (median age, 62.7 y). A total of 85% of patients had Child–Pugh class A disease. The majority (57%) had an Eastern Cooperative Oncology Group performance status of 1 at initial presentation. Most of the patients were white (95%).

Radioembolization Procedure

Radioembolization therapy was administered according to standard technique (23,24). Superior mesenteric and celiac angiography was performed on all patients for identification of potential anatomic variants (23). Embolization material included resin-based ^{90}Y microspheres (SIR-Spheres; Sirtex Medical, Sydney, Australia). Yttrium-90 dose was based on tumor volumetry and then adjusted by the pulmonary shunt fraction. The total dose was also adjusted to the total body surface (23,24).

Follow-up Postprocedural Imaging

All computed tomography (CT) and MR imaging studies were performed on multi–detector-row helical CT scanners (Light Speed VCT; GE Medical Systems, Milwaukee, Wisconsin) and on 1.5-T (GE Medical Systems) and/or 1.5-/3-T MR scanners (Siemens, Erlangen, Germany), respectively. Studies were performed with standard technique (ie, liver protocols) including