CLINICAL STUDY

Treatment of Hepatocellular Carcinoma with Tumor Thrombus with the Use of Iodine-125 Seed Strand Implantation and Transarterial Chemoembolization: A Propensity-Score Analysis

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ABSTRACT

Purpose: To evaluate the safety and efficacy of iodine-125 (^{125}I) seed strand implantation in combination with transarterial chemoembolization for the treatment of hepatitis B–related unresectable hepatocellular carcinoma (HCC) with portal vein invasion.

Materials and Methods: From January 2013 to June 2016, 76 HCC patients with type II tumor thrombus were included in this single-center retrospective study. Twenty patients underwent ^{125}I seed strand implantation combined with transarterial chemoembolization (group A; n = 20), while 56 patients underwent transarterial chemoembolization alone (group B; n = 56). The procedure-related and radiation complications were assessed. Overall survivals were compared by propensity-score analysis.

Results: The technique was successfully performed in all patients. The mean intended dose (r = 10 mm; z = 0; 240 days) was 62.6 ± 1.8 Gy. No grade 3 or 4 adverse events related to the procedure occurred in either group. After propensity-score-matching analysis, 19 patients were selected into each group, respectively. In the propensity-matching cohort, the median overall survival time was significantly longer in group A than in the group B (19 pairs; 28.0 ± 2.4 vs 8.7 ± 0.4 mo; $P = .001$). Treatment strategy, arterioportal shunt, and number of transarterial chemoembolization sessions were significant predictors of favorable overall survival time.

Conclusions: ^{125}I seed strand implantation combined with transarterial chemoembolization is a safe and effective treatment for HCC patients with portal vein invasion.

ABBREVIATIONS

HCC = hepatocellular carcinoma, ^{125}I = iodine-125, MPV = main portal vein, OS = overall survival, PVTT = portal vein tumor thrombus, SMV = superior mesenteric vein

Portal vein tumor thrombus (PVTT) is a common pattern of hepatocellular carcinoma (HCC) progression, found in ~10%–40% of patients (1). Without treatment, the interval between the formation of segmental PVTT and complete obstruction was <6 weeks (2). The prognosis of HCC with PVTT remains poor. In particular, tumor thrombus in the main portal vein (MPV) represents an end-stage condition, with a perioperative mortality rate of 0%–28% and a 5-year overall survival (OS) rate of 0%–26.4% (3,4).

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EDITORS' RESEARCH HIGHLIGHTS

- This single-center retrospective study reports overall survival (OS; primary end point), tumor radiologic response, time to progression, and adverse events following (*i*) conventional ethiodized oil transarterial chemoembolization plus iodine-125 (^{125}I) seed strand brachytherapy therapy (n = 20) versus (*ii*) conventional transarterial chemoembolization (n = 56) for treatment of unilobar, uni-/oligonodular, hepatitis B virus–related HCC with left or right portal vein invasion. Nineteen patients in each treatment arm were matched by 1:1 propensity-score matching for comparative assessment of clinical outcomes.
- ^{125}I seed strands loaded into a 4-F sealed plastic cannula were percutaneously implanted into the intravascular tumor thrombus via a 5-F vascular sheath immediately before conventional transarterial chemoembolization; the mean intended ^{125}I dose was 62.6 Gy, and all implantations were technically successful.
- Major study findings included longer OS favoring the combined treatment group (28.0 vs 8.7 months; $P = .001$ after propensity-score matching); improved modified Response Evaluation Criteria in Solid Tumors best tumor response rates favoring the combined treatment group (intrahepatic tumor disease control rate: 60% vs 29%, $P = .012$; intravascular tumor disease control rate: 90% vs. 34%, $P < .001$), and longer time to progression favoring the combined treatment group (18.5 vs 5.3 mo; $P < .001$). Notably, patients in the combined treatment group received more conventional transarterial chemoembolization sessions than the conventional transarterial chemoembolization alone group. There were no grade 3–4 Common Toxicity Criteria for Adverse Events version 4.0 adverse events in either treatment group.
- The results suggest that combined treatment of HCC with portal vein invasion by means of conventional transarterial chemoembolization and ^{125}I brachytherapy is safe and effective and may improve clinical outcomes compared with treatment by means of conventional transarterial chemoembolization alone.

Sorafenib was recommended as the first-line treatment for the advanced-stage disease, with OS of 6.5 and 10.7 months (5,6). Transarterial chemoembolization is considered to be an effective treatment (7,8); however, early MPV invasion is a significant predictor of OS (8).

Iodine-125 (^{125}I) seed implantation was recommended, with better survival results, by Huang et al (9), but subcapsular hemorrhage occurred in their study. Linear ^{125}I seed strand combined with a stent for HCC with MPV invasion was proposed by Luo et al (10). These pioneering works prompted us to conceive a safe and effective therapy that could inhibit MPV invasion. The present study was performed to evaluate the safety and efficacy of ^{125}I seed strand implantation combined with transarterial chemoembolization for HCC with PVTT.

MATERIALS AND METHODS

This was a single-center retrospective study. Local Institutional Review Board approval was obtained. We reviewed the electronic medical records of 97 consecutive patients with hepatitis B–related HCC and PVTT who were administered ^{125}I seed strand implantation combined with transarterial chemoembolization (transarterial chemoembolization–^{125}I) or transarterial chemoembolization alone from January 2013 to June 2016. Transarterial chemoembolization combined with sorafenib (transarterial chemoembolization-sorafenib) was primarily recommended. transarterial chemoembolization–^{125}I and transarterial chemoembolization alone were recommended for patients who declined transarterial chemoembolization-sorafenib. The final choices were made by the patients. No bias advice was given by doctors.

Patients

Intrahepatic HCC was diagnosed based on the American Association for the Study of Liver Disease guidelines (11). According to the standard recommended by Shah et al (12), a portal vein (PV) thrombus was considered to be neoplastic if one of the following criteria was met or bland if none of the criteria was met: (*i*) expansion of the involved vessel (vessel diameter ≥1.8 cm for the MPV, ≥1.6 cm for the right PV, or ≥1.8 cm for the left PV); or (*ii*) clear evidence of enhancement on dynamic contrast-enhanced computerized tomographic (CT) images during the arterial phase of dynamic imaging, compared with baseline images (≥20 HU on CT). The following criteria of PVTT classification (13) was adopted: type I, segmental/sectoral branches of the PV; type II, left/right PV; type III, MPV; and type IV, superior mesenteric vein (SMV).

Inclusion criteria: (*i*) 18–75 years of age; (*ii*) a single tumor with size ≥5.0 cm or multiple nodular tumors >3.0 cm; (*iii*) unilobar involvement; (*iv*) type II PVTT; (*v*) patent second-order branch before PVTT; (*vi*) Child-Pugh class A or B; and (*vii*) Eastern Cooperative Group performance status (ECOG) score of 0–2. These points represent eligibility criteria for the treatment.

Exclusion criteria: (*i*) type I, III, or IV PVTT; (*ii*) complete occluded portal vein; (*iii*) bilobar involvement; (*iv*) extrahepatic metastasis; (*v*) hepatic encephalopathy, severe ascites, esophageal, gastric fundal variceal bleeding, or other serious medical comorbidities; (*vi*) previous surgery, local-regional therapy (radiofrequency ablation, microwave ablation, cryoablation, yttrium-90 (^{90}Y) radioembolization, stereotactic body radiotherapy (SBRT), transarterial chemoembolization, or liver transplantation; (*vii*) previous sorafenib, systemic chemotherapy, or intra-arterial chemo-infusion; or (*viii*) malignant tumor in addition to HCC.

According to these criteria, 76 patients were included (group A, n = 20; and group B, n = 56; Fig 1). Baseline characteristics are presented in Table 1.