Research Article

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Increased survival in hepatocellular carcinoma with iodine-125 implantation plus radiofrequency ablation: A prospective randomized controlled trial

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Background & Aims: The purpose of this study was to evaluate whether use of combined radiofrequency ablation (RFA) and percutaneous iodine-125 (^{125}I) seed implantation results in better progression-free survival compared with the use of RFA alone in patients with hepatocellular carcinoma.

Methods: 136 patients were randomly assigned to undergo HCC treatment with RFA and percutaneous iodine-125 seed implantation (RFA-^{125}I, n = 68) or RFA-only (n = 68). A total of 91 patients had hepatitis B viral infection in both groups. Rates of tumour recurrence and overall survival were evaluated.

Results: The probabilities of recurrence at 1-, 3-, and 5-years were 4.5%, 22.1%, and 39.8% in the RFA-^{125}I group; and 14.8%, 35.3%, and 57.4% in the RFA-only group, respectively. The recurrence rate in the RFA-^{125}I group was significantly lower than in the RFA-only group (HR, 0.508; 95% CI, 0.317–0.815; $p = 0.004$ by log-rank test). Local and intrahepatic recurrence was significantly lower in the RFA-^{125}I group than in the RFA-only group (7.3% *vs.* 22.0%, $p = 0.012$ by log-rank test; 17.6% *vs.* 32.3%, $p = 0.041$ by log-rank test). The probabilities of survival at 1-, 3-, and 5-years were 100%, 86.7%, and 66.1% in the RFA-^{125}I group and 95.6%, 75.0%, and 47.0% in the RFA-only group, respectively. The survival rate in the RFA-^{125}I group was significantly better than in the RFA-only group (HR, 0.502; 95% CI, 0.313–0.806; $p = 0.003$ by log-rank test). Cox regression model indicated that the treatment group and tumour size were both recurrence-related and overall survival-related prognostic factors.

Conclusions: There were significant differences in overall survival and cumulative recurrence between RFA-^{125}I and RFA-only for patients with small HCCs ($\leqslant$3 cm). Treatment with RFA-^{125}I facilitated better local and intrahepatic tumour control and long-term survival compared with treatment of RFA alone. ClinicalTrials.gov Identifier: NCT01717729.

Keywords: Hepatocellular carcinoma; Radiofrequency ablation; Iodine-125 implantation; RCTs; Survival; Safety.

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Abbreviations: HCC, hepatocellular carcinoma; RFA, radiofrequency ablation; PEI, percutaneous ethanol injection; TACE, transarterial chemoembolization; BCLC, Barcelona Clinic Liver Cancer; ^{125}I, iodine-125; CT, computed tomography; MR, magnetic resonance; OS, overall survival; AFP, alpha fetoprotein; SPSS, Statistical Product and Service Solutions; SD, standard deviation; ALT, alanine transaminase; GBq, gigabecquerel; HBV, hepatitis B virus; HCV, hepatitis C virus; PTV, planning target volume; mPD, minimum peripheral dose; mCi, millicuries.

Introduction

Hepatic resection remains the 'gold standard' treatment for patients with hepatocellular carcinoma (HCC), and, when technically feasible, it offers a real chance of long-term survival or cure. However, in a large number of patients resection is not possible or appropriate because of liver dysfunction due to cirrhosis, concomitant medical problems or technical difficulties. Liver transplantation is another curative treatment for end-stage liver disease, but it is limited because of donor shortage or patient's refusal. Locoregional therapy such as radiofrequency ablation (RFA) has been widely performed for the treatment of small HCC because it is minimally invasive and is reported to be effective [1–4]. However, the complete tumour necrosis rate with RFA is less favourable, and the 3-year recurrence rate can be as high as 50%, even for HCCs smaller than 3.0 cm [1,2]. Thus, to improve treatment results, RFA with ethanol injection, combined with TACE have been used and were shown to be effective for the treatment of medium-sized (3 cm) HCCs [5,6]. Nevertheless, long-term results of these treatments have been inadequate and tumour control is still difficult.

Historically, external-beam radiotherapy has played only a small role in the treatment of patients with unresectable intrahepatic malignancies [7–9]. However, a resurgence of interest regarding the use of radiotherapy has occurred with the introduction of newer modalities, such as 3D conformal radiotherapy,

stereotactic radiosurgery, intensity-modulated radiotherapy, and brachytherapy [10–12]. Studies have reported on the use of isotopes, including high-dose-rate ^{192}Ir brachytherapy and ^{90}Y microspheres in the liver [10,13,14], but few studies have employed ^{125}I [15–17].

In the past three decades, the application of low-energy radionuclides, such as iodine-125 and palladium-103, extended the indication of brachytherapy [13,14,18]. The therapeutic efficacy was proven to be favourable, especially in prostate cancer [19]. In terms of hepatopathy, some studies have reported treatment of liver tumours with the use of ^{125}I implant seeds [15–17]. In our previous study, we showed that patient-accepted ^{125}I brachytherapy after liver resection could improve body immunity function [20,21]. Thus, the purpose of this study was to prospectively evaluate whether use of RFA-^{125}I results in a reduction of the recurrence rate and in an increase in the overall survival rate, and adverse reactions associated with this treatment compared with RFA alone.

Patients and methods

Patients

This study was approved by the ethical committee of the Second people's Hospital of Guangdong Province and was designed according to the CONSORT (Consolidated Standards of Reporting Trials) guidelines. All patients gave written informed consent before beginning the study.

Between January 2002 and August 2007, 136 patients with HCC were randomly assigned to undergo RFA-^{125}I (n = 68) or RFA-only (n = 68). The diagnosis of HCC was based on the diagnostic criteria of the European Association for the Study of the Liver [22]. A diagnosis of HCC was made when two different imaging examinations revealed typical features of HCC in a patient with an elevated α-fetoprotein level ($\geqslant$400 ng/ml) (n = 94) or when there was a cytologic or histologic diagnosis of HCC (n = 42). Inclusion criteria for this study were as follows: (a) a solitary HCC 3.0 cm in diameter or smaller or multiple (up to three) HCCs 3.0 cm in diameter or smaller; (b) lesions visible at computerized tomography (CT), with an acceptable and safe path between the lesion and the skin seen on the CT scan; (c) no extrahepatic metastasis; (d) no imaging evidence of tumour invasion into the major portal or hepatic vein branches; (e) no history of encephalopathy, ascites refractory to diuretics, or variceal bleeding; (f) Child-Pugh class A or B; (g) a platelet count of more than 40,000 cells/mm^3; (h) Karnofsky performance status (KPS) over 70; (i) no previous treatment for HCC; (j) ability to sign informed consent, and (k) heart, lung, and kidney functions of organs are normal. The 136 patients were from a group of 623 hospitalized patients with HCC, who met all of the inclusion criteria.

Patients were randomly assigned to receive RFA-^{125}I or RFA-only. At the data centre, allocation was done by telephone (Xiaopeng Duan) with a computer-generated list using a randomly permuted block design, stratified by tumour size (<1.0 cm *vs.* 1.0–2.0 cm *vs.* 2.0–3.0 cm). Each patient's treatment group assignment was concealed from the doctor prior to the treatment. In addition, patients were blinded to their treatment assignment. After treatment, BAND-AID® bandages (Johnson & Johnson range, 8–15) were applied on patients' skin for 14 days.

Treatment protocols

All patients underwent RFA performed by a surgeon (Kaiyun Chen) with expertise in the technique. Iodine-125 seed implantation was performed by the radiation oncologist (Guoan Xiang).

Prior to the performance of RFA-^{125}I, all patients underwent a detailed tumour volume study using CT scans with 5 mm thickness 1–2 weeks before iodine-125 seed implantation. Transverse images of the carcinoma were obtained at 5 mm intervals. The planning target volume (PTV) was outlined. The PTV included the entire tumour and extended 1.0 cm. These tracings were digitized onto a computer, and then used to define the target volume to which the minimum peripheral dose (mPD) of radiation was prescribed. The total activity and the number of ^{125}I seeds to be implanted were determined by the use of the Memorial Sloan-Kettering nomograph [23]. This calculation system ensured a minimal peripheral dose of 160 Gy to the target volume. The location and the target volume of the ^{125}I brachytherapy were determined jointly by the surgeon (Kaiyun Chen) and the radiation oncologist (Guoan Xiang).

RFA was performed with CT guidance. Patients were placed in the supine position. A local anaesthetic, 1% lidocaine, was injected from the insertion point on the skin to the peritoneum, along the planned puncture track. The skin was incised with a small lancet, and the needle was advanced to the chosen area. Conscious analgesic sedation with intravenous fentanyl citrate and droperidol was induced before the procedure (RFA-^{125}I or RFA-only).

RFA procedure

For RFA, we used a commercially available system (RF 2000; Radio Therapeutics, Mountain View, CA) and a needle electrode with a 15-gauge insulated cannula that had 10 hook-shaped expandable electrode tines with a diameter of 3.5 cm at expansion (LeVeen; Radio Therapeutics). The 15-gauge RFA needle was inserted into the tumour. After the 10 tines of the electrode were deployed, the radiofrequency generator was activated and initiated with of power 10 W and then was increased to 90 W at 10 W per minute. Radiofrequency energy was applied until there was a marked increase in impedance or until 15 min had elapsed. If a marked increase in impedance was not achieved, a second application was performed.

^{125}I seed implantation procedure

The ^{125}I seeds (0.8 mm in diameter and 4.5 mm in length) were enclosed in a NiTinol capsule (China Institute of Atomic Energy, Beijing). These seeds could produce 27.4–31.5 keV X-ray and 35.5 keV γ-ray, with a half-life of 59.6 days. The radioactivity per seed ranged from 0.5 to 0.6 millicuries (mCi). The temperature-sterilized seeds were implanted into the tumour tissue and the non-tumourous liver tissue adjacent to the tumour surface with 1 cm intervals.

After RFA, interstitial needles (17-gauge, stainless steel, hollow needles, 15 cm long) were inserted into the tumour, approximately 1 cm apart. CT was used to guide the placement of the needles. Precautions were taken to avoid puncture of large blood vessels (central vein and inferior vena cava). A median of 18.5 needles per patient was used (range, 8–45). A Mick applicator (Mick Radionuclear Instruments, Bronx, NY) was then sequentially attached to the distal end of each needle to place the ^{125}I seeds into the tumour, spaced approximately 1 cm apart along the needle track (Fig. 1). The needles were then removed. After finishing the iodine-125 implantation, 5 min of RFA were performed to stop the latent bleeding, produced by the needle's puncture. A median of 39 seeds (range, 18–69) was implanted per patient, with a median activity per seed of 0.5 mCi and a median total implanted activity of 19.5 mCi (range, 9–34.5 mCi). The final dose delivered to total decay was expressed in terms of the minimum peripheral dose (MPD). The median MPD was 160 Gy (range, 50–190 Gy).

Follow-up

Computerized tomography (CT) was performed 4 weeks after treatment. Thereafter, patients were followed-up every month for the first year. At each follow-up visit, chest radiography, ultrasonography, and blood tests, including liver function and serum α-fetoprotein tests, were performed. CT was performed every three months. After the first year, follow-up examinations were performed once every two months. Chest radiography and CT were performed every six months and six months, respectively. The follow-up was ended on August 31st, 2013 for all patients of the present study.

CT evidence of residual or recurrent viable tumour included intratumoural areas of enhancement on either arterial or portal venous phase images. Depending on the initial random treatment assignment, RFA-^{125}I or RFA-only was repeated and the follow-up time point was the initial follow-up. Magnetic resonance (MR) imaging was performed if there was uncertainty at CT as to whether residual viable tumour tissue was present.

The primary end point was recurrence, and the secondary end point was overall survival and side effects. Survival time was defined as the interval between the first treatment and either death or last follow-up visit. Tumour recurrence included local recurrence, intrahepatic recurrence, and extrahepatic metastasis. In terms of outcomes after complete tumour ablation and/or iodine-125 seed implantation was achieved, local recurrence was defined as the development of tumour staining at the margins on follow-up CT and/or MR images, intrahepatic recurrence was defined as the development of a separate new lesion in the liver more than 2.0 cm away from the primary lesion on these images, and extrahepatic metastasis was defined as a metastatic lesion outside the liver on these images.