Digestive and Liver Disease 48 (2016) 1082–1087

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Oncology

Iodine-125 implantation plus transarterial chemoembolization for the treatment of hepatocellular carcinoma of 3–5 cm: A propensity score matching study

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ARTICLE INFO

Article history:
Received 28 January 2016
Accepted 8 June 2016
Available online 15 June 2016

Keywords:
Hepatocellular carcinoma
Iodine-125
Propensity score matching
Transarterial chemoembolization

ABSTRACT

Background: Both iodine-125 implantation and transarterial chemoembolization (TACE) are feasible options for hepatocellular carcinoma (HCC). The aim of the research is to investigate whether iodine-125 implantation combined with TACE could improve the overall survival of patients with HCC of 3–5 cm.
Methods: 144 patients with HCC of 3–5 cm who underwent iodine-125 implantation plus TACE and TACE alone were retrospectively enrolled in this study. To reduce the selection bias, 55 matched pairs of patients were generated by propensity score matching (PSM). Their overall survival was compared by the Kaplan–Meier method. Independent prognostic factors were identified by Cox proportional hazards regression model.
Results: patients receiving iodine-125 implantation plus TACE have significantly better overall survival than patients receiving TACE alone ($P < 0.001$). After PSM, treatment of iodine-125 plus TACE still provide better survival (1-year, 89.1% vs. 65.5%; 3-year, 51.0% vs. 7.4%; $P < 0.001$). In multivariate analysis, BCLC stage, vascular invasion and treatment modality independently predicted the prognosis. No severe adverse events occurred in both groups.
Conclusion: for HCC patients of 3–5 cm for whom surgical intervention is not an option, iodine-125 implantation combined with TACE might be an effective and viable alternative to provide better overall survival.

1. Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer and second leading cause of cancer death worldwide [1]. Although screening for early-stage HCC has been well implemented, approximately 50% cirrhotic patients still have HCC larger than 3 cm when diagnosed [2,3]. According to Barcelona Clinic Liver Cancer (BCLC) system, merely the patients with BCLC stage A (single or 3 nodules ≤3 cm) could benefit from curative treatments such as resection and radiofrequency ablation (RFA) and patients with BCLC stage B should undergo transarterial chemoembolization (TACE) as recommended [4–6]. However, TACE provides limited survival benefit due to a low complete response rate ranging from 23% to 27% [7–9]. Attempting to completely sterile the tumour, locoregional treatment such as radiotherapy combined with TACE is a rapidly developing treatment option for unresectable HCC [10].

Traditionally, external beam radiotherapy was considered as a palliative treatment for extrahepatic metastases, because doses of radical radiotherapy for inoperable intrahepatic malignancies exceed the threshold for radiation-induced liver disease [10]. However, as new modalities of radiotherapy including three-dimensional conformal radiotherapy, intensity-modulated radiotherapy and brachytherapy emerged, radiotherapy has become a practical option for treatment of HCC [10–12]. Many previous studies showed favourable results by using yttrium-90 microspheres, iodine-131 lipiodol and Iridium-192 brachytherapy but only a few studies have reported the application of iodine-125 (^{125}I) in HCC [13–15].

Former researches have demonstrated that implantation of ^{125}I seeds combined with complete hepatectomy or RFA could provide better local control and long-term survival of patients with HCC smaller than 3 cm [16,17]. To our knowledge, the effects of therapy combining ^{125}I implantation and TACE on HCC of larger 3 cm remains unclear. Thus, in comparison with TACE alone, we carried

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http://dx.doi.org/10.1016/j.dld.2016.06.007
1590-8658/

out this retrospective study to investigate whether ^{125}I implantation plus TACE could improve the overall survival of patients with HCC of 3–5 cm.

2. Patients and methods

2.1. Patients

This study was approved by the ethics committee of the First Affiliated Hospital of Guangxi University of Chinese Medicine, and written informed consent was obtained from all patients.

This retrospective study enrolled 144 patients who were diagnosed with HCC and underwent ^{125}I seeds implantation along with or without TACE in the First Affiliated Hospital of Guangxi University of Chinese Medicine from January 2010 to December 2012. A diagnosis of HCC was made when one of the following criteria was met: (a) HCC radiological hallmark (contrast enhancement in the arterial phase and washout in the portal venous or delayed phases) showed in two imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI); (b) HCC radiological hallmark showed in one imaging technique combined with elevated level of alpha-fetoprotein (>400 ng/ml); (c) cytological or histological evidence. Barcelona Clinic Liver Cancer (BCLC) stage was determined according to the criteria revised by American Association for the Study of Liver [6]. The inclusion criteria are diagnosed with HCC; largest diameter of the tumour is between 3 and 5 cm; Child–Pugh class A or B; Eastern Cooperative Oncology Group (ECOG) score of 0–1; no previous treatment for HCC; normal laboratory test results for heart, lung and kidney; ability of signing the informed consent. In addition, for BCLC stage C, patients with segmental invasions (hepatic vein or portal vein tumour thrombus, PVTT) were recruited in this study, because brachytherapy of tumour could not affect distant tumour embolus in right/left and main portal vein, hepatic vein, superior mesenteric vein, and inferior vena cava [18].

2.2. Transcatheter arterial chemoembolization (TACE)

According to BCLC staging system, some participants in this study should receive surgery while they chose less risky treatment such as TACE instead. The procedure of TACE was started with the introduction of catheter into the superficial femoral artery by the Seldinger technique. After selective catheterization of the tumour supply artery with a microcatheter, conventional chemoembolization was carried out by injecting lipiodol (up to 25 mL, Andre Guerbet, Aulnay-sous-Bois, France) with pirarubicin (20 mg/m^2) and cisplatin (50 mg/m^2) into the supply artery until the flow was stopped. Thereafter, gelatine sponge was used to enhance the embolism of the supply artery. Artery-portal vein shunt, if found in the angiography, would be closed by gelatine sponge before chemoembolization. One month later, the effect of TACE was assessed by CT scan. TACE was repeated on a regular basis of four to eight weeks and 2–6 cycles in total.

2.3. Implantation of ^{125}I seeds

The ^{125}I seeds enclosed in a NiTinol capsule were purchased from China Institute of Atomic Energy, Beijing. They could emit 27.4–31.5 keV X-ray and 35.5 keV γ-ray, with a penetration of 1.7 cm, an incipient rate of 7 cGy/h, a half-life of 59.6 days, and activities of 0.5–0.8 mCi. One week before the implantation of ^{125}I, tumour images of 5 mm thickness were captured by CT scan and then transmitted to Treatment Planning System (TPS; HGGR-300, Hokai Medical Instruments Co., Ltd., Zhuhai, China). TPS determined numbers and positions of the ^{125}I seeds according to the minimum peripheral dose prescribed to each tumour (mPD, 90–165 Gy), so that they could cover the planning target volume, including the tumour and 0.5 cm adjacent non-cancerous tissue. The seeds were implanted into tumours at the interval of 1–1.5 cm by needles of 18 G and a turntable implantation gun (XinKe Pharmaceutical Ltd., Shanghai, China). The angle and placement of needles were guided by CT. Two weeks after the initial implantation, another CT scan was carried out to evaluate the distribution of ^{125}I seeds (Fig. 1). In this study, a median of 48 seeds (range, 12–75) was used per patient and all the cases were successfully implanted in one time. After the confirmation of successful implantation of ^{125}I seeds, patients underwent TACE immediately.

2.4. Follow-up

After the initial treatment, patients were followed at intervals of 3 months in the first two years and thereafter twice a year. Follow-up examination comprised physical examination, routine blood tests, liver function, tumour biomarkers and CT or MRI scan of the upper abdomen. Patients, if unable to return to the hospital for follow-up examination on time, were followed up by telephone. Overall survival was defined as the interval between the first treatment and either death or last contact.

2.5. Propensity score matching

Treatment allocation in this study was mostly based on treatment-related status and patients' decision rather than random assignation, therefore the bias in patient selection and potential confounding variables between groups might diminish the reliability of the results [19]. Aiming to reduce the influence of such selection bias and confounding variables, propensity score matching was applied in this study. Patients were matched to receive treatment on the basis of propensity score estimated by multivariable logistic regression models, in which the following baseline characteristics were used as covariates: gender, age, ECOG score, Child–Pugh class, BCLC stage, status of hepatitis B virus surface antigen (HBsAg), macrovascular invasion, extrahepatic metastasis, number of tumours, diameter of largest tumour, alpha foetal protein (AFP), alanine aminotransferase (ALT), total bilirubin, albumin and platelet count. A one to one matching without replacement was applied with a calliper of 0.2 [20].

2.6. Statistical analysis

All the statistical analyses were performed with SPSS Statistics 22 (IBM, Chicago, USA). Continuous variables were expressed as mean ± standard deviation and compared by *t*-test. For categorical variables, chi-square test or Fisher's exact test were used where appropriate. Overall survival was displayed by survival curves plotted by Kaplan–Meier method and compared by log-rank test. The COX regression model was employed to identify independent prognostic factors for overall survival. The P value was considered significant if less than 0.05. All the statistical tests were 2-sided.

3. Results

3.1. Patients

We retrospectively enrolled 144 patients with HCC of 3–5 cm in our hospital. Patients with BCLC stage A, B and C were 22, 48 and 74 (15.3%, 33.3% and 51.4%), respectively. Basically, surgery is highly recommended for patients with BCLC stage A, but they declined because of personal reason. The analyses of all patients comprised 66 and 78 patients who respectively underwent ^{125}I implantation