Digestive and Liver Disease xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Digestive and Liver Disease

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

Oncology

Radiofrequency ablation for HCC patients with multifocal tumours meeting the Milan criteria: A single-centre experience

Wei Zhang, Li Jiang*, Lunan Yan, Jiayin Yang, Bo Li, Tianfu Wen, Yong Zeng, WenTao Wang, Mingqing Xu

Department of Liver Surgery, Liver Transplantation Center, West China Hospital of Sichuan University, Chengdu, Sichuan Province, China

ARTICLE INFO

Article history:
Received 8 December 2015
Accepted 19 July 2016
Available online xxx

Keywords:
Hepatocellular carcinoma
Multifocal tumours
Overall survival
RFA

ABSTRACT

Background: Radiofrequency ablation (RFA) has been recommended as a curative treatment for patients with single early-stage unifocal hepatocellular carcinomas (HCCs) for years; however, the effect of this treatment on multifocal tumours has remained uncertain.
Aims: We conducted a retrospective study to evaluate the overall survival (OS) and recurrence-free survival (RFS) rates of early HCC patients with multiple tumours subjected to different RFA modalities.
Methods: One hundred fifty-four HCC patients with multifocal tumours who met the Milan criteria and underwent RFA were enrolled in this study. We divided the patients into 3 groups according to the surgical approach utilised (percutaneous, laparoscopic and open RFA; selection was based on the locations of the tumours for whether they were adhered to the subhepatic inferior vena cava or the gastrointestinal tract) and into 2 subgroups according to the tumour numbers and locations.
Results: No deaths occurred in the 30-day post-operation period, and there were no significant differences in the complication, OS or RFS rates between the 3 groups. The 1-, 3- and 5-year OS rates were 88.9%, 75.5% and 50.9% in the subgroup with 2 tumours, respectively, versus 91.3%, 56.3% and 17.5% in the subgroup with 3 tumours, respectively ($P = 0.001$). The corresponding values were 93.2%, 77.4% and 50.8% in the subgroup with tumours in the same segment and 82.4%, 54.8% and 23.0% in the subgroup with tumours in different segments ($P = 0.001$).
Conclusion: RFA was proven to be an effective and safe method for the treatment of multifocal HCCs. Among the patients with 2 tumours within the same segment, RFA achieved better long-term outcomes in terms of both overall and recurrence-free survival.

1. Introduction

Radiofrequency ablation (RFA) is the most widely accepted alternative to hepatic resection (HR) for early hepatocellular carcinomas (HCCs) [1,2]. The energy produced by RFA induces coagulative necrosis in the tumour and produces a safety margin in the surrounding tissue that might eliminate small undetected satellites. The best outcomes have been reported for Child–Pugh A patients with small single tumours, generally of less than 3 cm in diameter [1,2]. Among these patients, the 5-year survival rates can reach 40–70% [3,4]. Although the use of RFA in the treatment of patients with early HCCs has been reported by many centres [5–8], the majority of studies have been primarily focused on early HCC patients with single tumours. To the best of our knowledge, there are very few studies that have exclusively evaluated the outcomes of early HCC patients with multiple tumours who have undergone RFA. Thus, in this study, we report, the short- and long-term outcomes of RFA patients with multifocal tumours who met the Milan criteria ($\leq$3 nodules of $\leq$3 cm). To delineate the differential survival benefits using different RFA procedures in these patients, we identified prognostic predictors, such as survival rate and recurrence-free rate, and performed subgroup analyses.

2. Methods

2.1. Patients

This study was approved by the West China Hospital Ethics Committee and was conducted in accordance with the ethical guidelines of the Declaration of Helsinki. Fig. 1 illustrates the inclusion and exclusion criteria for the cohort. A total of 1032 patients with HCCs (not including patients with recurrent HCCs) underwent

* Corresponding author. Fax: +86 28 85422871.
E-mail address: jl339@126.com (L. Jiang).

http://dx.doi.org/10.1016/j.dld.2016.07.018
1590-8658/

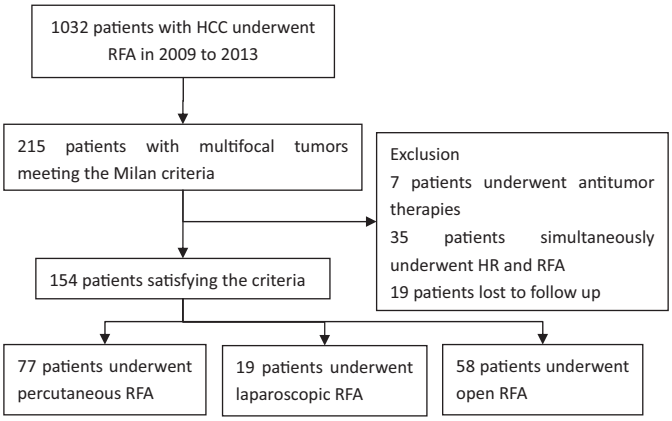

Fig. 1. 154 patients satisfying the criteria were involved in this study.

RFA between January 2009 and January 2013 in our centre. Of these patients, 215 patients had multifocal tumours that met the Milan criteria (≤3 nodules of ≤3 cm). Furthermore, 7 patients who had undergone other antitumour therapies were excluded, and 35 patients were excluded because they simultaneously underwent HR and RFA. After excluding 19 patients who were lost to follow-up, 154 HCC patients with multifocal tumours that met the Milan criteria who underwent RFA were ultimately enrolled in this study. These patients were monitored until May 2015 or until their deaths, and their medical records were retrospectively reviewed.

2.2. Definitions and diagnostic criteria

The Milan criteria are defined as follows: a single tumour of ≤5 cm or a maximum of 3 tumours with none exceeding 3 cm in patients without extrahepatic manifestations or vascular invasion [9].

Clinically relevant portal hypertension (PHT) is defined as the presence of oesophageal varices and/or a platelet count less than 100,000 per μL in association with splenomegaly [10].

At this stage, we defined a subgroup according to Couinaud's segmentation, which was proposed based on the distribution of the portal pedicles and the location of the hepatic veins [11].

The HCC diagnoses were confirmed by needle biopsy or by 2 types of clinical imaging [ultrasonography, computed tomography (CT) or magnetic resonance imaging (MRI)] in addition to a high serum level of α-fetoprotein (AFP) and a background of HBV infection. A hyperdense or hyperintense thin peripheral rim enhancement in the delayed venous phase images of the tumour capsule supported the diagnosis of HCC on the CT and MRI images [12]. If a diagnosis based on imaging and the AFP level was uncertain, a needle biopsy was performed.

2.3. Selection of the therapeutic method

All patients were informed that liver transplantation (LT), HR and RFA were the radical therapeutic methods for their disease and that LT should be the optimal treatment because it involves the largest possible hepatectomy and removal of the underlying cirrhotic tissue before they selected the final therapeutic method. Generally speaking, when all of the tumours have percutaneous puncture routes in normal or artificial serothorax conditions, the percutaneous RFA procedure was recommended. If one tumour was located near the subhepatic inferior vena cava or the gastrointestinal tract, the laparoscopic approach was recommended. If RFA could not be accomplished via either of these two approaches, the open method was recommended. All of the patients in our study were administered general anaesthesia prior to the performance of the RFA. Pain and discomfort were effectively prevented, particularly for nodules located in the subcapsular region. Furthermore, the patient's breathing was temporarily blocked control via intubation to aid the insertion of the needle when accessible could only be obtained during forced inspiration.

2.4. Follow-up and treatment of recurrence

The follow-up data were routinely collected in the outpatient clinic. AFP and hepatitis B virus deoxyribonucleic acid (HBV DNA) measures and abdominal ultrasonography were performed every 3 months. CT scans were performed every 6 months. When intrahepatic recurrence was difficult to ascertain, MRI or contrast-enhanced ultrasonography was performed. The identification of tumour recurrence was primarily based on radiographic evidence and/or the AFP level. The patients who exhibited recurrence were treated with the following alternatives: re-resection, RFA, salvage LT, transcatheter arterial chemoembolization (TACE), sorafenib, radiotherapy, and chemotherapy.

2.5. Statistical analysis

The SPSS 17.0 statistical software (SPSS Inc., Chicago, IL, USA) was used to analyse the relevant data. Categorical data are presented as numbers (per cents) and were compared using Pearson chi-square or Fisher's exact tests. Continuous variables are expressed as the mean value ± the SD and were analysed with *T*-tests. The overall survival (OS) and recurrence-free survival (RFS) rates were estimated with the Kaplan–Meier method, and differences between pairs of groups were determined with log-rank tests. The Cox proportional hazards model was used to test potential predictors of survival after RFA. The variables that exhibited statistical significance in the univariate analyses were subsequently included in the multivariate analysis, which was performed with a proportional hazard regression. For all tests, a 2-tailed $P < 0.05$ was considered statistically significant.

3. Results

3.1. Characteristics of all study patients

According to the different RFA procedures, the 154 patients were separated into 3 groups based on the ablation approach: group P ($n = 77$) consisted of the patients who underwent the percutaneous RFA procedure; group L ($n = 19$) consisted of the patients who underwent RFA via the laparoscopic approach; and group O ($n = 58$) consisted of the patients who underwent RFA via the conventional open method. Table 1 summarises the baseline demographic and clinicopathological data of all 154 patients. As illustrated in Table 1, group O had more patients with AFPs that exceeded 400 ng/mL than group L ($P = 0.045$), and the patents in group O had higher alanine aminotransferase (ALT) levels than did those in group L ($P = 0.023$). There were no significant differences in age, sex, largest tumour size, total bilirubin level, aspartate aminotransferase (AST) level, albumin level, prothrombin time, platelet count, or the percentages of patients with hepatitis B surface antigen (HBsAg) positivity, HBV DNA exceeding 1000 IU/mL, Child–Pugh class A or tumour number exceeding 2 (all $P > 0.05$).

3.2. Postoperative mortality and morbidity

No deaths occurred in the 30-day post-operation period in any of the 3 groups. Postoperative complications were evaluated using the Clavien-Dindo classification [13]. Most of the complications were grade I or grade II (Table 2). The common complications that exceeded grade II are listed. Nine patients suffered postoperative

Please cite this article in press as: Zhang W, et al. Radiofrequency ablation for HCC patients with multifocal tumours meeting the Milan criteria: A single-centre experience. Dig Liver Dis (2016), http://dx.doi.org/10.1016/j.dld.2016.07.018