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Post-recurrence survival in hepatocellular carcinoma after percutaneous radiofrequency ablation

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ABSTRACT

Background: Overall survival in hepatocellular carcinoma patients treated with percutaneous radiofrequency ablation is influenced by both recurrence and successive treatments. We investigated post-recurrence survival after radiofrequency ablation.
Methods: Data on 103 early/intermediate patients initially treated with radiofrequency ablation and followed for a median of 78 months (range 68–82) were retrospectively analysed. If intrahepatic disease recurrence occurred within or contiguous to the previously treated area it was defined as local, otherwise as distant; recurrence classified as Barcelona Clinic Liver Cancer stage C was defined by neoplastic portal vein thrombosis or metastases.
Results: A total of 103 patients were included (82.5% male; median age 70 years, range 39–86). During follow-up, 64 recurrences were observed. Median overall survival was 62 months (95% confidence interval: 54–78) and survival rates were 97%, 65% and 52% at 1, 4 and 5 years, respectively. Median post-recurrence survival was 22 months (95% confidence interval: 16–35). Child–Pugh score, performance status, sum of tumour diameters at recurrence and recurrence patterns were independent predictors of post-recurrence survival.
Conclusions: In patients with hepatocellular carcinoma after radiofrequency ablation, clinical and tumour parameters assessed at relapse, in particular the type of recurrence pattern, influence post-recurrence survival.

1. Introduction

Hepatocellular carcinoma (HCC) represents the third most common cause of cancer-related death and the leading cause of mortality among patients with cirrhosis [1,2]. Thanks to recent improvements in surveillance protocols and diagnostic tools, early HCC diagnosis is currently feasible in 30–60% of cases [3].

Radiofrequency ablation (RFA) is considered the first line treatment option for patients at early stage, who are not amenable to surgery or orthotopic liver transplantation (OLT). It is associated with a 5-years survival rate of 40–70% in this specific subset of HCC patients [4,5].

The best outcomes have been reported in HCCs classified as Barcelona Cancer of the Liver Clinic (BCLC) stage 0 (i.e. single nodule ≤2 cm) for which RFA has demonstrated a competitive efficacy compared to surgery in terms of overall survival (OS) [6,7].

In HCC patients treated with percutaneous RFA, long-term survival is influenced by the high percentage of intrahepatic or extrahepatic recurrences and by successive treatments, such as trans-arterial chemoembolization (TACE) or sorafenib. For this reason, it is important to identify prognostic factors that could influence further therapeutic options. Therefore, as in other cancer types, it is necessary to study post-recurrence survival (PRS) and investigate variables, such as progression pattern and liver function at recurrence that can influence OS. In fact, as reported in a recently published analysis performed for palliative treatment with sorafenib [8], clinical and tumour parameters assessed at

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radiological progression emerge as major confounders in understanding OS data.

However, despite this evidence, the role of the recurrence pattern and prognostic predictors of PRS after curative therapies are still unknown.

The aim of this study was to investigate prognostic factors for PRS and OS after percutaneous RFA, as such data would likely be useful for clinical trial design and second-line treatments after recurrence.

2. Materials and methods

2.1. Patients

Clinical, laboratory and radiological data on 103 patients initially treated with RFA for a first occurrence of HCC at the University of Foggia between April 2005 and February 2010 were retrieved from a prospectively collected database. Indications for percutaneous RFA were: (1) HCC diagnosed by histology or by non-invasive criteria according to the American Association for the Study of Liver Disease (AASLD) guidelines [9]; (2) patients with a single nodule <2 cm treatable with a percutaneous approach; (3) early HCC patients, as classified by BCLC, not suitable for surgical therapies such as hepatic resection or OLT; (4) intermediate HCC patients (BCLC B) not amenable to trans-arterial treatments, such as TACE, due to vascular anomalies (arterio-venous shunting through the tumour or atherosclerotic plaques) or hypovascular nodules.

Contraindications to RFA were decompensated liver cirrhosis and at-risk locations (superficial lesions adjacent to any part of the gastrointestinal tract). RFA was avoided also in case of nodules adjacent to hepatic vessels due to the risk of incomplete treatment because of the "heat-sink effect" (i.e. heat loss by convection).

This study was approved by our Institutional Review Board for retrospective evaluation of de-identified patients.

Patients who underwent previous treatments for HCC were excluded from the analysis. Follow-up ended in December 2013 (median 78 months, range 68–82).

The following parameters were recorded: demographics and medical history, ethology of underlying liver disease, treatments performed after RFA, liver function according to Child–Pugh (CP) score and Model for End-Stage Liver Disease (MELD), Eastern Cooperative Oncology Group (ECOG), Performance Status (PS), tumour stage according to BCLC, Cancer of the Liver Italian Program (CLIP), Okuda and American Liver Tumour Study Group (ALTSG) staging systems, presence of portal hypertension (defined by at least one of the following: oesophageal varices, platelet count <100,000 μL^{-1} and splenomegaly) [10].

2.2. Treatment protocol

RFA had been performed under ultrasound guidance with a 150 W generator (Model 1500 L; RITA Medical System, Mountain View, California), connected to an expandable 15–14-gauge electrode with a 2.0-cm-long exposed tip (expandable by means of seven hooks). After administration of analgesia (50–60 mg of propofol and 0.05–0.1 mg of fentanyl) as well as local anaesthesia (5–15 mL of 1% lidocaine) by an anaesthesiologist, an RFA needle was inserted into the tumour. The electrode was placed into the centre of the lesion maintaining the temperature of the needle tip at 80–110 °C for 10–12 min. After ablation, the needle was retracted maintaining its tip hot in order to prevent by thermal coagulation seeding or haemorrhage along the electrode track. For medium and large nodules, different applicator positions had been adopted to create overlapping coagulation zones. For patients with multiple nodules, all lesions had been treated in one single session. Every procedure had been aimed at obtaining a 5 mm safety margin around the treated lesions. No antibiotic prophylaxis or anti-inflammatory drugs had been administered prior to therapy.

2.3. Patient monitoring and response evaluation

Pain and fever occurring after the procedure were managed by means of intravenous ketorolac and paracetamol respectively. Clinical visits, including physical examination, laboratory analyses (transaminase, liver function panel, complete blood count and serum AFP), thoraco-abdominal multi-phase computed tomography (CT) scan evaluation and adverse events (AE) monitoring (mainly liver decompensation, hepatic abscess occurrence or abdominal pain), were performed on an outpatient basis at 30–50 days after the procedure. In case of complete response, follow up visits were scheduled every 4–6 months, otherwise, in case of incomplete response, a second treatment was planned in CP ≤B7 patients.

Tumour response was assessed according to modified RECIST (mRECIST) criteria [11]. For analytical purposes, in the case of consecutive procedures the best response achieved after the last RFA of the treatment series was considered.

Safety parameters were classified following the common terminology criteria for adverse events (CTCAE) 4.0 [12]. Liver decompensation was defined as the occurrence of any of the following signs within 1 month from the procedure: clinically detectable ascites, bleeding from oesophageal varices, hepatic encephalopathy, total bilirubin >3 mg/dL, and prothrombin time international normalized ratio >2.2 [10].

Disease recurrence patterns were defined by any of the following: local intrahepatic recurrence (development of new lesions contiguous to or within the treated area), distant intrahepatic recurrence (new nodules in other segments or in the same segment more than 2 cm away from the treated area), BCLC C recurrence (development of neoplastic portal vein thrombosis or metastases).

At recurrence, in case of intrahepatic disease the elective treatment was RFA for single nodules and TACE for multifocal HCC, sorafenib (Nexavar®, Bayer, Leverkusen, Germany) if portal vein thrombosis (PVT) or metastases occurred.

OS was measured from the date of the first RFA until the date of death. PRS was measured from the date of detecting recurrence at radiology until the date of death or last follow-up. The relationship between predictors and OS was determined in the whole cohort. The impact of prognostic factors on PRS was assessed in 64 patients who experienced tumour recurrence (Fig. 1).

2.4. Statistical analysis

Categorical variables are described as frequencies and percentages while continuous variables as median and range. Times to event data were estimated from the first procedure by Kaplan–Meier with plots and median [95% confidence interval (95% CI)] and compared by means of log-rank test.

The inferential analysis for time to event data was conducted using the Cox univariate and multivariate regression model to estimate hazard ratios (HR) and 95% CI. Statistically significant variables from the univariate Cox analysis were consistently included in the multivariate models.

The analysis was performed using R Statistical Software (Foundation for Statistical Computing, Vienna, Austria) and SPSSv.18 (SPSS, Chicago, IL), and significance was established at the 0.05 level (two-sided).