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ORIGINAL ARTICLE **CME**

Pre-procedure Prognostic Factors to Predict Survival of Patients after Radiofrequency Ablation of Hepatocellular Carcinoma

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ABSTRACT

Objective: *This study evaluated the clinical, biochemical, and imaging characteristics to identify pre-ablative prognostic factors for the survival of patients undergoing radiofrequency ablation of hepatocellular carcinoma. Radiofrequency ablation has now been adopted as a curative management for small hepatocellular carcinomas, particularly in patients not suitable for surgery. Studies have shown that it confers comparable patient survival to surgical excision for small tumours with adequate ablation margins. However, we wished to evaluate pre-radiofrequency ablation factors prognostic for survival, so as to guide our management with a combination of treatment modalities.*

Methods: *A total of 68 consecutive patients having radiofrequency ablation for hepatic tumours from July 2004 to July 2008 were recruited. From among these 68 patients, the findings of 51 patients (with 75 hepatocelluar carcinomas) were analysed. Overall cumulative survival and recurrence-free survival were estimated using the Kaplan-Meier method. To evaluate significant prognostic factors for survival analysis, clinical factors including patient age, Child-Pugh status, biochemical factors including alpha-fetoprotein level, findings from imaging including maximal tumour size, tumour multiplicity (solitary versus multiple nodules) were subjected to univariate and multivariate Cox regression.*

Results: *The mean age of patients was 63 (standard deviation, 12) years. Of 51 patients, 43 (84%) received percutaneous radiofrequency ablation. The mean tumour size was 2.5 (standard deviation, 0.96) cm. Mean alpha-fetoprotein levels at the time of hepatocellular carcinoma diagnosis was 563 (standard deviation, 1834) ng/ml. Patients were followed up for a median period of 509 (range, 3-1350) days. The mean follow-up time was 520 (standard deviation, 330) days. Overall recurrence including both intrahepatic (distant) and local progression ensued in 23 patients (44%). Twenty-one patients (41%) died during the follow-up period. The estimated median overall cumulative survival was 1000 (95% confidence interval, 564-1435) days. The overall estimated 6-, 12-, 18-, and 24-month survival rates were 84%, 73%, 66%, and 58% respectively. Tumour multiplicity was found to be a significant prognostic factor for overall survival (adjusted hazard ratio = 5.31; 95% confidence interval, 2.02-14.00; p = 0.001) and recurrence-free survival (2.69; 1.12-6.46; 0.026).*

Conclusion: *After radiofrequency ablation, tumour multiplicity was found to be a significant prognostic factor for predicting overall and recurrence-free survival in these patients.*

Key Words: *Carcinoma, hepatocellular; Catheter ablation; Liver neoplasms; Neoplasm recurrence, local; Prognosis; Survival analysis*

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中文摘要

預測肝腫瘤患者接受射頻消融術後存活率的術前因素

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目的：本研究評估接受射頻消融術治療肝腫瘤患者的臨床、生化及影像特性，從中識別預測患者存活率的術前因素。射頻消融術已成為治療小肝癌的一種方法，尤其是對於不適合手術的病人。有研究指出，只要小腫瘤有足夠消融範圍，此技術的病人存活率跟切除術相若。縱使如此，我們仍然希望評估預測存活率的術前因素，以便為結合不同治療方案的做法作一指引。

方法：收集2004年7月至2008年7月期間，所有68位接受射頻消融術治療肝腫瘤的病人資料，分析其中51人（共75個肝腫瘤）的結果。運用Kaplan-Meier方法估計病人的整體累積存活率及無復發存活率。並用單元及多元Cox回歸分析評估預測存活率的有效預測因素，包括臨床因素如病人年齡、Child-Pugh肝功能分級、生化因素如甲胎蛋白水平、以及影像結果如腫瘤最大體積、腫瘤多發性（孤立或多發結節）。

結果：病人平均年齡63歲（標準差12歲）。51位病人中，43位（84%）接受經皮射頻消融術。腫瘤平均大小為2.5 cm（標準差0.96 cm），確診時平均甲胎蛋白水平563 ng/ml（標準差1834 ng/ml）。隨訪期中位數509天（介乎3至1350天），平均520天（標準差330天）。包括肝內遠處轉移及局部原位復發在內，共計23位（44%）病人出現復發。隨訪期間有21位病人（41%）死亡。整體累積存活率的中位數估計為1000天（95%置信區間：564至1435天）。6、12、18及24個月的存活率分別估計為84%、73%、66%及58%。腫瘤多發性是整體存活率（調整後的危險比率5.31；95%置信區間：2.02至14.00；p = 0.001）及無復發存活率（調整後的危險比率2.69；95%置信區間1.12至6.46；p = 0.026）的一項有效預測因素。

結論：接受射頻消融術後的病人，其腫瘤多發性是一項預測整體及無復發存活率的有效因素。

INTRODUCTION

Recent advances in a variety of local / regional therapeutic options for the management of hepatocellular carcinoma (HCC) have been advocated and developed rapidly. They include radiofrequency ablation (RFA),[1-5] percutaneous ethanol injection, cryotherapy,[6] microwave coagulation therapy,[7,8] and more recently irreversible electroporation,[9] which is currently under clinical trial. These local / regional treatment options challenge the traditional belief that hepatectomy and resection was the only curative treatment option for HCC. RFA is widely used in managing HCC and it is now used as an alternative treatment to surgery for resectable HCCs (≤3 cm).[10,11] RFA is usually indicated for patients with 3 or fewer nodules, none of which should exceed 3 cm in diameter. However, these conventional criteria originated from the experience with ethanol injection and the limit has been challenged by studies entailing treatment of tumours larger than 5 cm. Tumour size and tumour number affect RFA treatment efficacy and the rate of complete tumour necrosis achieved after RFA. In addition, the rationale and criteria for selecting patients have to be balanced with their overall condition, expected survival benefits, and procedure risks associated with different treatment modalities. Such issues pose a dilemma to interventional radiologists and surgeons who have to choose the best treatment option for HCC patients. We therefore conducted this retrospective cohort study to evaluate the prognosis of patients who underwent RFA, based on a number of pre-ablative clinical and biochemical features. By evaluating clinical, biochemical and imaging characteristics, we set out to identify pre-ablative prognostic factors that might influence the survival of patients undergoing RFA of HCC.

METHODS

Patient Selection

Records of consecutive patients (68 in all) having RFA for hepatic tumours by interventional radiologists in a single regional hospital from 1 July 2004 to 31 July 2008 were reviewed retrospectively. Since 8 patients had ablation performed for secondary hepatic metastases, their findings were excluded from the analysis, 5

others were excluded because they had histologically proven dysplastic nodules, and 4 because at presentation they had ruptured tumours for which ablation was non-curative. Findings from 51 patients with 75 HCCs were therefore analysed. Formal consent was obtained from all patients regarding the indications and risks of these procedures. Approval from ethics committee was not sought due to the retrospective nature of this study.

Diagnosis of Hepatocellular Carcinoma

The diagnosis of HCC conformed to the guidelines of the Barcelona Clinic Liver Cancer group,[12,13] with the use of contrast computed tomography (CT), magnetic resonance imaging, and the level of alpha-fetoprotein (AFP). Some tumours were confirmed histopathologically with ultrasound-guided biopsy.

Procedure

Percutaneous RFA was performed with the patient sedated and analgesia given in the CT suite. In open or laparoscopic RFA, patients underwent general anaesthesia and the ablation procedures were performed by radiologists after a laparotomy or laparoscopy by hepatobiliary surgeons. Vital signs were continuously monitored during the procedure. RFA was performed under ultrasound or CT guidance. For most patients, both imaging techniques were used for tumour localisation and needle entry. The most appropriate approach for electrode insertion was selected based on the tumour location and size. For lesions located in the right lobe, an intercostal approach was preferred, with the patient in the left oblique position. For tumours located in the left lobe, a subcostal approach was used. If the tumour was close to adjacent structures such as the diaphragm, kidney, gallbladder or bowel, artificial ascites or a pleural effusion were induced by instilling 1 to 2 L 5% dextrose solution until there was a satisfactory space for needle insertion and sufficient separation from the nearby organs.

Two types of electrodes were used: 18-G internally cooled electrodes (Valleylab Cool-tip RF Ablation System; Valleylab, Boulder, USA) and the 15-G LeVeen electrode (Boston Scientific, Natick, USA). The selection of the electrode type was based on the size and location of the tumour. For tumours measuring 2 to 3 cm in diameter, a single electrode with 2 or 3 cm exposed metallic tip was used. For larger tumours, a multitined expandable LeVeen needle with an umbrella-shaped array or a cluster triple electrode (Valleylab Cool-tip RF Ablation System) with 3 internally cooled electrodes was used.

Dispersive electrodes or grounding pads were attached to the patients' thighs. Both RFA systems were connected to their designated generators, which have an impedance-based feedback system designed to accurately monitor the extent of tissue desiccation and permit continued delivery of radiofrequency energy. Both generators are capable of producing 200 W of power. For the Valleylab Cool-tip RF Ablation System, the electrodes were attached to a 500-kHz RF generator (CC-1; Radionics Inc, Burlington, USA). For the LeVeen electrode, the electrodes were connected to the RF 3000 Generator (Boston Scientific). The progress of tissue ablation was monitored by the impendence to signify the end of the procedure, using the ablation protocol provided by the manufacturer. The ablation time of each cycle was 12 minutes for the Valleylab Cool-tip RF Ablation System and up to 20 minutes for the LeVeen electrode system. Following ablation, the patient stayed overnight in the hospital, even in the absence of complications.

Follow-up Protocol

After RFA, patients were generally followed up regularly in our Interventional Radiology clinic. Regular CT scans of the liver with dynamic phases were performed to assess the tumour status with a structured CT imaging protocol at day 0, 1 month, 3 months, 6 months, 9 months, 12 months, 18 months, and 24 months after ablation. AFP levels, liver function test, and disease progress were regularly monitored. The follow-up period and the time of CT imaging were reviewed. Incomplete ablation, new tumour deposits, complications, and mortality were documented.[14,15]

Tumour recurrence was defined using the same criteria applied to the initial HCC. When HCC recurrence was identified, RFA was performed if the same criteria as for primary HCC were again satisfied. Tumour recurrence including both intrahepatic distant recurrences and local tumour progression were re-evaluated for new treatment options for all patients, with the options being ethanol injection, RFA, chemoembolisation, and radiotherapy.[12]

Statistical Analysis

Survival analysis was performed on a patient basis. The time of enrolment into this study was the date the HCC was diagnosed. The end-point was the date of death or the day of the last visit to the outpatient clinic so long it was event-free. Survival time was defined as the interval between the day of the diagnosis and

death or the last visit to the outpatient clinic until 31 July 2009. For patients who had a previous history of HCC with complete tumour resection, the day of diagnosis of the new HCC was taken as the day of enrolment. Recurrence-free survival was defined as the interval between the day without an accountable viable tumour after complete tumour ablation, and the time to recurrent tumour detection by CT. Overall cumulative survival and recurrence-free survival were estimated using the Kaplan-Meier method. Overall cumulative survival curves were stratified and compared using the log-rank test. To evaluate significant prognostic factors for survival analysis, clinical factors including patient age, presence of known history of previous hepatic operation, biochemical factors including AFP level (being categorised into ≤200 ng/ml vs >200 ng/ml), imaging parameters including maximal tumour size in longest dimension, tumour multiplicity (solitary vs multiple nodules) were included for analysis for both overall survival and recurrence-free survival. Univariate analysis of the Cox regression was performed for each factor. Multivariate analysis was then undertaken for statistical analysis with the backward stepwise selection method to evaluate independent prognostic factors. Differences with a $p < 0.05$ were considered statistically significant. All statistical analyses were conducted using the SPSS 16.0 (SPSS Inc, Chicago, USA).

RESULTS

Patient Demographic Factors

A total of 51 patients were selected for analysis in whom RFA of HCC had a curative aim. Forty-seven patients (92%) were male. The mean age of the patients at the time of HCC diagnosis was 63 (standard deviation [SD], 12) years. Forty-three patients (84%) received percutaneous RFA, and the rest via an open laparotomy or laparoscopic approach. All patients belong to Child-Pugh class A or B, 45 (88%) being in Child-Pugh class A.

Forty-one patients presented with HCC for the first time. Ten had previous history of wedge resection or segmentectomy for a previous HCC with evidence of complete resection of the tumour with an adequate margin, but later developed new HCC in a site distant from previous operated sites.

The mean tumour size was 2.5 (SD, 1.0) cm with a range of 0.7 to 5.4 cm. The mean AFP level at the time

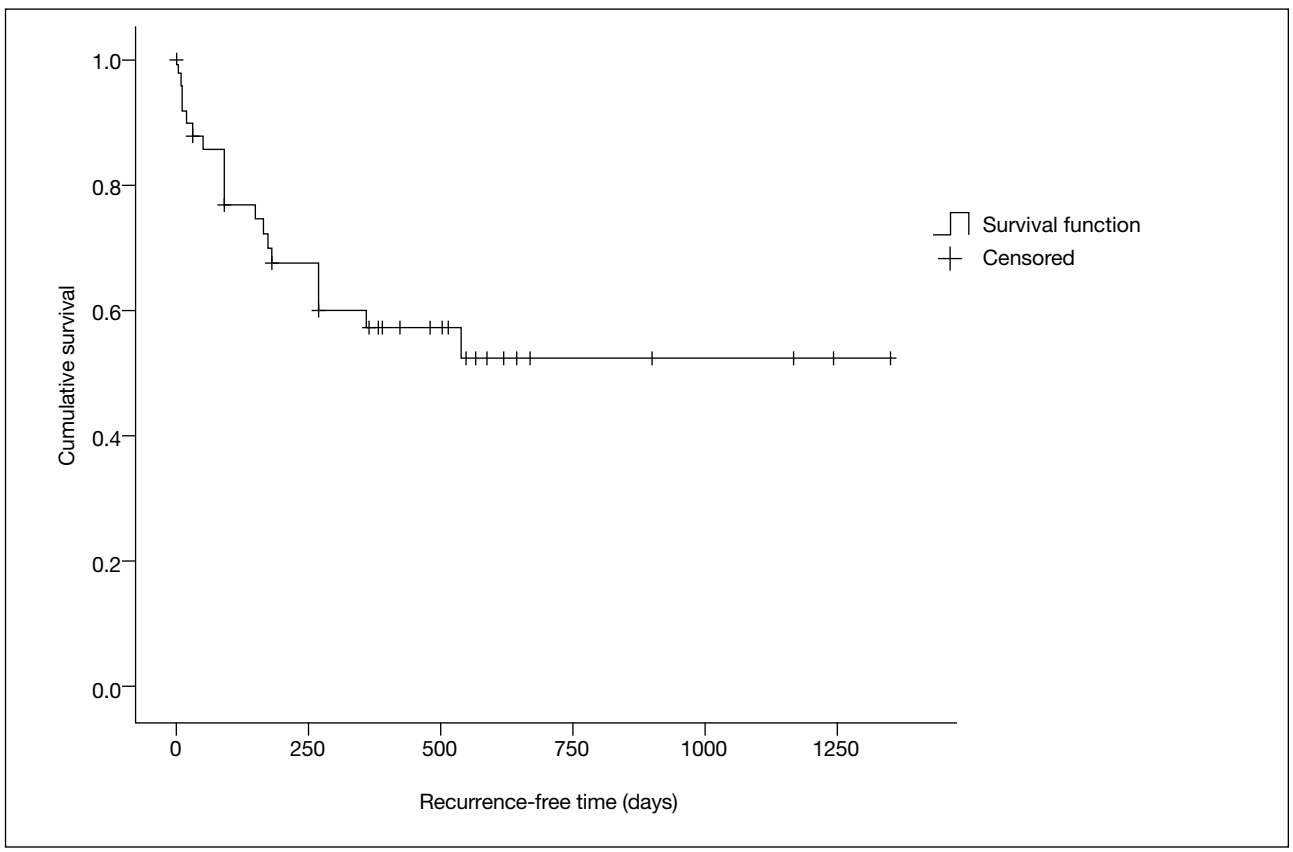

Figure 1. Survival plot for recurrence-free survival in hepatocellular carcinoma patients receiving radiofrequency ablation.

of HCC diagnosis was 563 (SD, 1834) ng/ml with a range of 2 to 11,642 ng/ml. Fourteen of the patients (27%) had more than one tumour treated in the same session on presentation; 10 had 2 tumours, 1 had 3 tumours, 3 had 4 tumours.

Tumour Recurrence

Patients were followed up for a median time of 509 (range, 3-1350) days. The mean follow-up duration was 521 (SD, 330) days. Recurrence including both intrahepatic distant lesions and local tumour progression was observed in 23 (45%) of the patients; the mean time to recurrence was 184 (SD, 148) days. Overall recurrence-free survival rates estimated at 6, 12, 18, and 24 months were 75%, 60%, 58%, and 52% respectively (Figure 1).

Survival

Twenty-one (41%) of the patients died during the follow-up period and 30 were censored (Figure 2). The overall estimated survival rates at 6, 12, 18, and 24 months were 84%, 73%, 66%, and 58% respectively. The stratified survival curves according to the tumour multiplicity (solitary vs multiple) showed significant difference (p = 0.005). Those with solitary tumour showed significantly better survival than those presenting with multiple tumours (Figure 3).

Multivariate analysis showed that tumour multiplicity was a significant prognostic factor for overall survival (adjusted hazard ratio = 5.31; 95% confidence interval, 2.02-14.00; p = 0.001) and recurrence-free survival (2.69; 1.12-6.46; p = 0.026) after adjusting for other variables (Table 1). Therefore, compared with those presenting with solitary tumours, patients presenting with multiple tumours were at higher risk both in terms of overall and recurrence-free survival (Figure 4). Other factors failed to show any statistically significant results.

DISCUSSION

In daily clinical practice, survival data on pre-ablative prognostic factors could help make decisions about optimal curative treatment option for patients with HCC. Current data on survival after RFA of HCC are mainly focused on small HCC tumours with sizes of less than 3 cm due to the higher rate of complete necrosis achievable after ablation.[12,16-18] Apart from tumour size as a criterion, our study showed that tumour multiplicity was an important prognostic factor for both overall

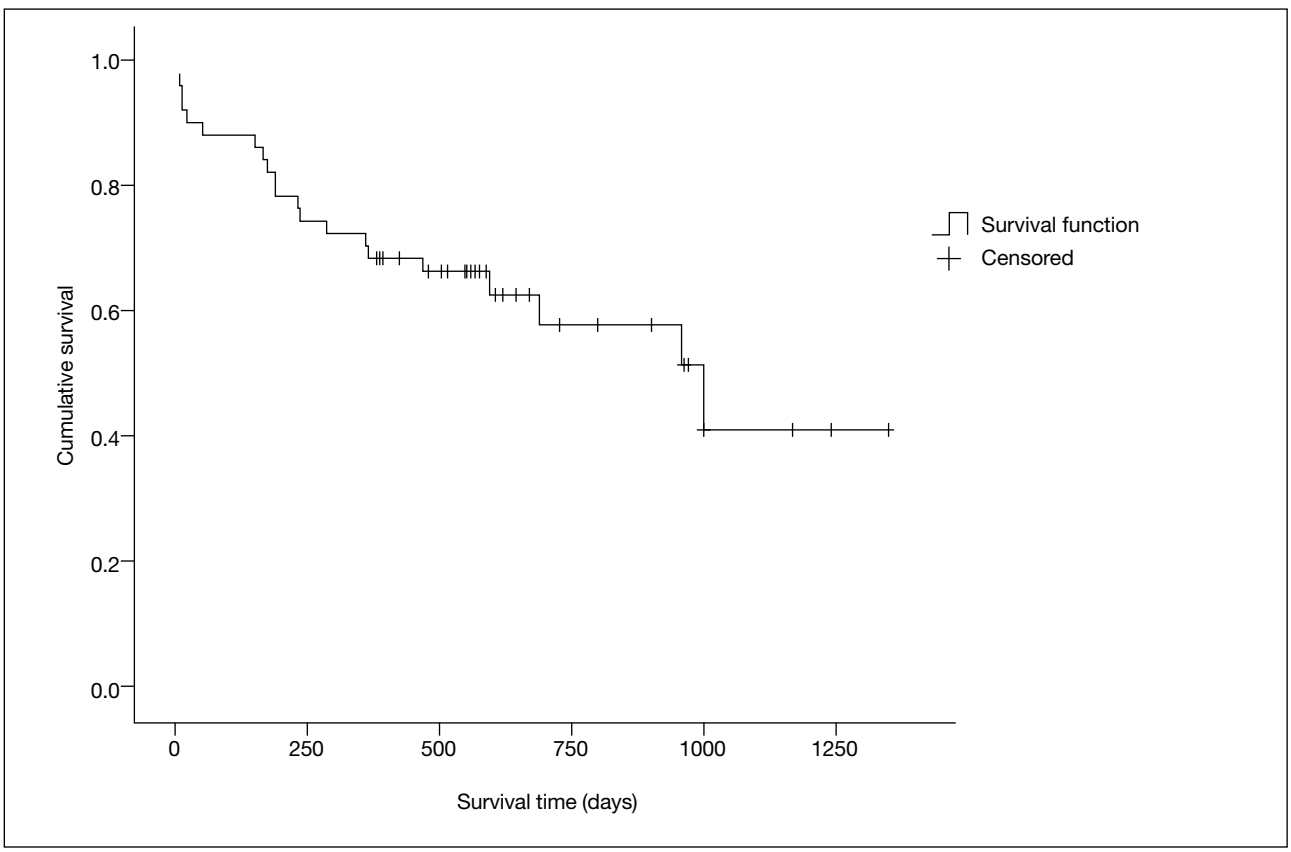

Figure 2. Overall survival plot in hepatocellular carcinoma patients receiving radiofrequency ablation.

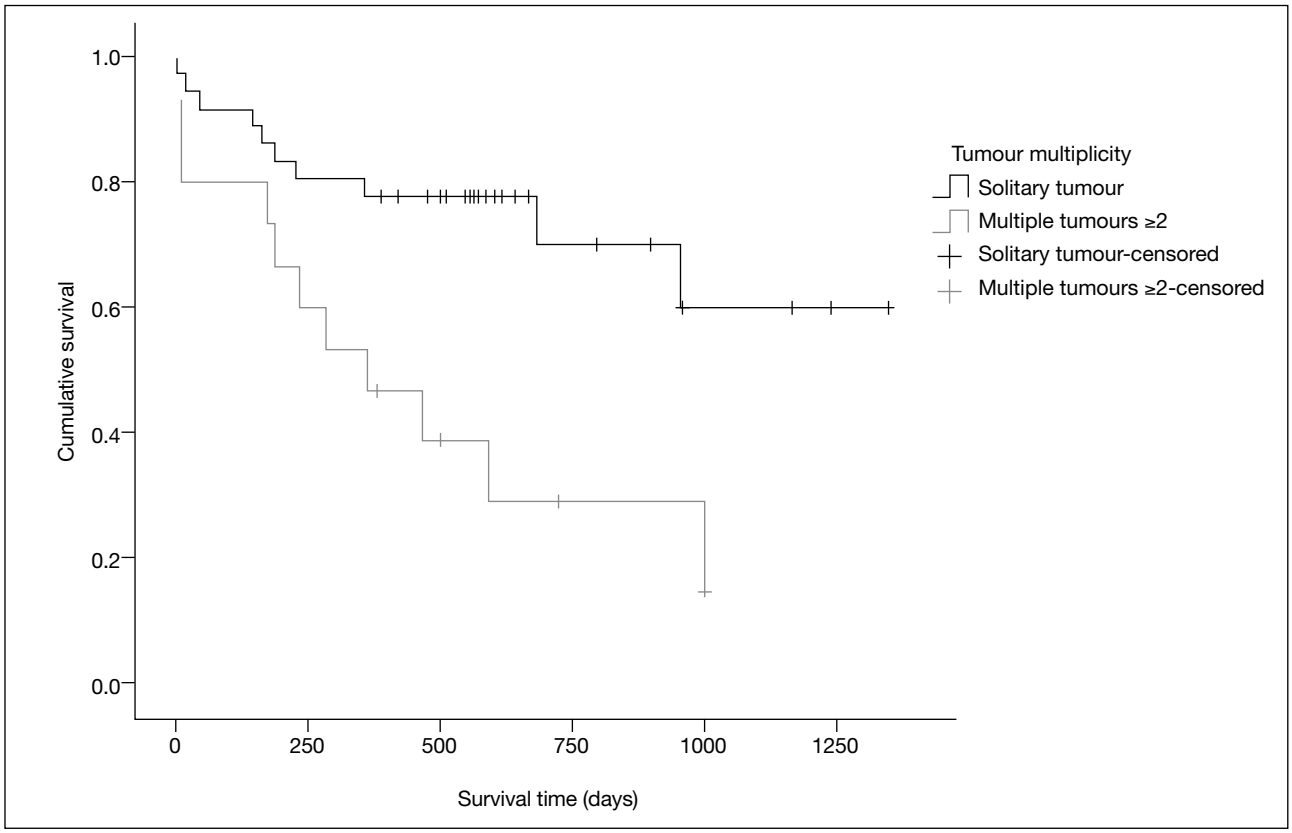

Figure 3. Survival plot for overall survival stratified by tumour multiplicity (solitary tumour versus multiple tumours).

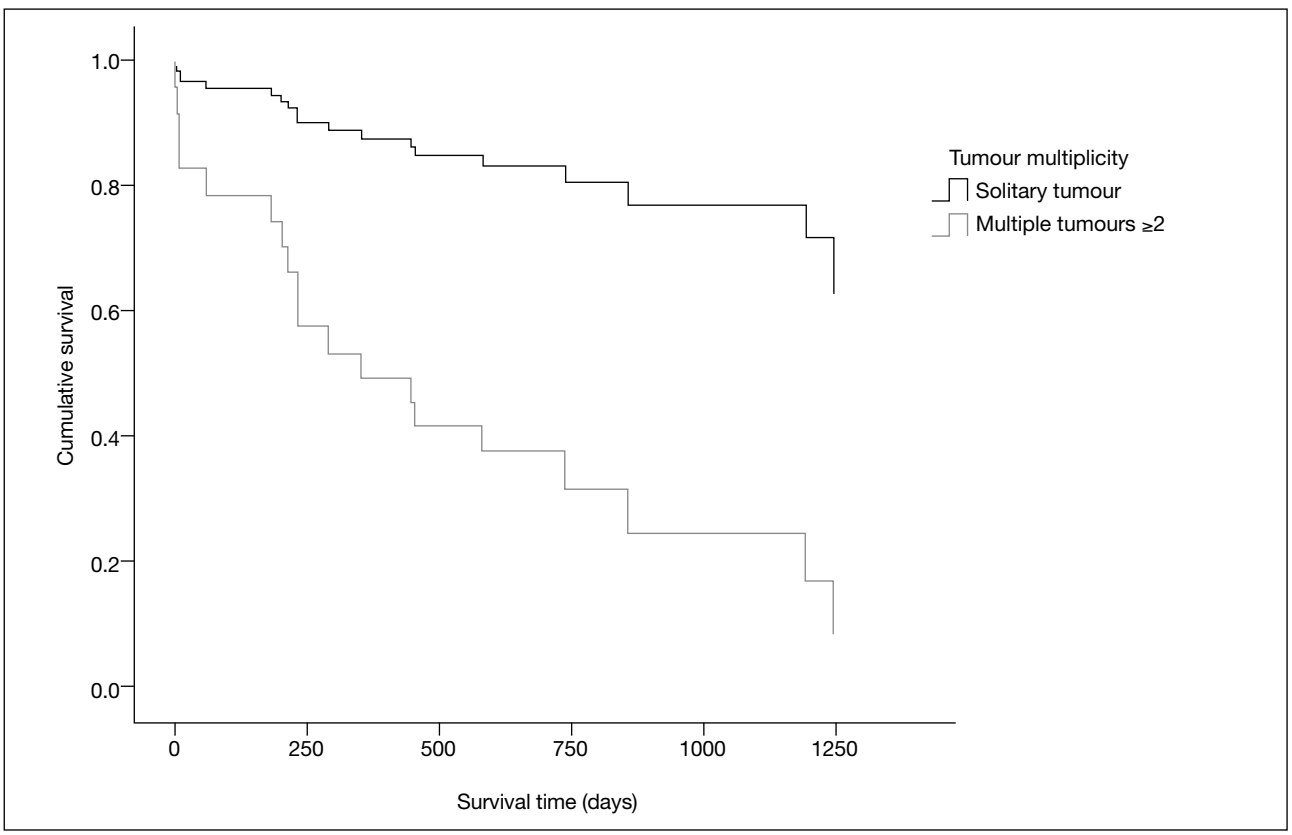

Figure 4. Survival plot of recurrence-free survival stratified according to tumour multiplicity.

Table 1. Final Cox regression models for overall survival and recurrence-free survival.

	Hazard ratio	95% Confidence interval	p Value
Overall survival			
Age (years)	1.05	0.10 - 1.10	0.057
Tumour multiplicity			
Multiple tumours	5.31	2.02 - 14.00	0.001
Solitary tumour	1		
Longest diameter of tumour size (cm)	1.16	0.67 - 2.02	0.594
AFP level			
>200 ng/ml	0.38	0.12 - 1.27	0.118
≤200 ng/ml	1		
Previous operation for HCC	0.57	0.16 - 2.04	0.386
Recurrence-free survival			
Age (years)	1.02	0.98 - 1.06	0.379
Tumour multiplicity			
Multiple tumours	2.69	1.12 - 6.46	0.026
Solitary tumour	1		
Longest diameter of tumour size (cm)	0.95	0.56 - 1.59	0.838
AFP level			
>200 ng/ml	1.66	0.67 - 3.96	0.254
≤200 ng/ml	1		
Previous operation for HCC	1.00	0.61 - 5.23	0.292

Abbreviations: AFP = alpha-fetoprotein; HCC = hepatocellular carcinoma.

Table 2. Level of evidence graded according to the Hierarchy of Evidence developed by the National Health and Medical Research Council of Australia.

Level of evidence	Source of evidence
I	A systematic review of all relevant RCTs
II	At least 1 properly designed RCT
III-1	Well-designed pseudo-RCTs (alternate allocation or some other method)
III-2	Comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomised, cohort studies, case-control studies, or interrupted time series with a control group
III-3	Comparative studies with historical control, 2 or more single-arm studies, or interrupted time series without a parallel control group
IV	Case series, either post-test or pre-test/ post-test outcomes

Abbreviation: RCTs = randomised controlled trials.

and recurrence-free survival. Our findings aligned with findings from previous literature all point to the importance of the number of tumours on patient survival.[19-23] To explain this finding, we speculate that in patients presenting with multiple nodules, the tumours may be more aggressive in nature or represent early intrahepatic dissemination.[24]

Our study showed no other significant prognostic factor. The limited sample size may account for the statistical insignificance with AFP level, which was shown to be a significant prognostic factor in other studies.[19-22] We arbitrarily categorised the APF levels into 2 groups using a cut-off value of 200 ng/ml, as this is conventionally used during diagnosis and management of HCC.[12]

One of the limitations of our study was the diversity of our patients. We included 10 patients who had previous hepatic surgery for HCC with complete tumour resection margin. They may represent a separate group with different prognostic profile, though this factor was not significant in both the univariate and multivariate analyses. We also included this factor in a multivariate analysis to adjust for possible confounding effect.

The level of evidence was graded according to the Hierarchy of Evidence developed by the National Health and Medical Research Council of Australia (Table 2). Currently, there is level III-3 and IV clinical evidence showing that RFA is an effective and safe treatment modality for intrahepatic recurrent HCC after hepatectomy.[18] For tumours of less than or equal to 3 cm, level II and III-2 clinical evidence showed that survival rates after RFA were comparable to surgical resection. There was uncertain evidence for tumour sizes of 3.1 to 5 cm and no evidence for resectable HCCs sized 5 cm or above.[12,18] Therefore, the conventional criterion of the presence of 3 hepatic nodules of less than 3 cm is not an absolute definitive criterion. A more recent study stratifying different prognostic factors showed that the hazard ratio of death increased continuously with the size and number of tumour nodules and no apparent threshold was observed.[21] With this perspective, the application of RFA to tumours above 3 cm with more than 3 tumour

nodules on presentation is feasible on the basis of patient survival.

CONCLUSION

Tumour multiplicity is found to be a significant pre-procedure prognostic factor in predicting the survival of patients after RFA of HCC. With the benefit that RFA is a safe and well-tolerated procedure with a low mortality rate of 0 to 1.2% and a complication rate of 3 to 7%,[25-28] further evaluation on patient survival and the efficacy of this technique outside the conventional criteria for HCC is needed to provide more robust evidence, expanding its use and guiding our decision in treatment option offering to our HCC patients.

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