Survival and Recurrences After Hepatic Resection or Radiofrequency for Hepatocellular Carcinoma in Cirrhotic Patients: A Multivariate Analysis

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Hepatic resection is still considered the treatment of choice for hepatocellular carcinoma in patients with liver cirrhosis. Radiofrequency ablation is a new emerging modality. The aim of this study was to compare two homogeneous groups of patients who underwent either surgical resection or laparoscopic radiofrequency, analyzing the factors predicting survival and intrahepatic recurrences with use of a multivariate analysis. From February 1997 to April 2003, 98 patients were enrolled in this prospective study. Inclusion criteria were a single nodule of less than 5 cm, Child A-B class of liver function, and no previous treatment: 40 patients were in the surgical group and 58 patients were in the radiofrequency group. The two groups were homogeneous as far as preoperative characteristics were concerned. Operative mortality was zero, and the rates of operative morbidity were similar. Actuarial survival at 4 years was not significantly different (61% after resection and 45% after radiofrequency). There was a significant higher incidence of intrahepatic recurrences after radiofrequency than after resection (53% versus 30%; $P = 0.018$). This was mainly due to local recurrences, whereas those appearing in other liver segments were similar in both groups. A multivariate analysis showed that the significant factors predictive of an intrahepatic recurrence were the level of α-fetoprotein, the etiology of cirrhosis, and the type of the treatment. On the other hand, multivariate analysis of the survival showed that only the level of α-fetoprotein was an independent predictor of survival. The results of our study showed a significant lower incidence of intrahepatic recurrences after resection compared with after radiofrequency. This seems not to significantly influence the overall survival, probably because of a prompt and effective treatment of the recurrences themselves. (J GASTROINTEST SURG 2005;9:62–68)

KEY WORDS: Hepatocellular carcinoma, hepatic cirrhosis, hepatic resection, hepatic tumor ablation, laparoscopic radiofrequency

Survival and intrahepatic recurrences represent the primary end points of the therapies performed for patients with hepatocellular carcinoma and liver cirrhosis. Surgical resection and interstitial therapies achieve a relatively high rate of complete response in properly selected candidates with liver cirrhosis and hepatocellular carcinoma (HCC).[1] However, postoperative recurrence rates after either liver surgery or interstitial therapies are high,[2] and there are no randomized clinical trials that compare these treatment options; the selection of a given approach should currently be individualized and based on analysis of prospective cohort studies.[2,3] The aim of our prospective study was to evaluate the efficacy (long-term survival and intrahepatic recurrences) of hepatic resection and radiofrequency under laparoscopy in two groups of patients with a single, small HCC on liver cirrhosis.

METHODS

From February 1997 until April 2003, 209 patients with HCC underwent an evaluation in our unit with

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the aim of a radical treatment. Patients included in this prospective analysis were selected on the basis of the following criteria: (1) single lesion, (2) tumor size less than 5 cm, (3) Child A-B class, (4) segmental or subsegmental resection (less than two segments) possible, and (5) no previous treatment of HCC.

Patients were assigned to either one or other of the two groups, surgical resection (SR) or laparoscopic radiofrequency (LRF), according to the chosen treatment.

The ultrasound scanner that was used was an Aloka SSD 1700 power color Doppler system (Aloka Co. Ltd., Tokyo, Japan). We used either an intraoperative or a laparoscopic probe with a multifrequency linear-array transducer. All examinations were performed by a surgeon trained in ultrasound techniques (R.S.). The development of laparoscopic ultrasound (LUS) scanning techniques of the liver was based on the standard intraoperative ultrasound examination performed during laparotomy.[4,5]

A 100-W, 500-KHz monopolar RITA generator (CC-1; Radionics, Burlington, MA) was used as the energy source. The technique of LRF was previously described.[6] Repeated needle placement into the lesion or the use of clustered electrodes (radiofrequency is applied simultaneously with three internally cooled electrodes spaced 5 mm apart) was performed when necessary.

The practical steps of the surgical technique used in this study are described here according to a standardized technique.[7] Briefly, after laparotomy has been carried out, an intraoperative ultrasound examination is performed, and the relative position of the main lesion and the vessels are determined. The porta hepatis is dissected; the lobe with the lesion is mobilized. Under ultrasound guidance, tattooing of the liver surface is obtained by injecting dye into the feeding portal branches of the nodule. An intermittent portal triad clamping is applied, with 15-minute clamping and 5-minute release periods. The liver parenchyma is dissected using a Kelly clamp (tissue fracture technique).

Sonography and dynamic computed tomography (CT) scanning was performed within 1 month after the treatment to assess the completeness of tumor destruction and cancer evolution. A *complete response* was defined as no enhancement or a thin peripheral rim of enhancement caused by an inflammatory response within 1 month of LRF. An *incomplete response* was defined as persistent nodular enhancement within 1 month of LRF. The post-treatment results were further evaluated by spiral CT after 3 months and then every 6 months thereafter. Recurrence was defined as *local* when a new lesion was found within 2 cm of the ablated nodule or resected area or *at distance* when the new nodule arose more than 2 cm from the original lesion.

Initial evaluation and subsequent follow-up data of both groups were collected in a dedicated database (FileMaker Pro; FileMaker Inc., Santa Clara, CA) for personal computer input (Macintosh G4; Apple Computer Inc., Cupertino, CA) and subsequent analysis (Statistica-Mac; Statsoft, Tulsa, OK). Cumulative actuarial curves were analyzed by the Kaplan-Meier method and were compared by use of the log-rank test. Comparison of means between and within groups was done by using the Mann-Whitney *U* test and the Wilcoxon matched pairs test. Data are expressed as mean ± SD. Comparison of proportions was done with the Fisher exact probability test. In all patients, a total of 19 preoperative and 10 intraoperative variables were recorded, and their influence on the survival and HCC recurrence in each treatment group was assessed by means of univariate analysis and either the logistic regression or the Cox's proportional hazards regression model.[8] The association of each parameter with the HCC recurrence rate was univariately estimated with the Spearman *R* test. The association of each parameter with the survival was univariately estimated by comparing actuarial curves (Kaplan-Meier product-limit method and log-rank test) after the categorization of the continuous variables in a multivariate setting.[9] Only those parameters showing a statistical value of $P < 0.1$ were included in the multivariate analysis. The results of the univariate analysis helped to substantially reduce the number of prognostic factors. For each parameter analyzed in the multivariate analysis, the regression coefficient (β), the t values (hazard ratio), and the 95% confidence intervals (CIs) are given.

RESULTS

Fifty-eight patients who underwent LRF and 40 who underwent SR were included in the analysis. The characteristics of both SR and LRF groups are shown in Table 1. No differences were found with regard to age, gender, or liver function (Child class). All the patients had cirrhosis. Impairment of some parameters of liver disease (prothrombin activity and AST) was more pronounced in LRF-treated cases. At the time of analysis (August 2003), no difference was evident with regard to the mean follow-up of patients submitted to SR (22.4 ± 16.7 months) or LRF (25.7 ± 17.5 months; $P = 0.346$).

The resection group included 37 segmentectomies or subsegmentectomies and 3 bisegmentectomies. The length of operation was significantly longer in the SR group (210 ± 43 minutes; median, 210 minutes; range, 150–406 minutes) than in the LRF