Comparable Survival in Patients With Unresectable Hepatocellular Carcinoma Treated by Radiofrequency Ablation or Transarterial Chemoembolization

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Hypothesis: The survival benefits of radiofrequency ablation (RFA) and transarterial chemoembolization (TACE) are similar for patients with unresectable hepatocellular carcinoma amenable to either treatment.

Design: Retrospective comparative study.

Setting: Tertiary care institution.

Patients: From February 22, 2001, to March 10, 2004, 91 patients with unresectable hepatocellular carcinoma (tumor diameter <5 cm and <4 tumor nodules) treated by either TACE or RFA were analyzed from a prospective database.

Main Outcome Measures: The treatment-related morbidity, mortality, overall survival, and time to disease progression.

Results: Forty patients received TACE and 51 patients received RFA during the study period. Demographic data were comparable in both groups of patients. The treatment-related morbidities of TACE and RFA were 10% and 28%, respectively ($P=.04$). There was no treatment-related mortality in either group. There was 1 patient (2%) with complete tumor remission in the TACE group, and the complete ablation rate in the RFA group was 96%. The time to disease progression was similar in both groups ($P=.95$). The overall survival rates at 1 and 2 years were 80% and 58%, respectively, in the TACE group and 82% and 72%, respectively, in the RFA group ($P=.21$).

Conclusions: The overall survival and time for disease progression were similar in both groups of patients. In terms of the survival result, the efficacies of RFA and TACE were comparable for patients with unresectable hepatocellular carcinoma.

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Hepatocellular carcinoma (HCC) is the leading cause of death among patients with hepatitis B, hepatitis C, and their related cirrhosis, and its incidence has increased over the past decade. This disease carries a poor prognosis if left untreated. Surgical resection and liver transplantation provide the only hope of cure. However, only 10% to 37% of the patients are suitable for surgery because of the limited hepatic functional reserve from the underlying chronic liver disease and shortage of liver grafts. Transarterial chemoembolization (TACE) has been used as a palliative treatment for patients with inoperable HCC and those with recurrence after resection. Two recent randomized trials showed that TACE improves survival of patients with unresectable HCC. A recent meta-analysis showed a significant survival benefit of treatment with TACE compared with conservative treatment. Among locoregional therapies that have been described for unresectable HCC, radiofrequency ablation (RFA) is the most recently developed modality. It is described as a safe, effective, and repeatable procedure with low morbidity (0%-12%) and mortality (0%-3%) rates. However, the lack of sufficient long-term follow-up data for the treatment is well recognized.

There are potential advantages and disadvantages associated with each treatment. To our knowledge, there has been no prospective randomized trial comparing the real impact of these 2 treatments. The aim of our retrospective study was to compare the 2 treatment modalities for the management of unresectable HCC in terms of treatment morbidity, mortality, and survival.

METHODS

PATIENT SELECTION

From a prospective database in which data were recorded for all of the patients with HCC managed at the Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong
Kong, patients with unresectable HCC who were treated by either TACE or RFA between February 22, 2001, and March 10, 2004, were retrospectively analyzed. The criteria for defining inoperability were significant comorbidities, bilobar diseases, tumor in close proximity to major vasculatures, poor liver functional reserve by measurement in the indocyanine green clearance test, and Child-Pugh status (class B or C precluding major resection). For this study, we included only patients with the tumor nodule smaller than 5 cm in the largest diameter and fewer than 4 nodules in total who were suitable for both therapies. Radiofrequency ablation is the preferred treatment of choice in most circumstances. However, for HCC requiring open RFA, TACE was recommended in patients who were at high risk for major surgery and general anesthesia. The exclusion criteria were the following: (1) major vascular invasion by the tumor and extrahepatic diseases; (2) having received combined treatment of hepatic resection or ethanol injection with RFA; (3) having undergone RFA for hemostasis of ruptured HCC during emergency laparotomy; (4) tumors unfavorable for RFA (eg, too close to hilar structures); or (5) severe arteriovenous shunting shown in angiography contraindicating TACE.

RADIOFREQUENCY ABLATION

In our center, we used the Cool-tip Radiofrequency System (Radionics, Burlington, Mass) to treat unresectable HCC. It was performed via the percutaneous, laparoscopic, or open approach depending on the site and size of the lesions. Experienced interventional radiologists (J.Y. and W.K.T.) performed percutaneous RFA under local anesthesia and intravenous sedation with ultrasonographic guidance. Laparoscopic and open RFA were performed by specialized liver surgeons (K.K.N., R.T.P.P., C.M.L., and S.T.F.). During the procedure, the electrode was introduced into the liver under ultrasonographic guidance. The radiofrequency generator produces a 200-W radiofrequency wave at 480 kHz that excites surrounding electrons to vibrate at a high frequency and thus generate heat energy. At a lethal temperature higher than 60°C, instantaneous protein coagulation occurs with irreversible damage of key intracellular enzymes, which contributes to coagulative necrosis of the target lesion. A single electrode was used for tumors smaller than 3 cm in diameter, and a clustered electrode was used for larger tumors. Further sessions of RFA were offered to patients with incomplete ablation or intrahepatic recurrence (≤4 tumor nodules). For patients with multifocal intrahepatic recurrence (>4 tumor nodules), TACE was offered as a salvage procedure. Nonetheless, patients were treated conservatively once they developed extrahepatic recurrence.

TRANSARTERIAL CHEMOEMBOLIZATION

Transarterial chemoembolization takes advantage of the relatively selective arterial vascularization of hepatic tumors. Chemotherapeutic agents are delivered with concomitant embolization to increase the local chemoatherapeutic dwell time and induce tumor ischemia. The technique of TACE in our center has been described in previous articles. Superselective cannulation of the artery supplying the tumor was performed whenever possible. An emulsion of cisplatin (1 mg/mL) and lipiodol (Lipiodol UltraFluide; Laboratoire Guerbet, Aulnay-Sous-Bois, France) at a volume ratio of 1:1 was injected up to a maximum of 60 mL depending on the size and the number of tumors. Embolization was performed with 1-mm³ particles of gelatin sponge (Spongostan; Johnson and Johnson Ltd, Skipton, England) mixed with 40 mg of gentamicin sulfate. Transarterial chemoembolization was repeated every 8 to 12 weeks. The treatment was stopped when there was progressive disease, development of extrahepatic diseases, severe life-threatening complications, or evidence of liver failure (serum bilirubin level >50 µmol/L, gross ascites uncontrollable with diuretics, or hepatic encephalopathy).

OUTCOME MEASURES

The treatment response, treatment-related morbidity and mortality, overall survival, and time to disease progression were the outcome measures. Time to disease progression was calculated from the date of disease response to treatment to the date of disease progression.

The efficacy of both treatment modalities was evaluated by using contrast computed tomography every 3 months after each intervention. Patients were followed up regularly in our outpatient clinic, and serum α-fetoprotein concentrations were monitored. The tumor response was mainly assessed by serial imaging studies using contrast computed tomography. Any arterial contrast enhancement was noted to determine the viability of the tumor. In the TACE group, the definition of tumor response was categorized according to the World Health Organization criteria: (1) complete response, disappearance of all viable lesions detected by imaging; (2) partial response, decrease of 50% or more in tumor size; (3) static disease, decrease of 50% or less in tumor size or increase of less than 25% in size; and (4) progressive disease, increase of 25% or more in tumor size or appearance of new lesions. Patients’ demographics, laboratory data, tumor characteristics, time to disease progression, and survival were compared.

STATISTICAL ANALYSIS

Normally distributed data were expressed as mean ± SD and other continuous data were expressed as median. Continuous variables were compared by the Mann-Whitney U test. Categorical variables were compared using the χ² test or Fisher exact test if appropriate. Overall survivals were analyzed by Kaplan-Meier survival curves, and comparisons were made by the log-rank test and Cox proportional hazards model. All of the reported P values were 2-tailed, and P<.05 was considered statistically significant. All of the analyses were performed using SPSS statistical software package version 11.0 (SPSS, Inc, Chicago, Ill).

A total of 91 patients treated by RFA or TACE between February 22, 2001, and March 10, 2004, were included for analysis. Patients’ characteristics are shown in Table 1. Patients’ demographic data and tumor characteristics in the 2 groups were comparable. There was a significantly higher complication rate in patients treated with RFA. The overall complication rates of TACE and RFA were 10% and 28%, respectively (P=.04) (Table 1). Skin burn from the grounding pad (1 patient [2%]), hemoglobinuria (4 patients [7.8%]), and portal vein thrombosis (1 patient [2%]) were the specific complications in the RFA group whereas liver failure, defined as an elevated total bilirubin level higher than 50 µmol/L, development of refractory ascites, or hepatic encephalopathy, was more common in patients treated with TACE (2 patients [4%]) (Table 2). There was no treatment-related death in either group. Among the 4 patients with hemoglobinuria after RFA, 1 patient developed chronic renal failure and was treated conservatively without the need
for renal replacement therapy. The reason for this complication was believed to be related to hemolysis within major blood vessels close to the RFA site. From our experience, this complication could be managed by vigilant perioperative fluid replacement and close monitoring of renal function. In the RFA group, 27 patients (53%) were treated by the open approach, 1 patient (2%) was treated by the laparoscopic approach, and the remaining 23 patients (45%) were treated via the percutaneous route under ultrasonographic guidance.

The changes in median $\alpha$-fetoprotein concentration in the TACE and RFA groups are shown in Figure 1. There was 1 complete remission (2%), 4 partial responses (10%), and 35 disease progressions (88%) in the TACE group. The complete local ablation rate was 96% (n = 49) after a single session of RFA ablation. During follow-up (median, 19 months), the local recurrence rate was 14% (n = 7), and 36 patients (71%) had disease progression in the RFA group. Twenty-two patients developed intrahepatic-only recurrence and 14 patients had both intrahepatic and extrahepatic recurrence. Among patients with intrahepatic-only recurrence, 15 patients received further RFA and 7 patients had TACE offered to them. The median time to disease progression was 9.5 months (range, 1.0-47.3 months) in patients treated with TACE and 10.4 months (range, 1.0-42.7 months) in patients treated with RFA ($P = .95$). The immediate tumor control rate was better for patients treated with RFA when compared with those treated with TACE (Table 3).

The follow-up duration was similar between the TACE and RFA groups (median, 23 and 19 months, respectively). The 1- and 2-year overall survival rates in patients treated with TACE were 80% and 58%, respectively, whereas those for patients treated with RFA were 82% and 72%, respectively ($P = .21$) (Figure 2). By the Cox proportional hazards model, there was no significant difference in overall survival between the TACE and RFA groups ($P = .20$). Seventeen and 12 patients died in the TACE and RFA groups, respectively, during the study period, and the causes of death are listed in Table 4. The median number of sessions for TACE was 6 sessions (range, 2-11 sessions) whereas the median number of sessions for RFA was only 1 session (range, 1-3 sessions).

The management of HCC has been evolving in the past decade. Liver resection and liver transplantation remain the standard treatment of choice for potential cure. Un-
of RFA on HCC focused on small HCC and hence the results were more favorable. Irrespective of this possible bias, many centers now choose RFA as a preferred treatment for small unresectable HCC, although there have been no concrete data to our knowledge showing that RFA is superior to TACE in terms of safety and long-term survival benefit. Like other centers, we gradually shifted the pendulum by using more RFA to treat unresectable small HCC after ascertaining its safety and efficacy from our initial experience. However, the long-term survival effect of RFA remains uncertain because of paucity of long-term follow-up data in the literature. Furthermore, to our knowledge, RFA has not yet been assessed in comparison with other treatment modalities in prospective randomized trials. The exact roles of local ablative therapies and TACE still need to be investigated. It may not be justified to conclude that RFA is superior to TACE without any prospective randomized studies in a group of patients with similar tumor characteristics and liver function. Indeed, there are articles showing that TACE might be as effective as hepatic resection in certain patients.

In this study, we compared groups of patients with small tumors amenable to both TACE and RFA who received either TACE or RFA for treatment of unresectable HCC. To our knowledge, this is the first study directly comparing the 2 treatments. Although this was a retrospective analysis, our study provided some clues about the impact of these 2 treatment modalities. The 2 groups were comparable, as there were no significant differences in patients’ demographic data and tumor characteristics. The complication rates were unexpectedly higher in patients treated with RFA when compared with published data, and most of the complications were treatment specific (eg, skin burn from the grounding pad). The relatively high complication rate in this study compared with the complication rates in other studies may be in part related to prospective documentation of complications and the high proportion of open RFA in this study. No complications resulted in mortality. One patient who received open RFA developed portal vein thrombosis and subsequently died from multifocal intrahepatic recurrences 3 months after the initial RFA. The complication rate of TACE, which was also prospectively documented, was lower than that of RFA in this study.
It can be difficult to assess the efficacy of local control on TACE for treatment of HCC because multiple factors have been cited as measures of success in different studies. These factors include patient survival, imaging response, biological response (ie, decrease in α-fetoprotein levels), quality of life, and symptomatic improvement. Given the relatively short life expectancy of patients with unresectable HCC, the most relevant factor would be patient survival.\(^\text{35}\)

The complete ablation rate of RFA for HCC approaches 100% in many series.\(^\text{12-17}\) However, local recurrence at the RFA treatment site is not infrequent, ranging from 6% to 39%.\(^\text{36}\) The complete local ablation rate and the local recurrence rate (96% and 14%, respectively) in our study were comparable with rates reported by other centers worldwide. Immediate tumor control of RFA was superior to that of TACE. However, many patients from the RFA group developed HCC in other parts of the liver within 1 year of initial treatment. Similarly, many patients from the TACE group developed multiple intrahepatic recurrences within 1 year after the procedure.

Short-term adverse effects of TACE included postembolization syndrome (fever, abdominal pain, and nausea), liver abscess formation, peptic ulcer disease, pancreatitis, liver failure, and ruptured HCC. Long-term adverse effects of TACE included progressive hepatic artery thrombosis, making future attempts of TACE not possible.\(^\text{37}\) Short-term adverse effects of RFA were more or less similar to those of TACE, but there were a number of specific complications such as grounding pad burns and hemoglobinuria. Long-term adverse effects of RFA included needle-track seeding of the tumor and delayed bile duct injury.\(^\text{36}\) More patients in the RFA group than in the TACE group experienced liver failure. One postulation was that we adopted a more open approach that might further jeopardize the already-compromised liver function.

The overall survival for patients with unresectable HCC treated with either TACE or RFA was similar. Although the claimed good local control of RFA was well documented in other studies\(^\text{12-17}\) as well as in this study, the time to tumor progression was similar in both groups of patients. This actually reflects the natural history and biology of the disease, which were not altered by local ablative therapies. In terms of patient survival, which was the most important outcome measure in cancer treatment, RFA was not superior to TACE for unresectable HCC. In the era of evidence-based medicine, there is an urgent need for a randomized controlled trial to document the real impact of TACE and RFA on unresectable HCC. Many centers are increasingly performing RFA rather than TACE as before. Our study highlights the need for randomized controlled trials to compare the 2 treatment modalities rather than simply considering RFA the preferred treatment based on perceived benefits. This study has potential drawbacks because of its retrospective nature. The power of our study was limited and the type II error may be significantly high. Nonetheless, it may serve as a reference to compare TACE and RFA in the future.

In conclusion, this study showed that although RFA appeared to offer better initial local tumor control when compared with TACE, the overall survival and time to disease progression were similar in patients with unresectable HCC treated with either TACE or RFA.

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REFERENCES


