

## LENTESYMPIOSIUM VVGE – Mechelen 20 april 2002

### Hepatocellulair carcinoma : ' To fry or to freeze ? '

B. Topal (Department of Abdominal Surgery, University Hospital Gasthuisberg, Leuven – Belgium)

#### Introduction

The treatment of hepatocellular carcinoma (HCC) is quite challenging and requires a multidisciplinary approach. At least 50 % - 60 % of all HCC patients have associated liver cirrhosis. The presence of liver cirrhosis presents a major challenge to the treatment of HCC, and one has to take into consideration the residual functioning liver reserve, associated coagulopathy, neutropenia, portal hypertension, ascites, hyperbilirubinemia, portal vein occlusion, and encephalopathy. Several treatment modalities for HCC are available as listed in table 1.

surgery	resection / transplantation
interstitial therapies	alcohol injection
	cryoablation
	hyperthermia
	radiofrequency
	microwaves
	laser (Nd-Yag)
	high-intensity focused ultrasound (HIFU)
trans-arterial (chemo-) embolization	
hepatic artery infusion (HAI) chemotherapy	
radiotherapy	
systemic chemotherapy : response rate 10-20 % ; no impact on survival	
biologic agents : experimental / trials	

Nevertheless, large-scale randomized clinical studies are necessary to determine the overall effectiveness of these therapies in comparison with each other and with conventional treatment techniques. The optimal treatment for HCC is surgical resection, offering a 5-year survival rate of 32 %. However, only a small percentage of patients are operative candidates. The prognosis for patients with unresectable HCC is poor. In patients with small HCC lesions who received no treatment, a mean 3-year survival rate of 12 % has been reported [Gastroenterology 1986;90:289-98]. Another retrospective analysis in patients with small (< 5 cm) HCC in Child A or B cirrhosis, showed the longest survival obtained with transplantation and surgery, and the worst with best supportive care. Costs per year of life saved were highest for transplantation and lowest for ethanol injection, with surgery being less expensive than chemo-embolization. This study confirms that patients with single, small HCC nodules in well-compensated cirrhosis should be treated [Eur J Gastroenterol Hepatol 2001;13:1217-24].

#### Percutaneous ethanol injection (PEI)

Studies on PEI in Japan and in Italy demonstrated the possibility to achieve complete alcohol-induced necrosis of small HCC lesions (3 cm or less in diameter) [Radiology 1988;168:313-317. AJR 1990;155:1221-1226]. Patients treated with PEI showed long-term survival rates comparable with those of patients submitted to surgical resection [Cancer 1992;68:926-929. AJR 1993;160:1023-28]. The greatest drawback of PEI is presented by the difficulty to treat HCC's larger than 3 cm. In these cases, alcohol diffusion is incomplete and residual viable neoplastic tissue can be found after PEI, particularly along the periphery of the tumor or in portions isolated by septa [Cancer 1991;68:1524-30].

#### Trans-arterial embolization (TAE)

Despite objective responses obtained after TAE in approximately one-half of the patients, randomized studies comparing TAE to chemotherapy or to supportive care have been unable to document an improvement in survival [Gastroenterology 1988;109:917 . J Hepatol 1990;11:181 . N Engl J Med 1995;332:1256 . Hepatology 1998;27:1578].

The risk of complication following TAE is clearly related to the degree of hepatic dysfunction. Treatment-related mortality is as high as 30 % in patients with Child-Pugh grade C [Ann Surg 1993;218:145]. Therefore, embolization generally is performed only for patients with Child-Pugh grade A or B. In addition, patients with portal vein occlusion tolerate arterial interruption very poorly, and presence of tumor thrombus in the main portal vein is considered a relative contraindication to embolization.

### **Transcatheter arterial chemo-embolization (TACE)**

TACE, most frequently performed by intra-arterially injecting an infusion of anti-neoplastic agents mixed with iodized oil (Lipiodol ®) , has been extensively used in the treatment of large HCC's [Radiology 1989;170:783-786]. However, although massive tumor necrosis can be demonstrated in most cases, a complete necrosis of the tumor has rarely been achieved with TACE, since residual tumor can be found in a non-negligible number of the treated lesions [Cancer 1991;67:81-86]. Indeed, although TACE results in objective response rates in a substantial proportion of the patients, randomized trials have failed to show any clear benefit of trans-arterial chemo-embolization with or without lipiodol administration over no treatment [Aliment Pharmacol Ther 1998;12:111].

### **Cryosurgery**

Although cryoablation of hepatic malignancies is safe in experienced hands, it is associated with a complication rate in up to 29 % of the patients. Moreover, mortality rates up to 8 % are described [JR Coll Surg Edinb 1998;43:141-54]. Not only is freezing of tumors near major vascular structures difficult because of the risks of bleeding, but complete freezing is virtually impossible because warm blood circulates in the vessels. Adequate survival data are lacking, and contain small patient series with short follow-up.

### **Radiofrequency ablation (RFA)**

The concept of the use of heat – hyperthermia – to kill tumors was described as early as 1700 B.C. Nowadays, three primary methods are used to produce localized hyperthermia : radiofrequency, microwave, and laser. These three techniques were introduced by Beer in 1910, Denier in 1936, and McGuff et al in 1963, respectively. However, it was in the last few years that the available technology was significantly improved to allow increased success in the use of these techniques for the treatment of hepatic tumors.

#### ***RFA : Mechanism and equipment***

The generators used in RFA are alternating electric current generators that operate in the radiofrequency range (200 – 1200 kHz). It is the alternating current, not the emitted radiofrequency waves, that causes thermal injury. There are three RFA devices currently in clinical use, and are manufactured by different companies, i.e. Radionics, RITA Medical Systems, and Surgical Company. Schematically, a closed-loop circuit is created by placing a generator, a needle electrode, a patient, and a large dispersive electrode (ground pad) in series. The objective of RFA is to desiccate the tissue by evaporating the intracellular water and thus produce localized coagulative necrosis. Both the needle and dispersive electrodes are active electrodes, whereas the patient acts as a resistor. The alternating electric field created in the tissue between the electrodes causes ionic agitation resulting in heat. The generated heat remains focused around the needle electrode due to the marked discrepancy between the surface areas of the needle electrode and the dispersive electrode. The ionic agitation and resultant heat are proportional to the intensity and duration of the alternating current. The heat is rapidly dissipated with increasing distance from the needle electrode.

#### ***RFA : Technique and indications***

Although the RFA procedure can be performed either via laparotomy or percutaneously, there is little information on its optimal approach. There are few data focusing on laparoscopic approach in the treatment of patients with unresectable hepatic malignancies. Besides detection of unsuspected intra-abdominal metastases with or without laparoscopic ultrasound, laparoscopic approach may have other potential benefits, such as direct visual control of the RFA procedure, exposure and isolation of the liver from surrounding tissues, ability to perform a Pringle-maneuver, handling of intra-operative bleeding following biopsy or other complications, ablation of several lesions during one operation, possibility of repeat laparoscopic RFA with low morbidity, minimal surgical trauma and post-operative pain, fast recovery time and shorter hospital stay. In Child grade B patients with unresectable HCC laparoscopic, ultrasound identified tumor not detected pre-operatively in 8,3 % of the patients [Am Surg 2001;67:1181-4]. Under ultrasonography guidance, a needle electrode is introduced into a selected portion of the tumor. The goal of the procedure is to ablate the tumor and a 5- to 10-mm margin of microscopically normal tissue around the tumor. Ultrasonography is used primarily as a guidance technique, but it is not useful for determining if the tumor has been completely ablated. Percutaneous RFA should be reserved for patients at high risk for anesthesia, those with recurrent or progressive lesions, and those with smaller lesions sufficiently isolated from adjacent organs. Complications can be minimized when these approaches are applied selectively. Ideal candidates for RFA are patients with unresectable hepatic tumors less than 5 cm in diameter. Surgical resection may be contraindicated for a variety of reasons, including poor clinical condition of the patient, marginal hepatic function, tumor localization, extra-hepatic metastases, patient refusal of surgery, and life expectancy of less than 6 months. Other indications for RFA are cirrhosis and HCC in patients who are waiting for hepatic transplantation. RFA can be performed in combination with surgical resection. It can also be applied after chemo-embolization for hepatic malignancies, in particular for tumors larger than 5 cm in diameter.

#### ***RFA : Outcome***

RFA is a safe and effective treatment modality to achieve tumor destruction in patients with unresectable hepatic malignancies [Radiology 1997;202:195-203 . Eur Radiol 1998;8:1205-11 . Ann Surg 1999;230:1-8]. In patients with unresectable HCC, RFA provides a 5-year survival rate of 40% [AM J Roentgenol 1996;167:759-68]. Local recurrence rate at the RFA site is 3,6 % ; while new liver tumors or extra-hepatic metastases develop in 45,5 % of patients with HCC in cirrhosis [Ann Surg 2000;232:381-91].

In patients with solitary small HCC (< 3 cm in diameter) RFA requires an average of 1,5 sessions to achieve complete necrosis, whereas PEI requires an average of 4,0 sessions [Jpn J Clin Oncol 2001;31:322-6]. RFA also requires fewer treatment sessions and a shorter hospital stay than percutaneous microwave coagulation therapy (MCT) to achieve complete necrosis [Oncology 2002;62 Suppl 1:64-8].

In a prospective analysis of 99 RFA operations to ablate 328 unresectable tumors in 76 patients, the mortality rate was 1 %, while major complications occurred in 7 %, and minor complications in 10 %. Local recurrence was identified in 9 % at a mean follow-up of 15 months. Tumor size, vascular invasion, and total volume ablated were associated with recurrence ( $p < 0.001$ ), but the number of tumors was not ( $p = 0,39$ ) [Arch Surg 2001;136:864-9]. In 92 patients with HCCs < 3 cm in diameter treated by MCT or RFA, distant recurrences were observed in 22 patients (24 %). A multivariate stepwise Cox hazard model revealed that patients who had more than two HCC nodules accompanied by HCV infection had a high incidence of recurrence of HCC in the remnant liver, even when coagulation by microwave or ablation by radiofrequency was complete [Cancer 2001;91:949-56]. In another prospective analysis 110 patients with cirrhosis and HCC (Child class A, 50; B, 31; C, 29) were treated using RFA. A total of 149 HCCs were treated with RFA. Median follow-up time was 19 months. Local recurrence at the RFA site developed in four patients (3,6 %), whereas new liver tumors or extra-hepatic metastases developed in 50 patients (45,5 %). There were no treatment-related deaths, but complications developed in 14 patients (12,7 %) [Ann Surg 2000;232:381-91].

#### ***RFA : KULAS experience***

A brief description will be given about the experience with RFA at the department of abdominal surgery in K.U.Leuven. The paper will be presented focusing on the feasibility and efficacy of laparoscopic RFA for unresectable liver malignancies. Twenty-three patients with unresectable hepatic

malignancies were entered into a prospective, non-randomized trial. RFA was performed percutaneously in 5 patients (HCC 3, colorectal metastasis 1, and cholangiocarcinoma 1), via laparotomy in 9 (28 tumors ; median diameter 38 mm, range 5 – 90 mm), and via laparoscopy in 9 (16 tumors ; median diameter 35 mm, range 8 – 58 mm). Patients treated with laparoscopic RFA were compared with those treated via laparotomy. Mortality and intra-operative complication rate was 0. Mean blood loss and hospital stay were 13 ml. vs. 421 ml., and 5,7 vs. 11,2 days in the laparoscopy vs. laparotomy group ( $p=0.0008$  and  $p=0.04$ ), respectively. After a median follow-up of 10,3 months, local recurrence occurred in 1 patient, while new metastases developed in 5.

## **Conclusion**

The treatment of hepatocellular carcinoma requires a multidisciplinary approach. The optimal treatment for HCC is surgical resection. However, only a small percentage of patients are operative candidates. The prognosis for patients with unresectable HCC is poor, indicating that these patients need other therapeutic approaches. Several treatment modalities for HCC are available although large-scale randomized clinical studies are necessary to determine the overall effectiveness of these therapies in comparison with each other and with conventional treatment techniques. RFA is a safe and effective treatment modality to achieve tumor destruction in selected patients with HCC. Laparoscopic approach is preferable, although patients with tumors larger than 4 cm in diameter or in close contact to the hepatic veins or inferior vena cava, and with 5 or more tumors should be considered for RFA via laparotomy.