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Percutaneous and surgical radiofrequency ablation of liver malignancies : a single institutional experience

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Abstract

Background : **the purpose of this study was to report a single academic institution's experience with radiofrequency ablation (RFA) of liver malignancies**

Methods : **Sixty-five patients underwent RFA technique through a percutaneous (Group I : 33 patients) or a surgical approach (Group II : 32 patients). The two groups were different according to type of disease selection (more hepatocellular carcinoma in Group I and liver metastases in Group II) and tumour features (smaller size but greater number of lesions in Group II). In Group II, RFA was associated to liver resection in 23 patients (72%).**

Results : **The 2-month postoperative mortality and complication rates were low in both groups. The postoperative hospital stay was longer in Group II. During a median follow-up of 24 months in Group I and 21 months in Group II, the local "in-situ" recurrence rate was 41.4% and 9.1%, respectively. For RFA-treated tumours < 30 mm in size, the local "in-situ" recurrence rate was 40.5% in Group I and 0% in Group II. Multivariate statistical analysis demonstrated that larger tumour and a percutaneous approach for RFA were independent predictive factors of local "in-situ" liver tumour recurrence.**

Conclusions : **RFA appears to be a safe technique for treating liver malignancies by both approaches. Tumour size and type of RFA approach are predictive factors of in-situ liver tumour recurrence.** (Acta gastroenterol. belg., **2007**, 70, **167-173**).

Key words : liver, tumour, malignancy, local ablation, morbidity, survival.

Introduction

Local tumour ablative techniques have been recently reported as being attractive for treating primary and secondary liver malignancies, by using ethanol injection, cryosurgery, interstitial laser photocoagulation, microwave tumour coagulation or more recently radiofrequency ablation (RFA). The use of RFA for treating liver malignancies was first suggested by ROSSI in 1993 (1). Since that time, significant clinical experience has been reported, either with hepatocellular carcinoma (HCC) (2-5) or liver metastases (LM) (6,7). Different approaches for RFA are used, including the percutaneous approach by interventional radiologists or the surgical approach by laparoscopic or open surgery. It is still uncertain which of these approaches affords the best results for patients, while each approach has its own limitations. The purpose of this study is to evaluate a single institution's experience with the RFA technique and to report the differences in treatment conditions when the technique is used by interventional radiologists or surgeons.

Material and methods

Patients

From December 1999 to December 2003, 65 consecutive patients underwent a RFA procedure for liver malignancies, 33 through a percutaneous approach (Group I) and 32 through laparotomy (Group II). During the study period, liver resection was performed in 140 other patients suffering from hepatobiliary malignancies. The decision to choose the ablative approach was based on the patient's performance status and the size, location, number and type of hepatic tumour. Patients suffering from hepatocellular carcinoma (HCC) on liver cirrhosis were considered at high-risk for surgical approach and were preferably selected for a percutaneous approach. Patients were classified according to the ASA (American Society of Anaesthesiology) score[8]. In the whole series, there were 26 patients suffering from HCC, 23 of whom had developed it from liver cirrhosis (from alcoholic origin in 5 patients and from hepatitis B and C viral infection in 3 and 15 patients, respectively), 29 patients suffering from colorectal liver metastases (CRLM) and 10 patients suffering from other type of LM (neuroendocrine : 4 and breast, thymoma, ovary, pancreatic adenocarcinoma, leiomyosarcoma and renal cancer in one patient each).

Demographic and clinical patient data and type of indications in both groups are detailed in Table 1. According to a different selection of patients, HCC was more frequently encountered in Group I while CRLM were more frequent in Group II. The longer delay between diagnosis and RFA treatment in Group II was related to previous chemotherapy treatment in patients suffering from liver secondaries.

All patients had undergone extensive preprocedural evaluation, including ultrasonography (US) (78%), computed tomography (CT) (66%), magnetic resonance

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Table 1. — **Demographic and clinical patient data, indications for treating liver malignancies by radiofrequency ablation (RFA) for**

	Group I (percutaneous)	Group II (surgical)
PATIENTS		
Number of patients	33	32
Sex ratio male / female	22 / 11	22 / 10
median age (years) (range)	67.0 (37-81)	65.5 (38-76)
ASA III physical status	13 (39%)	9 (28%)
median delay (months) between diagnosis and RFA (range)*	1 (0-9)	4 (0-35)
indications for RFA* • Hepatocellular carcinoma • Colorectal (CR) metastases • Non CR metastases	22 (67%) 6 (18%) 5 (15%)	4 (12%) 23 (72%) 5 (16%)

* : $p < 0.05$.

imaging (MRI) (97%) and FDG-positron emission tomography (PET) (83% in the group of patients suffering from liver secondaries). All tumours were localized within the liver parenchyma according to the segmental classification of COUINAUD (9).

Previous tumour treatment frequently included attempted alcohol ablation for HCC patients in Group I and chemotherapy for liver metastases in Group II. Four patients in Group I (12%) and 6 in Group II (19%) underwent previous liver resections (minor and major hepatectomies in 4 and 6 patients, respectively). A total number of 153 liver tumours were detected pre- and per-operatively in the entire series of 65 patients (Group I : 54 tumours, Group II : 99 tumours). Twenty-six patients harboured multiple tumours (median number of tumour per patient : 2, range : 2-14). Features of tumours treated by RFA in both groups are detailed in Table 2. In Group II, there were significantly more multiple but smaller tumours. Six patients in Group I (14%) harboured tumours exceeding 30 mm in size.

Operative procedures

The percutaneous procedure was performed in the radiology suite exclusively under real-time transcutaneous ultrasonography guidance, under local anaesthesia and conscious sedation with Propofol and Ketalar. Continuous blood pressure, cardiac and pulse oximetry monitoring was routinely employed. The surgical procedure was performed with patients under general anaesthesia and with intraoperative ultrasound guidance through a bilateral subcostal incision, after complete exposition of the liver. Three different surgical approaches were used for RFA technique : RFA alone (for single or multiple lesions), a combination of RFA and liver resection for multiple and bilobar lesions or RFA-assisted liver resections. The concept of RFA-assisted liver resection is based on multiple applications of RFA at the deepest site of the tumour in order to extent the final in-situ surgical margin. In Group II, indications for selecting RFA alone included multiple bilobar lesions in 8 patients, combination with liver resections for bilobar lesions in 8 patients, repeat hepatectomy in 6 patients and unresectable lesions by major hepatectomy in 11 patients (high-risk, elderly patients or insufficient remaining liver or chronic liver disease). Major hepatectomy was defined as a resection of at least 3 liver segments.

The same RFA equipment was used in both groups, comprising a RF 3000 generator system (RadioTherapeutics Corporation, Sunnyvale, CA, USA) with a 15-gauge, 12- to 15-cm-long, insulated Le Veen monopolar array needle and containing 10 individual hook-shaped electrode arms. After ultrasound-guided placement within the tumour, the Le Veen electrode is deployed in-situ like an umbrella. A 2 cm, 3.5 cm or 4 cm needle electrode was used depending on the tumour size. The RF energy is then applied following an established treatment algorithm (5). For tumours larger than 3 cm in Group II, multiple placements and deployments of the electrode array in different directions may be necessary for complete destruction of the tumour. In both groups of patients, the technique attempted to obtain complete destruction of tumour but in Group II, an attempt was also made to ablate at least a 1-cm zone of surrounding normal liver parenchyma around the tumour (to obtain the equivalent of 1-cm free surgical margin). A radical RFA procedure was defined as complete tumour necrosis at 3 months' radiological control for the RFA procedure alone and as complete surgical tumour resection with a macroscopic and microscopic tumour-free margin for associated liver resections or RFA-assisted liver resections.

End-points

Postoperative (in-hospital or within 60 days of surgery) death, complications, reoperations and post-

Table 2. — **Liver tumour features in patients treated by percutaneous (Group I) and surgical (Group II) radiofrequency ablation (RFA)**

	Group I (percutaneous)	Group II (surgical)
TUMOUR		
Total number of tumours treated by RFA	43	38
Number of patients with liver tumour treated by RFA*		
• single liver tumour	31	22
• multiple liver tumour	2	10
median size (mm) of tumours treated by RFA (range)*	18 (10-50)	13 (5-40)
Size distribution of tumours treated by RFA alone		
• < 30 mm	37	37
• 31-40 mm	4	1
• > 40 mm	2	0
Intrahepatic tumour location according to COUINAUD		
• segments I	0	1
• segments II to VI	28	17
• segments VII or VIII	15	20
previous tumour treatment		
• alcohol ablation	4	0
• arterial chemoembolization	2	4
• chemotherapy*	6	18
• portal vein embolization	1	3
• liver resection	4 (12%)	6 (19%)

* : $p < 0.05$.

operative hospital stay were recorded. The postoperative complications were categorized according to the CLAVIEN classification (10). Perioperative antibiotic prophylaxis was routinely administered. A routine contrast-enhanced CT scan was performed one week after the procedure to assess local complications. Completeness of the ablative procedure was assessed at an interval of 3-4 months after the procedure by contrast-enhanced CT or MRI and always correlated to PET in case of liver metastases. At this time, inflammatory reaction around the necrotic zone has usually subsided. Persistence of contrast-enhanced tissues on CT or MRI scans correlated to hypermetabolic areas on PET scans at the site of the initial tumour was considered as suggestive of "in-situ" local recurrence. Final diagnosis of recurrence was confirmed by long-term disease progression. Follow-up of all patients included contrast-enhanced helical CT scanning or MRI of the liver every 6 months postoperatively, assessing the patient for disease recurrence and in-situ recurrence. The median duration of follow-up was 24 months (range : 6-45 months) in Group I and 21 months (range : 3-50 months) in Group II.

Statistics

Statistical tests were performed using Statistical Packages for Social Sciences (SPSS) (software version 11.0, SPSS Inc, Chicago, Il). Patient survival and disease-free survival curves were estimated using the Kaplan-Meier product limit method, and compared between groups using the log rank sum test. Numerical variables were expressed as median and range, and compared using the Mann-Whitney U test. Multivariate analysis was performed using logistic regression by maximum likelihood to assess the potential impact of several variables on in-situ liver recurrence.

Results

Operative procedures

Details of the operative procedures are given in Table 3. In Groups I and II, 33 and 32 patients underwent 41 and 33 procedures (including 8 and one repeat procedures), respectively. Despite attempts in all patients, 10 tumours in Group I and 2 tumours in Group II were finally not treated. Reasons for non treatment included in Group I the absence of detection during exclusive US-guidance or proximity to major vessels in 9 and one tumour, respectively, and in Group II, the absence of detection in a severely steatosic liver and proximity to major biliary trunk in one tumour each. In Group I, RFA technique was associated to alcohol ablation in one patient. In Group II, 8 patients underwent RFA alone (treating a total of 38 tumours) and 23 patients (72%) underwent combined liver resection (20 minor and 6 major liver resections treating

Table 3. — **Operative data of patients suffering from liver malignancies having undergone radiofrequency ablation (RFA) techniques**

	Group I (percutaneous)	Group II (surgical)
Patients (procedures)	33 / 41	32 / 33
Total number of tumours treated • by RFA alone : • by liver resection • by alcohol ablation • not treated	 43 0 1 10	 38 55 (14 RFA assisted) 4 2
median number of applications per tumour (range)*	2 (2-8)	4 (1-8)
Associated procedures per patient • Pringle manoeuvre • selective HV control • minor hepatectomy • major hepatectomy • RFA-assisted hepatectomy	 0 0 0 0 0	 0 2 10 6 10 (31%) (14 tumours)
* Radical RFA treatment per procedure	31/41 (75.6%)	28/33 (84.8%)
* Operative time for RFA procedure (minutes) (range) *	19 (6-51)	42 (6-240)
* Peroperative complications	1 (2.4%)	1 (3%)

* : $p < 0.05$.

55 tumours), including RFA-assisted liver resection in 5 patients (treating 14 tumours).

The number of RFA applications per tumour and the duration of RFA procedures were higher in Group II. Portal triad clamping was not used in Group II, while selective hepatic vein control was employed in 2 patients for tumours close to hepatic veins in order to avoid the so-called cooling effect. The incidence of perioperative complications was low, including superficial liver haematoma in one patient in Group I and segmental portal vein thrombosis (segment VIII) in one patient in Group II. Radical RFA treatment was achieved in 31 procedures in Group I (75.6%) and 28 procedures in Group II (85%). Reasons for non-radical RFA procedures in Group I included the absence of tumour detection (9 patients) and inaccessible tumour in segment VII (one patient). By comparison, non-radical RFA treatment in Group II was related to the absence of tumour detection (one patient), close proximity to main biliary trunk (one patient), diffuse bilobar lesions (one patient) and to final positive surgical margin in RFA-assisted liver resections (2 patients). However, despite an additional deeper ablated margin obtained by RFA being left in-situ in these latter patients well beyond the final surgical margin, one patient presented with tumour recurrence and was ultimately successfully retreated by right hemihepatectomy following portal vein embolization.

Postoperative outcome

In Group I, an 81 year-old ASA III male patient died from severe cardiac and infectious pulmonary complications. There were no deaths in Group II. The overall complication rate was 12.2% in Group I and 18% in Group II, with only one patient with severe complications in Group II (3%) (abdominal abscess requiring percutaneous drainage). The postoperative hospital stay was longer in Group II (Table 4).

Late disease outcome

Details concerning long-term overall and disease-free survival, incidence and type of tumour recurrence are given in Table 4. The "in-situ" liver recurrence rate was 41.4% in Group I and 9.1% in Group II. When taking into consideration only tumours with a largest diameter < 30 mm being detected and treated in both groups by RFA technique alone (37 tumours in each group, the non detected tumors being excluded), the "in-situ" liver recurrence rate was 40.5% in Group I and 0% in Group II. The single patient in Group II and 4 out of 6 patients (67%) in Group I with tumour size exceeding 30 mm presented with "in-situ" liver tumour recurrence. After having excluded the non treated lesions, multivariate statistical analysis demonstrated that independent clinical factors predictive of "in-situ" liver tumour recurrence were maximum tumour size ($p = 0.0062$) and type of approach for the RFA technique (percutaneous versus surgical) ($p < 0.0065$).

Treatment modalities of tumour recurrence are detailed in Table 4. Type of treatment for tumour recurrence included liver resections (for 2 patients in each group), liver transplant (for one HCC patient in Group I) and repeat RFA techniques (for 7 patients in Group I and 2 patients in Group II).

Table 4. — **Postoperative results and late survival of patients suffering from liver malignancies having undergone radiofrequency ablation (RFA)**

	Group I (percutaneous)	Group II (surgical)
Patients / Procedures	33 / 41	32 / 33
POSTOPERATIVE COURSE		
* 60-days mortality	1 (2.4%)	0
* 60-days complications (CLAVIEN classification) • grade I and II : • grade III and IV :	 5 (12.2%) 0	 5 (15.1%) 1 (3%)
* median POHS (days) (range) *	3 (1-19)	10 (6-20)
LONG-TERM FOLLOW-UP		
* median follow-up (months) (range)	24 (6-45)	21 (3-50)
* Recurrence rate • in-situ liver recurrence* • hepatic recurrence • distant metastases	 17/41 (41.4%) 23/41 (56.1%) 8/41 (19.5%)	 3/33 (9.1%) 13/33 (39.4%) 13/33 (39.4%)
* Treatment of recurrence • arterial chemoembolization • liver resection • liver transplant • percutaneous RFA • chemotherapy • Alcohol therapy	 8 (HCC) 2 1 (HCC) 7 8 (LM) 3	 1 (HCC) 2 0 2 15 (LM) 1
* 3-year patient overall survival • HCC • CRLM • NonCR LM	 52.9% 62.5% 75%	 100% 80% 80%
* 3-year disease-free survival • HCC • CRLM • NonCR LM	 11% 20% 25%	 75% 33% 60%

HCC : hepatocellular carcinoma ; CR : colorectal ; LM : liver metastases.
* : $p < 0.001$.

Discussion

The role of ablative techniques in the radical treatment of primary and metastatic liver malignancies remains controversial, surgical resection being still to date considered to be the gold-standard treatment (11). Several approaches for RFA techniques are also available. The purpose of this study is to report a single institution's experience both with percutaneous and open surgical approaches. However, both groups are different concerning preoperative indications, tumour features (number and size) and procedural features (number and duration of applications). These differences reflect a difference in treatment conditions between hepatobiliary surgeons and interventional radiologists. In the percutaneous group, selection of HCC patients on a cirrhotic liver was made by hepatologists, considering RFA technique as a less invasive therapy compared to surgical resection. By the way, three patients suffering from "in-situ" hepatic recurrence in this group were ultimately treated by liver resection or transplantation without mortality. Moreover, because the percutaneous approach is usually performed under patient sedation, the technique allows a limited number and duration of applications. On the contrary, full liver mobilization in a patient under general anaesthesia allow multiple electrode array placements into the tumour in different sites and directions, a condition that is difficult to replicate in a non-anaesthetized patient. Another limitation of the percutaneous approach in the present series, in which the technique was exclusively performed under ultrasound-guidance by an expert interventional radiologist, was related to the lack of US detection of isoechoic tumours, a feature encountered in 17% of the tumours. The performance of percutaneous RFA under CT guidance will certainly avoid this problem. Other reported limitations of the percutaneous approach included the lack of intraperitoneal staging, the risk of diaphragmatic or intestinal burn for subcapsular lesions (12) and the lack of tumour accessibility in all intrahepatic segmental locations, a feature encountered in the present study in one patient with a tumour located in liver segment VII

On the other hand, in the surgical group, RFA was mainly used as an alternative to resection in high-risk patients (unfit, elderly patients or liver remnant insufficient for major hepatectomy), in multiple bilobar

Table 5. — **Multivariate statistical analysis of predictive factors for «in-situ» liver recurrence in 65 patients treated by RFA procedures**

Clinical factors	Odd ratio	95% CI	p value
Maximun tumor size > 20 mm	16,805	2,233 – 126,448	0,0062
Percutaneous versus surgical	33,499	2,673 – 419,753	0,0065

disease, for repeat hepatectomy or as an adjunct to liver resection in order to increase oncological radicality. Additionally, the open RFA technique was performed with the same intention as R0 radical hepatectomy, including treating all lesions visible on intraoperative ultrasonography and achieving a 1cm "in-situ" tumour-free margin, as reported to be the rule for surgical resection of primary (13-16) and secondary (17-18) liver malignancies. This objective is more easily obtained under general anaesthesia and with complete exposure of the liver by an open surgical approach for RFA, allowing a significantly greater number and duration of RFA applications. Another benefit of the surgical approach is the facility to perform portal or hepatic vein clamping during the RFA procedure for tumours close to major vascular trunks, in order to increase treatment efficacy by avoiding the so-called "cooling effect" (19-20) due to tumour proximity. The counterpart of the better efficacy of the surgical approach in the present series was a longer postoperative hospital stay, but this was not associated to an increased mortality or per- or postoperative complication rates. By the way, as widely reported, this series confirms again the safety of the RFA procedure whatever the type of approach for treating liver malignancies (12,22-24).

Late disease progression was mainly due to extra- and intrahepatic recurrence outside of RFA sites of treatment, as well in HCC on chronic liver disease as in colorectal liver metastases. Differences were observed concerning the local "in-situ" hepatic recurrence rate between both groups : 9% in the surgical group and 41% in the percutaneous group. These results are comparable to previous features reported either in percutaneous (5% to more than 50%) (2,3,25-27) or in surgical RFA techniques (2% to 12%) (22,24,28). The heterogeneous patient's selection does not allow comparison between tumour types in both groups in the present series. However, tumour size was significantly smaller in the surgical group, despite the fact that 97% in the surgical group and 86% in the percutaneous group included tumour size < 30 mm in size. However, when considering in both groups only treated tumours < 30 mm, the local "in-situ" hepatic recurrence rate remains higher in the percutaneous group of patients (40.5% versus 0%, respectively). Additionally, a multivariate statistical analysis in the present series identified tumour size > 20 mm and percutaneous approach as independent predictive factors of local tumour recurrence. These results are however in contradiction with those of CURLEY and al. who reported only 4% of local recurrence in HCC on chronic liver disease and no difference in term of recurrence between open versus percutaneous RFA (22).

In conclusion, whatever the approach used, RFA is a safe and efficient treatment of primary and secondary liver malignancies, especially when adequate selection concerning tumour size is respected. Differences in results between surgical and percutaneous approaches are explained by differences in treatment conditions and in tumour size selection. Better results of percutaneous RFA should probably be obtained by performing the procedure under CT guidance and general anaesthesia.

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