Radiofrequency thermal ablation of liver carcinoma
Prospective study of 82 lesions

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SUMMARY
Objectives — The aim of this prospective study was to evaluate the feasibility of radiofrequency ablation of hepatic tumors. We studied the rates of mortality, morbidity, and recurrence and recorded overall and disease-free survival.

Methods — All patients aged over 18 years with histologically proven malignant liver disease inaccessible to surgical treatment (one to four tumor localizations) were eligible for inclusion in the study. Child-Pugh score > B9, platelets count ≤ 50.10^3/mm^3, prothrombin index ≤ 50% and pregnancy were exclusion factors.

Results — Between July 2001 and June 2004, 51 patients (13 women, 38 men, mean age 66 ± 9 years) were included and underwent 61 radiofrequency thermal ablation procedures for 82 hepatic lesions: hepatocarcinoma (N = 44), cholangiocarcinoma (N = 1), metastatic tumors (N = 37). Hospital morbidity and mortality were 11.5% and 2% respectively. Recurrence rate at 3 years was 20.6%. In multivariate analysis, only tumor size > 3 cm was correlated significantly with recurrence (P = 0.03). Actuarial 1-, 2- and 3-year survival rates in the hepatocarcinoma group (N = 31) were 84.7%, 57.7% and 34.6% respectively. Actuarial 1-, 2- and 3-year survival rates in the metastasis from colorectal adenocarcinoma group (N = 14) were 90%, 54% and 54% respectively (P = 0.72).

Conclusion — Radiofrequency thermal ablation is an effective treatment for hepatic tumors measuring less than 3 cm. There is a low risk of complications and open surgery can be associated. However in the absence of randomized studies comparing radiofrequency and surgery, respective indications cannot be defined in detail.

RÉSUMÉ
Objectifs — Le but de cette étude était d’étudier la faisabilité de la radiofréquence dans le traitement de tumeurs hépatiques malignes. Les taux de mortalité, de morbidité, de récidive et les survies avec et sans récidive à moyen terme ont été évalués.

Méthodes — Tous les malades, hommes ou femmes, âgés de plus de 18 ans, porteurs d’une ou plusieurs lésions hépatiques (maximum 4 lésions), dont la preuve de la nature tumorale avait pu être faite, ont été inclus dans cette étude. Le traitement chirurgical seul de ces lésions ne pouvait être envisagé pour des impératifs techniques ou liés au malade. Étaient exclus les malades ayant une fonction hépatique altérée (Child-Pugh > B9), ceux ayant des troubles de la coagulation (plaquettes ≤ 50.10^3/mm^3, taux de prothrombine ≤ 50 %) et les femmes enceintes.

Résultats — Entre le 13 juillet 2001 et le 1er juin 2004, 51 patients ont été inclus. Soixante et une séances de radiofréquence ont été réalisées permettant de traiter 82 lésions. Il y avait 13 femmes et 38 hommes d’un âge moyen de 66 +/- 9 ans. Il y avait 44 carcinomes hépatocellulaires, un cholangiocarcinome et 37 métastases d’origine diverses. Le taux de mortalité était de 2 % et le taux de morbidité hospitalière était de 11,5 %. Le taux de récidive à 3 ans était de 20,6 %. En analyse multivariée le seul facteur de risque de récidive retrouvé était une taille tumorale supérieure à 3 cm (P = 0,03). Le taux de survie globale à 1, 2 et 3 ans était de 84,7 %, 57,7 % et 34,6 % pour le groupe carcinome hépatocellulaire (N = 31). Pour les malades porteurs de métastases d’adénocarcinome colorectal (N = 14) le taux de survie globale à 1, 2 et 3 ans était respectivement de 90 %, 54 % et 54 % (P = 0,72).

Conclusion — La radiofréquence est un traitement efficace des tumeurs hépatiques de moins de 3 cm de diamètre. Ce traitement peu invasif permet l’épargne du parenchyme hépatique, rendant son association avec la chirurgie intéressante. Cependant en l’absence d’études randomisées la comparant au traitement de référence qui est la chirurgie, ses indications sont à l’heure actuelle mal définies.

Introduction
Currently, surgical resection is the best solution for potentially curative treatment of primary or secondary hepatic tumors. The 5-year survival rate after surgical resection of hepatic metastases from colorectal cancer ranges from 28% to 40% [1, 2]. For hepatocellular carcinoma, surgical resection affords a survival of 20-35% at five years [3], but the tumor is accessible in only 30% of patients [4]. Liver transplantation can provide better survival, to the order of 70% at five years, for patients with hepatocellular carcinoma [5], but can only be proposed for about 3% of patients. Thus, surgery would be the treatment of choice for most patients, but can actually be proposed for very few [6].

In 1891, d’Arsonval used for the first time a device delivering an alternative electrical current with a frequency above
were expressed as mean and Student's t test or the Mann-Whitney test for quantitative variables. The chi-square test or the Fisher's exact test were applied as appropriate for qualitative variables and Student's t test or the Mann-Whitney test for quantitative variables. At univariate analysis using the best likelihood method (odds ratio), variables associated with the dependent variable with P < 0.15 were considered independent. The Kaplan-Meier method was used to establish the actuarial survival curves which were compared with the log-rank test. P < 0.05 was considered significant. Logistic regression was used for the multivariate analysis.

Results

Between July 2001 and June 2004, 51 patients were prospectively included in this study. These patients underwent 61 radiofrequency sessions which were used to treat 82 tumors. The series included 38 men and 13 women, mean age 66 ± 9 years (range 41-83). Their mean body mass index was 26.4 ± 4.2 kg/m\(^2\). The patients were noted ASA 1 (N = 1), ASA 2 (N = 30), ASA 3 (N = 3), and ASA 4 (N = 0). Performance status was scored 0 for 41 patients and 1 for ten patients. Mean follow-up was 21.9 months (range 3-39 months).

Liver tumor

The 61 radiofrequency ablation sessions were used to treat 82 liver tumors. There were 44 hepatocellular carcinomas, one cholangiocarcinoma, and 37 metastatic tumors from diverse cancers: colorectal adenocarcinoma (N = 28), neuroendocrine tumors (N = 6), squamous-cell carcinoma of the anus (N = 2), pancreatic adenocarcinoma (N = 1). Mean tumor size was 26.7 ± 12.9 mm (range 8-80 mm) (figure 1).

Radiofrequency procedure

For the 82 tumors treated, 47 were treated percutaneously and 35 via a surgical approach (laparoscopic approach for one tumor). Ultrasound guidance was used for all sessions except for one case where CT-guidance was used for a percutaneous procedure. Mean duration of the radiofrequency sessions was 20.6 ± 14.7 minutes (range 6-88 min). Median duration was 16.5 minutes.

Pringle's maneuver (intraoperative clamp on the hepatic pedicle) was used for four tumors. An intermittent clamp was used on the suprahepatic veins during the treatment of one tumor.

Sixteen patients underwent hepatectomy, major hepatectomy for six (left hepatectomy for three and left lobectomy for three associated with atypical resections). Two patients required an associated procedure performed at the same time as the radiofrequency ablation: total colectomy for one patient and anterior resection of the rectum for another. The liver tumors were metastases from colorectal adenocarcinoma in these two patients.

Hospital stay

Mean hospital stay was 7.3 ± 5.2 days (range 2-24 days). For the 38 percutaneous procedures, mean hospital stay was 5 ± 3.8 days. For the 23 surgical procedures, mean hospital stay was 11.2 ± 5 days (P < 0.0001).

Morbidity and mortality

One patient died giving a hospital mortality of 2%. This patient underwent laparotomy for hepatocellular carcinoma and died one day after surgery from massive pulmonary embolism.

Six patients presented seven complications during their hospital stay, giving a hospital morbidity of 11.5%. Five complications were related to the radiofrequency procedure (8.2%): intra-hepatic abscess formation (N = 1), hemorrhage associated with thrombosis of the inferior vena cava treated with triple hepatic clamping with suture of the infraduodenal inferior vena cava (N = 2), plaque burn (N = 1), pleural effusion (N = 1). Two complications were not related to the procedure...
(3.3%): one transient ischemic event and one pelvic abscess in a patient who also underwent colectomy during the same operative time.

Five patients developed late complications (8.2%): needle tract seeding, recurrent intra-hepatic abscess, intercostal pain, and thrombosis of the portal vein (N = 2).

Survival

Patients were divided into two groups for the survival analysis: hepatocellular carcinoma or metastasis from colorectal adenocarcinoma.

Overall survival rates for the hepatocellular carcinoma group (N = 31) were 84.7%, 57.5%, and 34.6% at 1, 2, and 3 years respectively. For the metastasis group (N = 14), the overall survival rates were 90%, 54%, and 54% at 1, 2, and 3 years respectively (P = 0.72) (figure 2).

For the hepatocellular carcinoma group (N = 31), recurrence-free survival rates were 39.9%, 14.2% and 14.2% at 1, 2, and 3 years respectively. For the metastasis group (N = 14) the recurrence-free survival rate at 3 years was 34.1%, all recurrences taking place during the first year (figure 3).

Recurrence

At 3 years 17 of the 82 tumors treated by radiofrequency ablation recurred in 16 patients (20.7%). In the metastasis group (considering all types of primary tumors) 6 of 37 tumors recurred (16%). In the hepatocellular carcinoma group, 11 of 44 tumors recurred (25%). There was no recurrence of the cholangiocarcinoma (table I).

At univariate analysis, only tumor size greater than 3 cm was a risk factor for recurrence. The Threshold for significance of tumor size was 3.5 cm. At multivariate analysis, only tumor size above 3 cm was an independent factor predictive of recurrence with an odds ratio of 1.23 [1.10-10.7] (P = 0.03).

Discussion

The purpose of this study was to examine the feasibility of radiofrequency ablation of hepatic tumors inaccessible to surgery, and to assess outcome. Although surgery is the preferred treatment for isolated liver metastases [1, 2] and primary hepatocellular carcinoma [3], less than 30% of tumors are resectable [4]. Radiofrequency ablation appears to be a safe technique with little morbidity. Mortality has varied from 0.09% reported in one large multicentric trial [10] to 0.9% observed in a monocentric study [11]. In 2002, a review of the literature reported mortality at 0.5% (20 deaths among 3670 treated patients) [12]. In our study, mortality reached 2% due to the small number of patients (1 death among 51 treated patients). In the literature (table II), morbidity has varied from 2.43% [10] to 25% [13].

Globally, considering the 82 largest series reported from 1990 to December 2001 [12], for 3670 patients treated with radiofrequency (all approaches considered together), morbidity reached 8.9%, a rate similar to ours. The three most frequently reported complications are hemorrhage, infection, and injury of the biliary tract (mainly stenosis). Morbidity related to radiofrequency ablation can be reduced by careful patient selection (bilio-digestive Anastomosis is a contraindication), coagulation of the needle tract, avoiding perpendicular puncture of intracapsular tumors, and preferential surgical approach when infracapsular tumors are in contact with neighboring organs.

Table I – Risk factors of recurrence, univariate analysis.

<table>
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<th>Factor</th>
<th>Number of recurrences</th>
<th>Number of tumors</th>
<th>P</th>
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<tr>
<td>SEX</td>
<td></td>
<td></td>
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</tr>
<tr>
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<td>Female</td>
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<td>14</td>
<td>0.72</td>
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<td>&gt;3 cm</td>
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The main problem is determining the efficacy of radiofrequency ablation. Two studies in patients who first underwent a radiofrequency ablation then surgical resection showed that the surgical specimens exhibited irreversible destruction of the cells which were devoid of enzymatic activity [14, 15]. Livragi et al. [16] reported 90% complete destruction of small hepatocellular carcinoma tumors treated with an open perfused needle. Curley et al [17] reported 98% success for the treatment of hepatocellular carcinoma and metastases in 123 patients. Globally, results in the literature have demonstrated complete destruction to the order of 8-9% [21]. The rate of local recurrence is to the order of 8-9% [21, 22]. More recently, Gugliemi [23] reported a 6.8% recurrence rate in patients with hepatocellular carcinoma. All of the tumors which exhibited local recurrence measured more than 4.7 cm.

Several risk factors for recurrence have been identified: tumor size > 3 cm, tumor located near a vessel, type of tumor, and approach used. In our series, only tumor size > 3 cm was significantly associated with recurrence, in agreement with the literature. This has led us to exclude larger tumors measuring more than 3 cm from radiofrequency treatment. Localization of the tumor in the vicinity of a vessel was not found to be a risk factor; this type of localization only concerning a small group of tumors (N = 15) in our study (pedicular clamps were used while treating four of these tumors). In our series, the approach nearly reached the level of significance (P = 0.07). In certain series, multivariate analysis has identified approach as predictive of complete tumor destruction [24]. The question is to determine whether radiofrequency ablation should be performed via a surgical approach, as advocated by certain authors who reserve the percutaneous method for patients with a contraindication for surgery. It must be emphasized however that the probable reduction in recurrence rate with the surgical approach (4/35 versus 13/47 in our series) has a cost in terms of higher morbidity and longer hospital stay. Unlike other reports in the literature, the histological type of the tumor did not appear to have an influence in our series.

At the present time, the problem is that follow-up has been too short to evaluate the real efficacy of radiofrequency ablation. The earliest series reporting preliminary results were performed in the 1990s [8, 9]. Since that time, needles have been modified [25] and indications refined. In one series limited to hepatocellular carcinoma, overall survival rates were 87%, 63%, and 45% at 1, 2 and 3 years respectively [23]. In this same series, recurrence-free survival was 75.7% at one year and 42.5% at two years. Rossi et al. [20], reported a series of patients with hepatocellular carcinoma and found survival rates of 94%, 86%, 68% and 40% at 1, 2, 3, and 5 years respectively. In our series, overall survival at three years was 34.6% and recurrence-free survival at three years was 14.2%, rates which are lower than reported in the literature. This might be explained by the fact that tumors measuring more than 3 cm were treated by radiofrequency early in our experience. There could also be a learning curve effect as with any new technique as demonstrated by Poon et al [24]; most of the tumors were hepatocellular carcinomas during the early part of our study. Most of the metastases (71%) were also treated via a surgical approach versus 26% percutaneously. The approach used could have an effect on the risk of recurrence. For patients with metastases, the overall survival at four years is 22% for radiofrequency ablation alone and 36% for radiofrequency ablation associated with surgery [22]. In our series, the overall and recurrence-free survival rates at three
years were 54% and 34.1% respectively for metastases patients, similar to findings in the literature.

Because of the lack of sufficient evaluation, indications for radiofrequency ablation are rather vague. At the present time, no consensus has been reached concerning appropriate indications for radiofrequency ablation of liver tumors. The objective is to achieve local control of the liver disease. Conversely, it has been demonstrated that incomplete treatment does not provide any benefit for the patient [26]. Radiofrequency ablation can be used alone or in association with surgery in order to achieve complete cure [27]. Radiofrequency treatment of hepatic tumors has enabled more broad indications for hepatic resection. Several authors have thus proposed associating more or less extensive hepatic resection with radiofrequency treatment for tumors situated in the remnant liver in order to improve resectability [28].

In light of the most recent data in the literature and from the results of the present study, it would appear that radiofrequency ablation of hepatic tumors measuring less than 3 cm is an effective treatment. The rate of local recurrence is often associated with tumor size greater than 3 cm [22]. Beyond 5 cm, radiofrequency ablation should not be proposed. A recent study demonstrated that the maximal diameter for reproducible tumor necrosis is 3.4 cm [29].

In conclusion, radiofrequency ablation of hepatic tumors is feasible and reproducible with low morbidity and mortality. This minimally invasive technique (particularly when using the percutaneous route) spares the hepatic parenchyma and can thus be advantageously associated with surgery. The main limitation is the tumor volume which must not exceed 3 cm in diameter. Several avenues of research are being explored to palliate this inconvenience.

Several questions remain open:

— is physical destruction of hepatic tumors as effective as surgical resection?
— which approach is best?
— what is the best imaging method to guide the procedure and for follow-up?

Further studies should be performed to respond to these interrogations. These studies should help better identify appropriate indications for radiofrequency ablation for the treatment of hepatic tumors and the role of this technique in the therapeutic strategy.

REFERENCES


