**The impact of radiofrequency-assisted transection on local hepatic recurrence after resection of colorectal liver metastases**

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**ABSTRACT**

Resection is the gold standard in the treatment of liver metastases from colorectal cancer. An internal cooled radiofrequency electrode was described to achieve tissue coagulation to a greater margin width. The aim of this study is to determinate if a RF-assisted transection device (RFAT) has any effect on local hepatic recurrence (LHER) compared to conventional technologies.

A study population of 103 patients who had undergone a hepatic surgical resection was retrospectively analysed. Patients were classified into two groups according to the device used: a RF-assisted device (RFAT group; n=45) and standard conventional devices (control group; n=58). LHER was defined as any growing or enhancing tumour in the margin of hepatic resection during follow-up. Cox proportional models were constructed and variables were eliminated only if p>0.20 to protect against residual confounding. To assess the stability of Cox's regression model and its internal validity, a bootstrap investigation was also performed.

Baseline and operative characteristics were similar in both groups. With a mean follow-up of 28.5 months (range 2-106), in patients with positive margins, we demonstrated 0% of LHER in RFAT vs. 27% in control group (p=0.032). In the multivariate analysis five factors demonstrated significant influence on the final model of LHER: RFAT group, size of the largest metastases, number of resected metastases, positive margin and usage of Pringle-manoeuvre.

This study suggests that parenchymal transection using a RFAT able to create deep thermal lesions may reduce LHER especially in case of margin invasion during transection.

**Keywords:** colorectal cancer, local hepatic recurrence, liver resection, radiofrequency

**INTRODUCTION**

Colorectal carcinoma (CRC) is one of the most common malignant tumours and accounts for at least one million new cases worldwide each year. Liver metastases occurs in 40-60% of CRC patients [1].

Liver resection has been accepted as ‘gold standard’ for treatment, resulting in 5-year survival rates of up to 58% [2]. However, after resections with curative intention, recurrences in the remaining liver are observed in up to 50% of patients and are among the most important determinants of survival [3, 4]. Traditionally, 1-cm margin was considered necessary to avoid liver recurrence and optimize long-term survival [4–14]. Ambiru *et al.*[3] described micrometastases located at a median of 3 mm from the metastatic tumour edge in 31% of their patients. Also, it has to be taken into account, that minimal margins are frequently linked with extensive disease and greater tumour burden[15–17]. These findings may account for a poorer liver disease outcome in patients with lower resection margin [16, 18, 19]. In any case, resection margin involvement (positive margin) is one of the leading independent predictors for hepatic recurrence [18, 19]. In this regard, few studies have evaluated the local hepatic recurrence -LHER- (or its surrogate variable, the local recurrence-free survival) in the resection margin after resection of the liver [20, 21], especially in relation to the positive margin of the liver resection.

Radiofrequency assisted transection of the liver (RFAT) is a relatively new technique of liver resection that employs similar currents (in 300 -500 kHz range) and devices than Radiofrequency ablation (RFA) of the liver but with different aim and approach [22, 23]. Whereas RFA is based on delivering the current in the tumour itself by electrodes with the aim of ablating the tumour without its removal, and with similar or sometimes worse results than tumour resection [24, 25]. RFAT aims to remove the tumour in a bloodless way by means of margin ablation of the remnant liver. Interestingly, some radiofrequency-assisted (RF-assisted) devices have been shown to improve resection margin during hepatectomy [26]. However, to our knowledge, no previous references have demonstrated any definitive effect on LHER. Previous studies of our group have shown that RF-assisted liver transection could achieve a wide ablation margin (up to 1 cm) without increasing the risk of thermal damage in nearby structures [22, 27–30]. In this setting, the aim of this study was to determinate whether RF-assisted liver transection reduces local hepatic recurrence over the standard methods especially when this margin was positive.

## MATERIAL AND METHODS

From September 2006 to July 2015, all patients who underwent partial hepatectomy at the Hospital del Mar (Barcelona, Spain) were considered to be included in this study. Patients were entered prospectively into a computer database. This database was created for this study and was filled during follow up of the patients and retrospectively analysed. The inclusion criteria were colorectal liver metastases to be removed by any type of liver resection, via open or laparoscopic surgery with no evidence of unresectable extrahepatic disease. The exclusion criteria were primary liver and cyst tumours, metastases of non-colorectal origin and those patients treated only by tumour ablation.  With these criteria, 103 patients were enrolled in the study and were allocated either to the control group (n=58) or radiofrequency-assisted transection group (n=45) (see Figure 1).

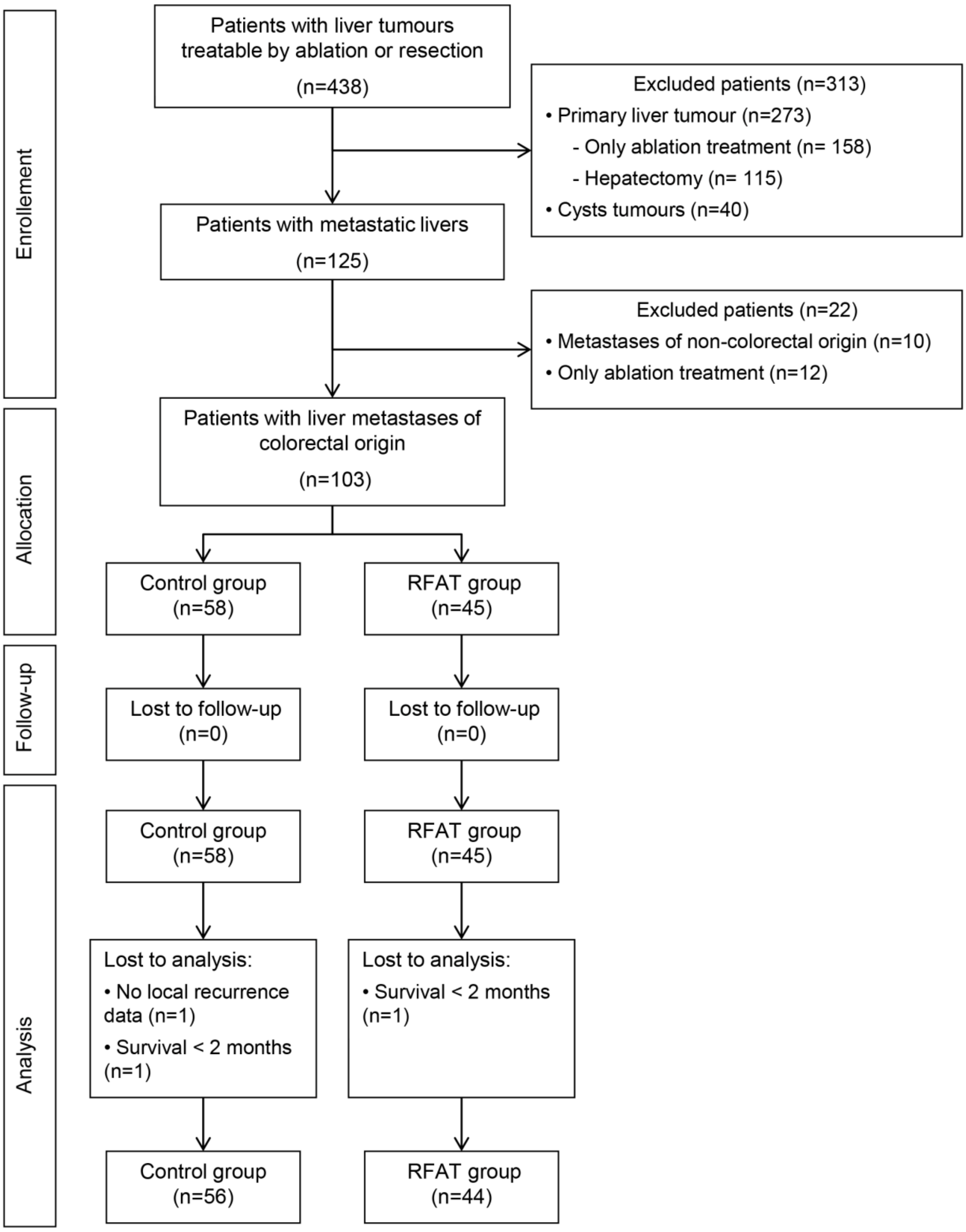


**Figure 1.** Flow chart of the study

All patients signed an informed consent before surgery. All patients also underwent careful preoperative assessment of their disease, including spiral computed tomography or magnetic resonance imaging.

All the procedures were performed by the same surgeons (F.B., I.P. and L.G.). For open surgery, the procedure was similar to that described in Phase I-II studies [29, 30]. Alternatively, in the laparoscopy, after the pneumoperitoneum was established and the exposure obtained, laparoscopic ultrasound was used to identify the tumour. In both groups the dissection was carried out with standard devices such as CUSA (Cavitron, Stamford, CT, USA), stapler transection, bipolar forceps and Ligasure (Valleylab, Boulder, CO, USA). Hemostasia was obtained in the control group with a combination of stitches, bipolar forceps and Ligasure including even sutures or clips and in the RFAT group (RF-assisted transection) it was performed with Coolinside RF-assisted device (Apeiron Medical, Valencia. Spain) which has been described in detail elsewhere [22, 27–30]. The hemostasia in RFAT group was achieved by the above mentioned device by delivering RF power through an internally cooled electrode and creating larger coagulation zones (up to 1 cm) depending on the ablation time. The decision to use RFAT was based on preferences to get complete hemostasia and availability of the system but never based on neither tumoral stage, size or number of nodules.

In patients subjected to laparoscopy approach in the RFAT group, it was introduced through a 12-mm trocar, and then the resection line was marked on the liver capsule using a conventional electrocautery or the RF device itself.

After discharge, a follow-up appointment was made with all patients in the first month and then every 6 months. At each follow-up visit, in addition to a clinical examination and determination of the carcinoembryonic antigen level, computed tomography or magnetic resonance imaging was performed. While all the clinical variables were considered as secondary outcomes, the primary outcomes of the study were overall survival, hepatic and local hepatic recurrence and positive margins.

The overall survival (OS) time was defined as the interval between the first liver operation and death or the last visit to the outpatient clinic through January 2016. Positive margin was defined as the presence of any exposed tumour along the line of transection or the presence of tumour cells at the line of transection detected by histological examination according to Figueras *et al.* [18]. Similarly to Zorzi *et al.*[20], LHER was pragmatically defined when a later follow-up CT demonstrated any growing or enhancing tumour in the margin of hepatic resection specifically reviewed to this aim. On the other hand, hepatic recurrence (HER) was considered when any growing in the rest of the liver or/and in the margin of transection was detected. Furthermore, we evaluated the extrahepatic disease (EED) similarly to Evrard *et al.*[21], which was defined as the presence of cancer disease outside the liver at any time of the study.

Other definitions of variables employed in this study were:

- Resection margin: minimum distance from the edge of the nearest metastases to the transection line measured in millimetres, according to Pawlik *et al.*[16]
- Number of metastases: number of metastases assessed by appropriate histopathological study in the liver specimen.
- Liver failure: an increased international normalized ratio and concomitant hyperbilirubinemia (according to the normal limits of the local laboratory) on or after postoperative day 5, according to Rahbari *et al.* [31]

**Statistical analysis**

Patient's demographics, primary and liver tumour characteristics, surgical therapy, history of chemotherapy and follow-up information were entered prospectively into the computer database. Patients were distributed in two groups: RFAT group and control group. The chi-square test was used to compare frequencies, whereas mean values of variables were compared using the Student t-test between both groups. Concerning the overall survival (OS), HER and LHER, we performed both a global statistical analysis and a stratified analysis according to a positive or non-positive resection margins. Given that, the main goal was to construct a model that explained causality on OS, HER and LHER, predictors necessary to face validity, as well as those that behave like confounders were included in the model [32].

Thus, following *Maldonado and Greenland* [33], the potential confounders in both univariate and multivariate analyses (using Kaplan-Meier or Cox proportional models) were eliminated only if $p>0.20$, in order to protect against residual confounding. These low cut-points to include variables in the model are especially advisable in order to adjust for covariates in therapeutic studies to appropriately select even weak factors for the next step of the analysis [34]. For the rest of the remaining analyses, differences in variables were considered to be significant at a threshold of $p<0.05$. To assess the stability of Cox's regression model and its internal validity a bootstrap investigation was performed similarly to Nordlinger *et al.*[11], and based on the method described by Altman [35]. The bootstrap method was based on the observation samples drawn from original population. Bootstrapping is a method for deriving robust estimates of confidence intervals for estimates such as the regression coefficients. In our study, ten thousand of the same sample size was obtained by randomly drawing records with replacement from the data set.

Results were expressed as regression coefficients (β) with their corresponding bootstrap estimates (bias, bias-corrected accelerated (or BCa) percentile intervals and significance). In that regard these confidence intervals may be wider than the conventional ones but are credited to be more robust an accurate than them because fewer assumptions about normality are required. Statistical analyses were carried out with statistical software SPSS (Chicago, IL, USA).

## RESULTS

### Patient's and liver resection characteristics

During the study period, 438 patients were assessed for eligibility for this study (see Figure 1). One hundred and three patients suffering from colorectal liver metastases underwent hepatic resection and were allocated in the control group (n=58) or the RFAT group (n=45). During the analysis there were one withdrawal in the RFAT group because of period of survival being less than two month, and two in the control group because of period of survival being less than two month and unavailable local recurrence data, respectively.

Table 1 summarizes the baseline and operative characteristics. According to the significance threshold previously described, no differences were found in variables among groups.

As shown in Table 2, no differences were observed in the rate of complications between groups. No significant differences were observed in mortality either.

**Table 1**. Baseline characteristics of patients involved in the study.

| | **Control group (n=58)** | **RFAT group (n=45)** | ***p*** |
|---|---|---|---|
| Gender | | | |
| Male | 38 (67.2) | 30 (66.7) | 0.676 |
| Age (years) [a] | 67.1 ± 9.5 | 66.5 ± 11.1 | 0.765 |
| Primary rectum | 15 (25.9) | 13 (28.9) | 0.922 |
| CEA (ng/ml) [b] | 57 ± 353 | 49 ± 109 | 0.888 |
| Dukes | | | 0.597 |
| A | 7 (12.1) | 3 (6.7) | |
| B | 22 (37.9) | 20 (44.4) | |
| C | 29 (50) | 22 (48.9) | |
| Positive colorectal nodes (pN) [a] | 2.58 ± 6.1 | 2.11 ± 5.4 | 0.685 |
| Synchronic presentation | 30 (51.7) | 24 (53.3) | 0.981 |
| Bilobar presentation | 21 (36.2) | 20 (44.4) | 0.397 |
| Major hepatectomy [c] | 24 (41.4) | 17 (37.8) | 0.711 |
| Number of metastases [a] | 2.07 ± 2 | 2.09 ± 1.7 | 0.876 |
| Size of the biggest metastases [a] | 3.21 ± 2 | 3.81 ± 3.1 | 0.269 |
| Morbidity | 25 (43.1) | 15 (33.3) | 0.313 |
| Mortality | 2 (3.4) | 2 (4.4) | 0.795 |
| Adjuvant chemotherapy after colorectal surgery | 31 (53.4) | 21 (46.7) | 0.495 |
| Neo-adjuvant chemotherapy before hepatic surgery | 18 (31) | 17 (37.8) | 0.474 |
| Adjuvant chemotherapy after surgery | 39 (67.2) | 22 (50) | 0.079 |
| Positive margin | 15 (26) | 15 (33) | 0.408 |
| Extrahepatic disease at hepatectomy | 9 (15.6) | 5 (11.1) | 0.518 |
| Laparoscopic approach | 18 (31) | 16 (36) | 0.628 |
| Pringle maneuver (min) | 8.4 (17.1) | 3.5 (8.4) | 0.060 |

Differences in variables were considered to be significant at a threshold of $p<0.05$ and those with a p value <0.02 were included in the univariate and multivariate analysis.

Values in parentheses are percentages. [a]Continuous variables are expressed as mean ± standard deviation. [b]CEA, carcinoembryogenic antigen expressed as mean ± standard deviation. [c]At least three liver segments were removed

**Table 2**. Mortality and morbidity in patients included in the study.

| Complications | Control group (n=58) | RFAT group (n=45) | Total | *p* |
|---|---|---|---|---|
| Mortality | 2 (3%) | 2 (4%) | 4 (4%) | 0.795 |
| Abscess | 2 (3%) | 2 (4%) | 4 (2%) | 0.243 |
| Biliary leak | 4 (7%) | 7 (16%) | 11 (11%) | 0.158 |
| Hemoperitoneum | 1 (2%) | 1 (2%) | 2 (2%) | 0.856 |
| Liver failure | 8 (14%) | 4 (9%) | 12 (12%) | 0.442 |
| Wound infection | 4 (7%) | 5 (11%) | 9 (9%) | 0.452 |
| Pneumonia | 0 (0%) | 1 (2%) | 1 (1%) | 0.254 |
| Other complications | 11 (19%) | 9 (20%) | 20 (19%) | 0.895 |
| Blood transfusion | 12 (21%) | 5 (11%) | 17 (17%) | 0.194 |

Differences were considered to be significant at a threshold of $p<0.05$.

## Univariate analysis of prognostic factors on OS, HER and LHER

With a mean follow-up of 28.5 months (range 2-106), the 1, 3 and 5-year global OS was 93%, 62% and 42%, respectively. The global cumulative HER were 20%, 43% and 49% and LHER were and 5%, 11% and 11% for 1, 3 and 5-year, respectively. In this last set of results, six patients presented LHER in the control group (according to the above definition) and just one, in the RFAT group (see Figure 2). Concerning the management of the local recurrence, just one of them was intended for hepatic resection, but during the exploration peritoneal dissemination was also found (in addition to histologically proven recurrence at the site of the previous hepatic resection). In the remaining patients, no surgical option was possible due to the progression of the illness. However, five patients were subjected to adjuvant chemotherapy (4 in control group and 1 in the RFAT group).

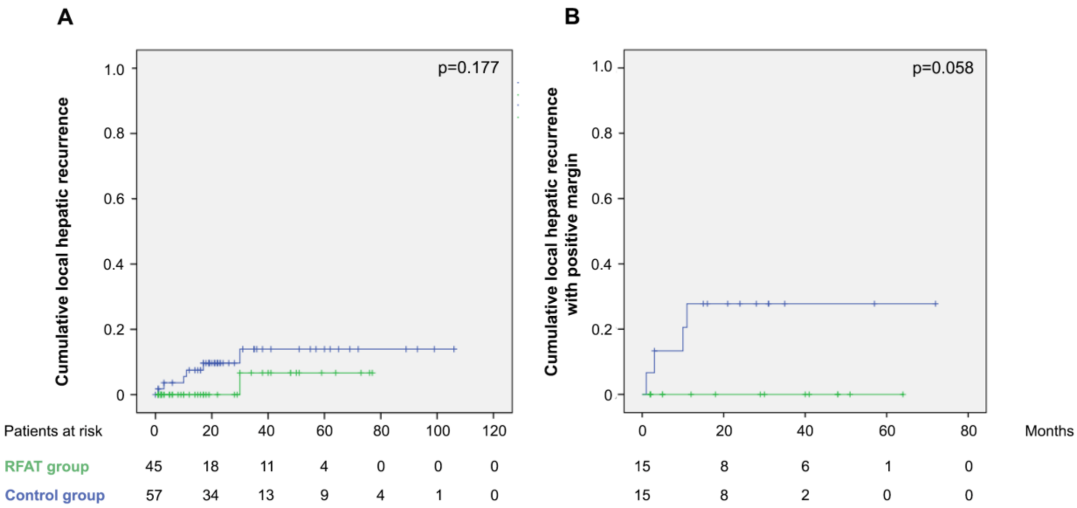


**Figure 2.** (**A**) Local hepatic recurrence in all patients **(**LHER) (**B**) and LHER in cases with positive margin stratified by treatment group using Kaplan-Meier method with a mean follow-up of 28.5 months. The log-rank test demonstrated a significance of 0.177 and 0.058, respectively.

Six variables demonstrated influence on OS taking into account the significance threshold previously described: RFAT group, size of the biggest metastases, morbidity, adjuvant chemotherapy, extrahepatic disease and Pringle manoeuvre usage during hepatectomy (Table 3). Similarly on HER, the following variables showed significant influence: RFAT group, size of the biggest metastases, node-positive of the primary tumour, number of metastases, bilobar presentation, morbidity, neo-adjuvant chemotherapy, extrahepatic disease and Pringle manoeuvre usage during hepatectomy.

However, only six variables showed significant influence on the LHER analysis: RFAT group, size of the biggest metastases, number of metastases, positive margin, extrahepatic disease and Pringle manoeuvre usage during hepatectomy.

**Table 3.** Univariate and multivariate analysis of prognostic factors on OS, HER and LHER.

| **Variable** | **OS** | | | | **HER** | | | | **LHER** | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | **Bootstrap estimates#** | | | | **Bootstrap estimates#** | | | | **Bootstrap estimates#** | | |
| | **β** | **Bias** | **BCa 95% Confidence Interval** | **p** | **β** | **Bias** | **BCa 95% Confidence Interval** | **p** | **β** | **Bias** | **BCa 95% Confidence Interval** | **p** |
| RFAT group | -0.9 | -0.05 | -1.7, -0.2 | 0.04 | -0.8 | -0.06 | -1.8, 0.001 | 0.06 | -1.6 | -4.0 | -19.8, 1.5 | 0.1 |
| Size of the biggest metastases | 0.07 | -0.002 | -0.03, 0.2 | 0.04 | 0.1 | -0.009 | -0.04, 0.2 | 0.01 | 0.2 | 0.3 | -3.2, 9.2 | 0.01 |
| Number of node-positive primary | | | | | 0.04 | -0.002 | -0.03, 0.09 | 0.02 | | | | |
| Number of metastases | | | | | * | | * | * | 0.1 | -1.5 | -7.1, 0.3 | 0.2 |
| Bilobar presentation | | | | | * | | * | * | | | | |
| Morbidity | 0.6 | 0.06 | -0.2, 1.7 | 0.1 | * | | * | * | | | | |
| Neo-adjuvant chemotherapy | | | | | 0.6 | 0.03 | -0.2, 1.5 | 0.09 | | | | |
| Adjuvant chemotherapy | -1.5 | -0.06 | -0.06, -0.8 | <0.01 | | | | | | | | |
| Positive margin | | | | | | | | | 2.0 | 3.5 | -11.4, 99.9 | 0.04 |
| Extrahepatic disease | 0.9 | 0.05 | 0.04, 2.0 | 0.02 | 1.9 | 0.1 | 0.9, 3.6 | <0.01 | * | | * | * |
| Pringle manoeuvre | * | | * | * | * | | * | * | 0.05 | 0.03 | -1.7, 1.2 | 0.001 |

In order to protect against residual confounding, data are eliminated only if $p>0.2$. Provided data are adjusted variables in the final multivariate model. *Variables above this significance threshold in univariate analysis which did not remain significant in the multivariate analysis. #Bootstrap estimates are based on 10000 samples.

**Multivariate analysis of prognostic factors on OS, HER and LHER**

Five variables on each survival variable demonstrated significant influence in the final model taking into account the same significance threshold. Two of them were present on OS, HER and LHER: RFAT group and size of the biggest metastases (see Table 3). Interestingly, on LHER three additional variables remained in the final model: number of metastases, positive margin and Pringle manoeuvre use. Specifically on LHER, all factors increased the risk of local hepatic recurrence except RFAT group which seemed to reduce the associated risk ($\beta = -1.6$).

**LHER in positive resection margins**

When we selected patients with positive margins, 4 patients out of 15 presented LHER in the control group (27%), while no patients out of 15 presented LHER in the RFAT group (0%). These differences were statistically significant in this univariate analysis (*p*=0.032, chi-square test). This difference among groups nearly reached significance in the Kaplan-Meier method (*p*=0.058) (Figure 2-B). On the contrary, as expected, LHER in patients with negative resection margins was similar between control and RFAT group (p=0.98 in chi-square test and p=0.765 in Kaplan-Meier test).

**DISCUSSION**

The resection margin of colorectal metastasis is currently the most important factor that is under the surgeon's control[7, 12] with a significant impact on hepatic recurrence and a determinant of survival [4, 14, 16, 19, 36–38]. Recent publications have advocated that a subcentimeter resection margin should not preclude colorectal metastases resection since a non-positive margin can be obtained [18]. The incidence of

LHER ranges from 7 to 17% [20, 21] or even higher when non-anatomical resections were performed and it is usually linked with positive margin during hepatectomy in a risk-ratio of over 10% [20]. In spite of its relevancy, this variable is rarely reported because requires careful and time-consuming evaluation of the margin status over time with appropriate image-study of each patient. In our study, with a mean follow-up of 28.5 months we demonstrated 0% LHER in the RFAT group when a positive margin was observed during hepatectomy in comparison to 27% in the control (p=0.032 and Figure 2-B). This low risk of LHER in patients with positive margins in the RFAT group can be explained by a wide resection margin (up to 1 cm) due to the ablation effect of RF-assisted device employed in this study as it was demonstrated in preclinical studies (also see Figure 3) [22, 27, 28]. As expected this positive effect was not observed when the margin resection was negative.

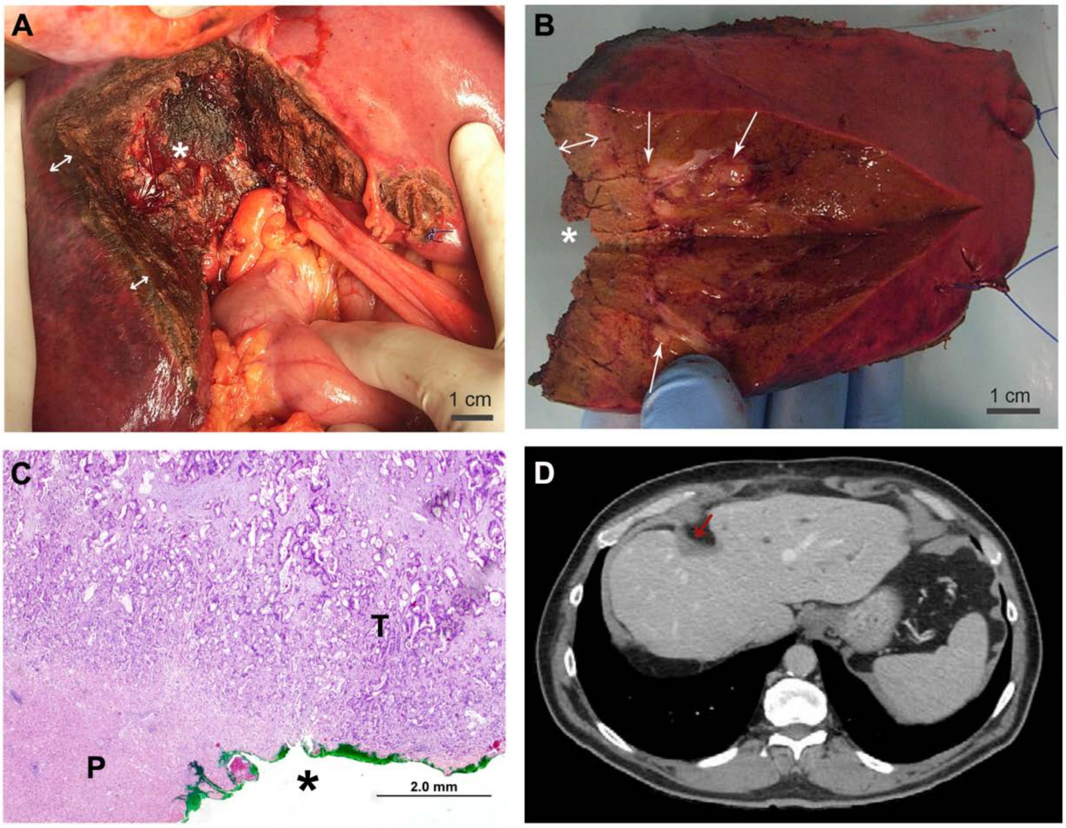


**Figure 3.** (**A**) Photograph showing the remnant liver after removing the specimen (RFAT group, central hepatectomy). Notice the coagulated tissue in the remnant liver (two headed arrow) and the resection margin (asterisk). (**B**) The liver specimen of the same patient showing the margin of resection and the thickness of coagulated tissue (two headed arrow) which is in contact with the metastasis (arrows). The asterisk shows the correct position of the specimen. (**C**) Histological section of the resection margin of the specimen (see asterisk for correct position). Resection margin is marked with green ink. See tumor ("T") and coagulated parenchyma ("P") in contact with the margin. Notice that coagulated tumor did not impair correct evaluation of margin invasion. (**D**) CT of the same patient after 56 months of this liver resection, where no signs of local hepatic recurrence is observed. See the remaining ablated tissue in the margin (red arrow).

The benefit of the ablation effect on the resection margin may be weaker or diluted when all of the patients are taken into account (with positive and non-positive margin) but, in fact, the global analysis with an appropriate selection of confounding factors found some effect on all conventional survival analysis (OS, HER and LHER) which were confirmed by bootstrapping resampling methods in all cases. Bootstrapping is very useful to assess internal validity when the assumptions of parametric methods are in doubt (as in the case of regression models with heteroscedastic residuals fit to small samples or not normal distributions). In our regression model the bias of the estimates and their variability were measured with this robust statistical method which confirmed the influence of the referred variables.

Several limitations of this study should be also addressed:

- Accurate assessment of the resection margin in hepatic surgery can be difficult. Therefore, the lack of more direct metastases measurements is related to CT or MR sensitivity.
- Even though this is a controlled study of an homogeneous cohort of patients, it is not a randomized study. That is why a high control for confounding factors has been applied in univariate and multivariate analysis.

In conclusion, our findings provides evidence supporting the concept that radiofrequency assisted transection of the liver associated with a deep thermal lesions may reduce local hepatic recurrence, especially in case of margin invasion during transection. However, in spite of this positive effect on local hepatic recurrence, surgeons should continue to endorse the conventional guidelines of negative margin preservation. In any case, this technique could be especially advantageous when R0 resection is difficult to obtain in order to enhance the margin.

## Disclosure

The authors did not receive any funding from any company.

RQ, EB and FB declare stock ownership in Apeiron Medical S.L., a company that has a license for the patent US 8.303.584.B2, on which the device Coolinside employed in the RFAT group. The other authors report no conflict of interests or financial ties to disclose.

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