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

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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.

1. 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

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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.

2. 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 Fig. 1).

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].

2.1. 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