New technique to increase resection margins during mini-invasive liver resection: a propensity score-matched study

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Background: The application of radiofrequency (RF) energy in liver resection has been shown to be an effective method to minimize bleeding. However, the role of this technology in greater resection margin width and its relevance in local recurrence (LR) is still debatable at this time. This study aims to evaluate the effect of the RF energy during the resection liver surface on LR compared to conventional technologies.

Methods: This is a retrospective study of patients who underwent laparoscopic radical hepatectomy for colorectal liver metastases (CRLM) between September 2006 and September 2020 was performed. After 1:1 propensity score matching (PSM), cases were divided into two groups (with or without application of RF to liver resection).

Results: Once the PSM is applied, LR rate resulted to be significantly higher in the Control compared with the RF group [8 (7.84%) *vs.* 2 (1.9%) patients, P=0.046]. The final LR free-survival at 1, 3, and 5 years of the control and RF group patients were 86.5%, 83.9%, 80.1% and 100%, 100%, 92.3%, respectively (P=0.045). The RF energy is related to lower LR [hazards ratio (HR) =4.69; 95% confidence intervals (CI): 0.983–22.40; P=0.053].

Conclusions: Compared to conventional haemostatic technologies, liver resection with the use of RF on the resection surface can reduce local hepatic recurrence.

Keywords: Colorectal liver metastases (CRLM); liver recurrence; radiofrequency (RF) ablation

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Introduction

Hepatectomy remains the gold standard treatment for liver malignancies, offering the best chance for long term survival (1).

However, despite liver resection, several factors may affect long-term survival. Some of them are related to the tumor inner biology, such as tumoral size and numbers, increased tumoral markers serum level and mutated KRAS; some others are related to the surgical procedure itself, such as surgical margins (R0 *vs.* R1 resection) (2). It is well known that the R1 resection negatively impact disease-free and overall survival (OS) rates in all liver malignancies, therefore, whenever possible, the gold standard of treatment is to achieve enough margins to decrease the potential recurrence (3).

However, depending on tumor malignancy, length margin may vary. Furthermore, currently, definition of margin status still lacks of uniformity. For instance, because of the tendence of hepatocarcinoma for vascular invasion as well as metastatic spread along the portal venous system, a margin wider than 1 cm is generically desirable (4). For hepatocarcinoma, several studies found that the 1 cm margin can be an independent predictor of disease-free survival for tumors >2 cm (4). In this case, even anatomic resection has been proposed as a means to provide increased resection margins and survival (5).

Many studies have addressed surgical margins for colorectal liver metastases (CRLM), even if it still remains an issue among scholars (3). Some series concluded that a minimum margin higher than 1 mm is associated with a better prognosis and that a margin >1 cm achieved an even better prognosis (3). For CRLM, resected tumors with margin within 1 cm are considered to be at potentially risk of recurrence (3).

Furthermore, some authors for tumors involving hepatic veins, suggested that an R1 resection with detachment of CRLM from vessels, defined as vascular R1 resection, achieve an acceptable survival compared with local treatment without resection (6,7).

However, the extent of the liver resection should consider what may be the underlying hepatic dysfunction and functional hepatic reserve of the patient. Sometime a proper R1 resection, that may require extended resection or vascular resection, cannot be achieved with acceptable morbidity. In addition, in the current era of neoadjuvant chemotherapy, most of the cases underwent preoperative treatment, therefore, the R1 resection margins concept should be reconsidered in light of the recently highly effective regimens.

In cases with important underlying hepatic dysfunction or with large tumors, to achieve wide margins may be challenging, or aiming to increase resection margins in all liver resection, several techniques have been described (8-11).

The application of the radiofrequency (RF) to the liver during resection is a relatively new technique that use similar currents (around 400 kHz) compared with the traditional RF ablation commonly used for the local treatment of liver nodules, but, with different aim and approach. The RF ablation is based on delivering energy in the tumor itself aiming to ablate it without its resection, therefore, with potential worst survival rate. Conversely, RF applied along liver transection has the aim to resect the tumor in a bloodless fashion applying margin ablation to the remnant liver, as well.

In previous reports, we have been able to show the positive impact of recurrence rate for primary and secondary liver malignancies by using a specific RF device for liver transection (12).

The aim of this study is to investigate the impact of RF assisted transection on local recurrence (LR) rate for high risk cases (margins <1 cm) focusing selectively on CRLM resected laparoscopically at our center. We present the following article in accordance with the STROBE reporting checklist (available at https://dmr.amegroups.com/article/view/10.21037/dmr-21-106/rc).

Methods

Patient eligibility and data collection

A retrospective analysis from clinical data of patients underwent liver resection for CRLM from September 2006 to September 2020 at our center was done. The study protocol was approved by the Clinical Research and Ethics Committee of Hospital del Mar, Barcelona, Spain (ID 2020-9397) (13). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Clinical Research and Ethics Committee of Hospital del Mar (Barcelona, Spain) (No. 2020-9397) and individual consent for this retrospective analysis was waived.

Inclusion criteria are: (I) patients older than 18 years old; (II) CRLM removed by laparoscopic liver resection. Exclusion criteria are: (I) benign lesions; (II) non-colorectal metastases; (III) absence of extrahepatic metastases; (IV) patients treated with only RF ablation; and (V) incomplete clinical data. We included only patients with a margin width 1 cm. Patients were divided in two groups depending on the fashion as haemostasis was performed: with conventional haemostatic devices (Control group), or with an additional coagulation area by means of an RF-based device (RF group). In two groups hepatic parenchymal transection was performed by the Cavitron ultrasonic surgical aspirator, stapler transection or Ligasure. The final haemostasis was achieved in the Control group through stitches, clips, monopolar or bipolar energy device and Ligasure. In the RF group, haemostasis was performed with the Coolingbis device (14-16). After liver resection in the RF group, the RF energy were applied and repeated if necessary until no further spurting hemorrhage and to increase the safety margin width (up to 1 cm). Coolingbis was used according to the habits of the surgeons in terms of hemostatic effectiveness only. All surgeries are performed by the same team of surgeon.

Outcome indicators

The follow-up is done starting from almost 30 days from

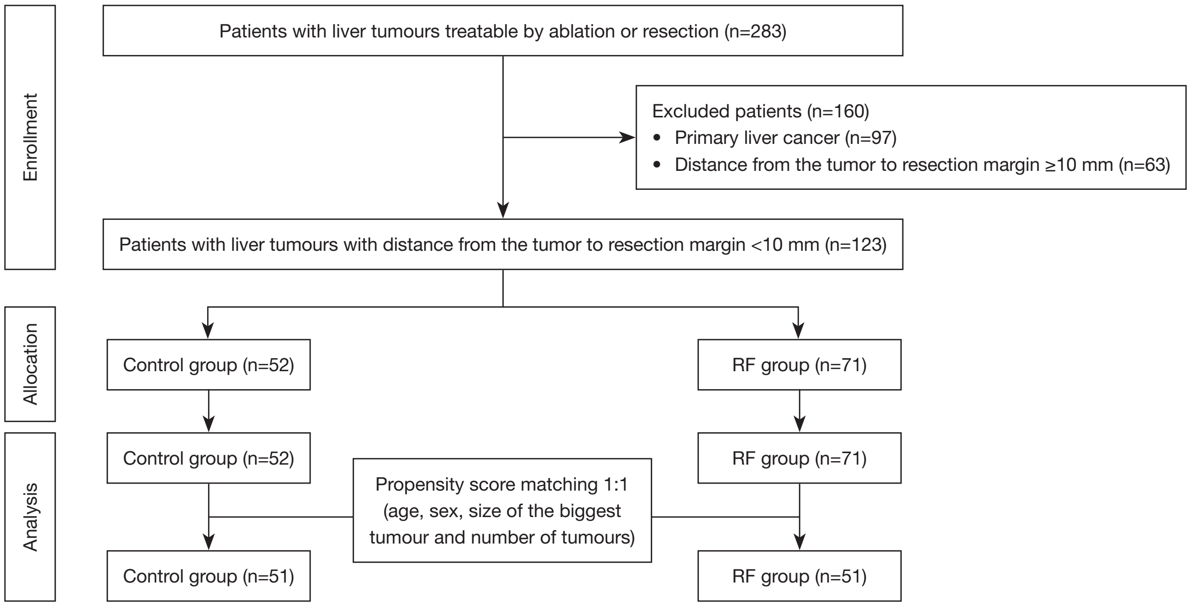


Figure 1 Flow chart of the study participants and PSM. RF, radiofrequency; PSM, propensity score matching.

surgery and then every 6 months after hospitalization with blood tests and imaging (CT scan and MRI). Data are obtained from our prospective database recorded up to September, 2020.

Main end-point is LR and secondary end-points included clinical variables, OS, and postoperative complications. LR is defined as the presence of any growing or enhancing tumour along the surgical margin or the presence of tumor cells at the surgical margin detected by microscopical final examination. Specimen-tumor margin is defined as the shortest distance from the edge of the tumor to the line of transection measured in millimetres at final pathological study. Survival are defined from the operation up to the latest follow-up. Post-operative complications are classified according to Clavien-Dindo and comprehensive complcation index (CCI) (17,18); a severe complication is defined when ≥3 was used for comparing cumulative severity complications between groups (17). Complications were recorded up to 90 days from surgery. The standard "50-50 criteria" defined the post-operative hepatic failure (19).

Statistical analysis

To balance the groups preoperative data, we used propensity score matching (PSM) to perform 1:1 matching between the two groups. The PSM system was based on logistic regression with various matching variables, including age, sex, number of tumours, size of the biggest tumour with a calliper value of 0.03. The Kolmogorov-Smirnov test is used to check the normality of the data and the Levene test for equality of variances. Categorical variables are reported as number and percentage, and continuous variables are reported as mean and standard deviation (SD) when the distribution was considered normal or using the median and interquartile range (IQR). Comparison were made through the Mann-Whitney U test or Student's *t*-test before PSM. The Wilcoxon test or Student's *t*-test is performed after PSM. Chi-square test and McNemar's test were used to compare categorical variables before and after PSM respectively.

Survival data are calculated through Kaplan-Meier, and the log-rank test is used to compare survival. Hazards ratio (HRs) with 95% confidence intervals (CI) was used to measure the association between additional margin coagulation and LR. P value lower than 0.05 is considered statistically significant. Analyses were performed with SPSS version 25.0.

Results

Patients characteristics

A total of 283 patients with liver tumors who underwent the ptectomy between September 2006 and September 2020 were evaluated (*Figure 1*). According to the inclusion

Table 1 Baseline characteristics of the patients involved in the study

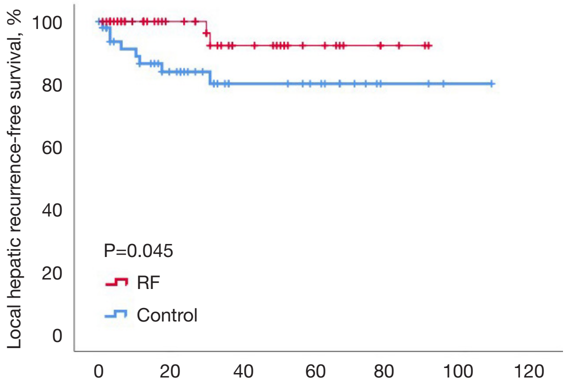
Baseline characteristics	Before propensity score-matching			After propensity score-matching		
	Control group (n=52)	RF group (n=71)	P value*	Control group (n=51)	RF group (n=51)	P value**
Male sex	33 (63.5%)	43 (60.6%)	0.744[a]	33 (32.4%)	30 (29.4%)	0.700[d]
Age (years), mean (SD)	68.4 (10.3)	66.9 (11.6)	0.437[b]	68.4 (10.4)	66.3 (11.1)	0.318[e]
Number of metastases			0.970[a]			0.261[d]
Solitary tumors	30 (57.7%)	41 (57.7%)		29 (28.4%)	28 (27.5%)	
2 to 3 tumors	15 (28.8%)	19 (26.8%)		15 (14.7%)	16 (15.7%)	
4 to 5 tumors	5 (9.6%)	7 (9.9%)		5 (4.9%)	4 (3.9%)	
≥6 tumors	2 (3.8%)	4 (5.6%)		2 (2.0%)	3 (2.9%)	
Size of the biggest tumor (cm), median (IQR)	2.9 (22.0–0.4)	2.5 (8.5–0.4)	0.236[c]	2.9 (0.4–10.0)	2.2 (0.4–8.0)	0.320[f]
Distance to resection margin			0.883[a]			0.380[d]
0 mm	20 (38.5%)	27 (38.0%)		20 (19.6%)	20 (19.6%)	
1–4 mm	20 (38.5%)	25 (35.2%)		19 (18.6%)	17 (16.7%)	
5–9 mm	12 (22.1%)	19 (26.8%)		12 (11.8%)	14 (13.7%)	
Surgical data						
Operative procedure			0.019[a]			1.000[d]
Right hepatectomy	11 (21.2%)	6 (8.5%)		10 (9.8%)	3 (2.9%)	
Left hepatectomy	2 (3.8%)	7 (9.9%)		2 (2.0%)	5 (4.9%)	
Segmentectomy/ bisegmentectomy	11 (21.2%)	6 (8.5%)		11 (10.8%)	4 (3.9%)	
Atypical resection	28 (53.8%)	49 (69.0%)		28 (27.5%)	36 (35.3%)	
Other liver resection	0 (0.0%)	3 (4.2%)		0 (0.0%)	3 (2.9%)	
Laparoscopic approach	22 (42.3%)	38 (53.5%)	0.219[a]	22 (21.6%)	26 (25.5%)	0.523[d]
Pringle maneuver (min), median (IQR)	0 (0.0–60.0)	2 (0.0–86.0)	0.203[c]	0 (0.0–60.0)	1 (0.0–83.0)	0.914[f]

Differences in variables were considered to be significant at a threshold of P<0.05. Cumulative length of Pringle maneuver (min). *, P value for the difference between Control group and RF group before propensity score-matching; [a], chi-squared test; [b], Student's *t*-test; [c], Mann-Whitney U test; **, P value for the difference between Control group and RF group after propensity score-matching; [d], McNemar test; [e], paired samples Student's *t*-test; [f], Wilcoxon test. RF, radiofrequency; SD, standard deviation; IQR, interquartile range.

and exclusion criteria, finally, 123 patients were selected (160 cases are excluded for reasons including distance from the tumor to resection margin ≥10 mm, n=63; primary liver tumor, n=97). There were 52 (42.3%) patients in the Control group and 71 (57.7%) patients in the RF group. Patient baseline and preoperative characteristics of the two groups before and after PSM are summarized in *Table 1*. All patients completed follow-up The baseline patients' characteristics before PSM showed relevant differences in surgical procedure (P=0.019) (*Table 1*). After 1:1 PSM, a total of 51 cases in both groups with similar baseline characteristics have been included (*Table 1*).

LR analysis

Regarding the primary endpoint of the study, overall 10 (9.8%) out of 102 patients developed LR, that was significantly higher in the Control group then the RF group [8 (7.84%) *vs.*



Patients at risk (censored)	Time, months						
Control group	51 (0)	30 (14)	15 (28)	11 (32)	3 (40)	1 (42)	0 (43)
RF group	51 (0)	30 (21)	17 (32)	9 (40)	3 (46)	0 (49)	0 (49)

Figure 2 Kaplan-Meier curve of local hepatic recurrence-free survival in patients with liver tumors with distance from the tumor to resection margin <10 mm. Log-rank test P=0.045. RF, radiofrequency.

2 (1.9%) patients, P=0.046]. The 1-, 3-, and 5-year LR rate were 86.5%, 83.9% and 80.1%, respectively, in the Control group and 100%, 100% and 92.3%, respectively, in the RF group (P=0.045) (*Figure 2*). The RF group was associated with reduced LR (HR =4.69; 95% CI: 0.983–22.40; P=0.053).

Postoperative outcomes and OS analysis

Th overall stay resulted lower in the RF group compared with the Control group (median, 8 *vs.* 5 days, P=0.009) (*Table 2*). The rates of general complications in terms of liver failure, bike leak or abdominal abscesses did not differ between the groups. Mortality was similar among the groups.

Twenty-three of 51 (45.1%) patients in the Control group and 10 of 51 (19.6%) in the RF group had died after a median follow-up period of 60 months. The 1-, 3-, and 5-year global cumulative OS were 93.5%, 71.5% and 37.5%, respectively, in the Control group and 95.4%, 87.4% and 67.8%, respectively, in the RF group (P=0.012).

Discussion

As involved margins are related with higher chance of recurrence, the achievement of enough resection margins for liver malignancies is one of the most important goals during liver transection (20).

After curative resection, liver represents the most frequent site for malignant recurrence for CRLM, occurring up to 50% within the first 2 years from resection (1).

As it has been defined above, margin still represent an important prognostic factor. Some decades ago, at the beginning of laparoscopic liver resection development, it has been claimed that minimally invasive approach may increase affected margin rate (1). However, with increased experience, it has been lately showed that traditional open and minimally approach entails similar pathological outcomes, but with better recovery (21).

Nevertheless, the type of approach, intraoperatively, the assessment of the required surgical margin is challenging and for this reason the rate of R1 resection rate after liver resection for CRLM can achieve a rate up to almost 30% even in experienced centers (1,2). Therefore, it is paramount for a surgeon achieve enough margins to assure a low recurrence rate after resection.

Giving this background, we analyzed in a matched-pair analysis the impact of the RF assisted liver transection on surgical margin compared with the standard technique. The findings from this study indicated that LR for the RF group is significantly lower compared with the standard technique being lower compared with the standard Control group (7.84% *vs.* 1.9%). This data is further confirmed by the higher OS of the RF group after liver resection, as it is shown in *Figure 1*. This result can be explained by the additional ablation effect of RF device used in this study.

In this study we decided to include only CRLM patients at higher risk to develop recurrence after resection, being <1 cm the selection criteria. This decision belongs from the results of a recent meta-analysis for CRLM which concluded that, whenever possible, according to previous studies, surgeons should obtain a minimum 1-cm margin along liver resection (3). Whenever a new technology is introduced, it is paramount to assess its safety and effectiveness, as well. As depicted in the *Table 2*, our results showed that the RF assisted liver transection is a safe and affective technique. Main immediate post-operative outcomes are similar in both groups.

We reckon limitations of the present study. It is a retrospective and single-center study with a relatively small sample size; therefore, the selection bias could not be entirely eliminated. However, biases after PSM assessment were minimized.

In conclusion, our results provide rationale to study the effect of RF liver transection device among CRLM patients in future prospective randomized studies.

Table 2 Mortality and morbidity in propensity score-matched patients

Complications	Control group (n=51)	RF group (n=51)	Total	P value
Morbidity	27 (52.9%)	17 (33.3%)	44 (43.1%)	0.078[a]
Abscess	11 (21.6%)	4 (7.8%)	15 (14.7%)	0.118[a]
Biliary leak	1 (2.0%)	5 (5.9%)	6 (5.9%)	0.625[a]
Hemoperitoneum	0 (0.0%)	1 (2.0%)	1 (1.0%)	1.000[a]
Liver failure	3 (6.0%)	4 (8.0%)	7 (6.9%)	1.000[a]
Wound infection	4 (7.8%)	3 (5.9%)	7 (6.9%)	1.000[a]
Pneumonia	0 (0.0%)	1 (1.0%)	1 (1.0%)	1.000[a]
Other complications	17 (33.3%)	12 (23.5%)	29 (28.4%)	0.424[a]
Blood transfusion	6 (6.0%)	4 (4.0%)	10 (9.8%)	0.754[a]
Red packed cells transfusion, median (IQR)	0 (0–7)	0 (0–4)	–	0.566[b]
Clavien-Dindo grades*				0.164[a]
No	23 (45.1%)	33 (64.7%)	17 (54.9%)	
1	5 (9.8%)	4 (7.8%)	9 (8.8%)	
2	7 (25.5%)	4 (7.8%)	11 (10.8%)	
3a	13 (39.0%)	10 (32.3%)	23 (22.5%)	
3b	1 (2.0%)	3 (5.9%)	4 (3.9%)	
4a	1 (2.0%)	1 (2.0%)	2 (2.0%)	
4b	0 (0.0%)	0 (0.0%)	0 (0.0%)	
5	1 (2.0%)	1 (2.0%)	2 (2.0%)	
CCI score, median (IQR)	8.7 (0–100)	0 (0–100)	–	0.164[b]
Reoperation*	2 (3.9%)	2 (3.9%)	4 (7.8%)	1.000[a]
Length of stay (days), median (IQR)	8 (1–31)	5 (1–49)	–	0.009[b]
90-day mortality	1 (2.0%)	1 (2.0%)	2 (2.0%)	1.000[a]

Data as absolute numbers and percentages in parenthesis unless otherwise stated. Statistical differences were considered to be significant at a threshold of $P<0.05$. [a], McNemar test; [b], Wilcoxon test; *, within 90 days. RF, radiofrequency; IQR, interquartile range; CCI, comprehensive complcation index.

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Footnote

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