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**COMBINING RADIOFREQUENCY ABLATION WITH HEPATIC RESECTION FOR  
LIVER-ONLY COLO-RECTAL METASTASES: A PROPENSITY-SCORE BASED  
ANALYSIS ON LONG-TERM OUTCOMES**

Fabio Giannone MD<sup>1,2,3</sup>, Aurélien Grollemund MD<sup>1</sup>, Emanuele Felli MD, PhD<sup>4</sup>, Theo Mayer MD<sup>5</sup>,  
Zineb Cherkaoui MD<sup>1,3</sup>, Catherine Schuster PhD<sup>2</sup>, Patrick Pessaux MD, PhD<sup>1,2,3</sup>

<sup>1</sup> Department of Visceral and Digestive Surgery, University Hospital of Strasbourg, Strasbourg, France

<sup>2</sup> Université de Strasbourg, Inserm, Institut de Recherche sur les Maladies Virales et Hépatiques, U1110, Strasbourg, France

<sup>3</sup> Institut Hospitalo-Universitaire (IHU), Institute of Image-Guided Surgery, Strasbourg, France

<sup>4</sup> Liver Transplant and Surgery Department, Trousseau Hospital, Tours, France

<sup>5</sup> Department of Radiology, University Hospital of Strasbourg, Strasbourg, France

Running Head: Prognostic role of radiofrequency ablation in colo-rectal liver metastases.

Corresponding Author:

Patrick Pessaux, MD, PhD

Department of Visceral and Digestive, Surgery, University Hospital of Strasbourg,

1, Place de L'hôpital

Nouvel Hôpital Civil

67100 Strasbourg, France

Phone number : +33 (0) 369550552

Email: [patrick.pessaux@chru-strasbourg.fr](mailto:patrick.pessaux@chru-strasbourg.fr)

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## **SYNOPSIS**

Radiofrequency ablation during liver resection for colorectal liver metastases represents a safe alternative to extensive resections with comparable long-term outcomes. Furthermore, increasing the number of simultaneous ablations does not seem to adversely affect risk of recurrence and patient survival.

## **ABSTRACT**

**Background:** Combining liver resection (LR) with radiofrequency ablation (RFA) is nowadays an accepted option to treat colorectal liver metastases (CRLM) but number of lesions ablated is regularly described as a recurrence risk factor. In this study, we report our experience and determine the impact of RFA on long-term outcomes.

**Method:** This is a retrospective study including patients undergoing LR with or without RFA for CRLM. All variables influencing disease-free survival (DFS) and disease specific survival (DSS) were examined through a Cox regression analysis before and after a propensity-score matching (PSM).

**Results:** Among the 128 patients included, 71 (55.5%) underwent LR alone and 57 (44.5%) underwent LR+RFA. At univariate analysis, LR+RFA showed a significantly worse DFS than LR alone ( $p=0.028$ ), which was not confirmed after PSM ( $p=0.064$ ). Thermal ablation did not influence DSS before and after matching ( $p=0.282$  and  $p=0.189$ ). When analyzing the subgroups of patients according to number of RFA performed, no difference in long-term outcomes was observed (after PSM:  $p=0.192$  for DFS and  $p=0.624$  for DSS). Analysis of site of recurrence revealed that neither performing a RFA ( $p=0.893$ ) nor number of lesions ablated ( $p=0.093$ ,  $p=0.550$  and  $p=0.087$  for 1, 2 and  $\geq 2$  RFA) are associated with an increased risk of liver-only relapse.

**Discussion:** In the setting of a parenchymal sparing strategy, combining RFA with LR is safe in terms of oncological outcomes. Tumor burden rather than RFA performed independently influence risk of recurrence and patient survival.

## INTRODUCTION

According to the world health organization, colorectal cancer represents today the fourth most frequent cancer and the third leading cause of tumor-related mortality.<sup>1</sup> About 22% of these cancers are metastatic at diagnosis which leads to an impaired life expectancy, with a 5-year survival dropping from 90% in case of a localized disease to approximately 15% when distant localizations are found.<sup>2</sup> Liver resection represents undoubtedly the best curative option, although colorectal liver metastases (CRLM) are resectable in a small minority of new diagnosed cases.<sup>3,4</sup> Reasons contraindicating surgery are an extensive number of hepatic lesions with an unresectable disease, an insufficient future liver remnant or an altered performance status of the patient. In most of these cases chemotherapy can be effective in reducing tumor burden, allowing a safe liver resection. Among the strategies which can further improve resection rate, radiofrequency ablation (RFA) has shown an excellent safety profile with equivalent long-term outcomes.<sup>5-7</sup> With this technique, deep lesions without major vascular or biliary contacts can be treated, avoiding extreme resections and risk of liver failure. Compared to surgical resection, the non-inferiority of RFA has been demonstrated for small solitary metastases as well as in multiple bilobar localizations in the setting of parenchymal sparing procedures.<sup>8</sup> Although significant advances have been made in this field, as more effective probes or augmented reality guidance,<sup>9</sup> some issues are still present when thermal ablation is used by the surgeon in combination with hepatic resection. Ultrasound (US), for instance, does not allow a precise tridimensional orientation and, when heat starts to spread around the needle, the effect is a local artifact which hinders peri- and post-treatment evaluation. Millimetric peripheral residual zones are likely equivalent to the surgical R1 margin and thus increase the risk of recurrence. Furthermore, in patients with high metastatic tumor burden, the surgeon could apply a parenchymal sparing policy by performing more than one RFA during the same liver resection. The number of lesions treated simultaneously during hepatectomy has been poorly studied in the literature for CRLM and oncological consequences are unknowns.

In this study we aim to compare long-term outcomes of a strictly selected and homogeneous cohort presenting CRLM treated by surgical resection with or without a concurrent RFA in a tertiary center. The number of lesions ablated during the same procedure was as well assessed and analyzed in terms of risk of recurrence and survival.

## **METHODS**

### *Study design*

This is a retrospective study. Data were collected from a prospective database maintained at our hepato-biliary and pancreatic surgery unit. Study design, data collection and analysis followed the items of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.<sup>10</sup> Patients who underwent liver surgery for CRLM between January 1<sup>st</sup>, 2014 and December 31<sup>st</sup>, 2020 were initially considered for the inclusion, with at least a FU of 12 month. Exclusion criteria were operation for liver recurrence, RFA not performed in a liver resection scenario, simultaneous extra-hepatic metastases (M1*b* according to the TNM 8<sup>th</sup> edition)<sup>11</sup>, peritoneal dissemination (M1*c*) and uncomplete two-stage liver surgery for non-oncological reasons (i.e. complications after first stage). Patients with incomplete data and lost to follow-up were as well excluded from the analysis. In our unit, indications for RFA associated with liver resection included i) initially unresectable diseases converted to resectable after chemotherapy (CT), ii) resectable hepatic diseases with an insufficient future liver remnant (FLR) by hepatic resection alone and iii) small centrohepatic lesions necessitating a major hepatectomy in debilitated patients with a poor performance status or with high anesthesiology risk. Indications were validated at the oncological multidisciplinary meeting. Tumor size was another morphological criterion for RFA feasibility, with lesions that should not exceed 20 mm in perioperative US evaluation so that they can be treated by thermal ablation. In case of proximity to first and second order porto-biliary branches or main hepatic veins RFA was contro-indicated for the risk of vascular thrombosis and extended necrosis. The whole cohort was split into two groups, a liver resection alone group (LR) and those who underwent LR combined with RFA (LR+RFA). Patients with a two-stage hepatectomy that benefit

of at least one RFA during one of the stages were included in the LR+RFA group. All clinico-pathological features were collected and compared between the two cohorts. Nodule number was estimated from lesions found in histological assessments and any putative metastasis submitted to RFA treatment. This variable was classified as binomial in less than 4 or  $\geq 4$  lesions, being this cut-off a prognostic factor for recurrence.<sup>8</sup> Largest tumor size and margin status were evaluated upon histological findings, taking into account both stages in case of two-stage hepatectomies. Similarly, peri- and post-operative features considered both surgical resections, except for type of approach and extension of hepatectomy which were exclusively related to the second stage. Post-operative complications were classified according to Clavien-Dindo classification and included 90-day morbidity and mortality.<sup>12</sup> Patients undergoing LR+RFA were further subdivided according to the number of ablations performed – in case of two-stage hepatectomies all RFA in both resections were considered – so as to identify any correlation with risk of tumor recurrence and disease-related survival. Three subgroups were thus created to include one, two or more than two concurrent thermal ablations, respectively. Follow-up included a CT-scan with CEA and CA 19-9 measurement every 3 months for the first two years and then every 6 months up to five years. Data regarding first site of recurrence were collected in all patients and classified into liver recurrence or extrahepatic/multi-metastatic relapse. This factor was then matched with the two LR and LR+RFA groups and with other main variables to assess a possible predictor of specific site recurrence.

#### *RFA technique*

RFA was performed using the Covidien (GI Solutions, Sunnyvale, CA, USA) Cool-tip RF ablation system. A 17G cool-tip electrode of 15cm in length with 2 or 3 cm active tip was placed under US guidance within the lesion, with contrast-enhancement US if necessary. The ablation started at a low intensity of 5 watts then a progressive increase in intensity was applied (5 to 10w per minute to avoid carbonation) until the maximum value was reached. At the end of the procedure, the needle was removed by cauterizing the path.

#### *Statistical analysis*

Continuous data were displayed as median with range and compared using Student's t test or Mann-Whitney U test in case of normal distribution. Categorical data were reported with relative proportions (%) with distribution between groups assessed using the  $\chi^2$  test and Yates' correction if necessary. Kaplan-Meier curves were reconstructed and survival outcomes were compared using log-rank test for categorical variables and Cox test in case of continuous data. Variables with a p-value equal or lower than 0.05 in the univariate analysis were included in the final multivariate model. A propensity-score matching (PSM) was then performed to create two homogeneous cohorts and to reduce the bias of treatment selection. Covariates used to create the new model were synchronous/metachronous metastases, number of nodules and two-stage hepatectomy. A nearest neighbor matching was applied without replacement with a ratio 1:1. Survival analysis were repeated between the two new groups. Finally, a binomial logistic regression was performed to assess the association between specific recurrence site and the most important variables, such as RFA and number of ablations performed. All tests were 2-tailed and level of significance was set at  $p < 0.05$ . All statistical computations were performed using SPSS (SPSS Statistics for Macintosh, version 26.0, IBM Corp) or R (R Project for statistical computing, version 4.2.2 for Mac, R Core Team).

## **RESULTS**

### *General features*

After exclusion of all cases that did not meet the inclusion criteria, a total of 132 patients were eligible for the analysis. **Supplementary Figure 1** shows the flow-chart of patient screening process according to the STROBE guidelines.<sup>10</sup> Three patients (2.3%) experienced disease progression at CT scan reevaluation before second stage hepatectomy and were thus excluded from the cohort. In these 3 cases the first surgery combined atypical resections and one ablation through RFA of the left liver with the perspective of a right hepatectomy. One patient (0.7%) in the LR group died after the second stage of an ALPPS for post-hepatectomy liver failure (PHLF) and was as well not considered for the analysis. Clinico-pathological features of the final cohort of 128

patients are shown in **Table 1**. Of these, in 57 cases (44.5%) liver resection was associated with RFA whereas 71 patients (55.5%) underwent hepatectomy alone. Median number of RFA was 4 (range 1-9). The two groups did not differ in terms of clinico-demographic and pathological characteristics. Concerning tumor-related features, patients in the LR+RFA group exhibited more frequent synchronous metastatic diseases (75.4%) compared to those undergoing liver resection alone (47.9%,  $p= 0.002$ ) as well as bilobar tumor distribution (73.7% vs 49.3% in the LR group,  $p= 0.009$ ). In 37 cases (64.9%) treated with surgery and thermal ablation, patient had 4 or more lesions preoperatively, which is significantly higher than in the other group (38%,  $p= 0.002$ ). **Table 2** shows peri and post-operative characteristics of the whole cohort and in the two subgroups. Two stage hepatectomies were more often performed when associating liver resection with RFA (29.8%) than with simple resection (11.3%,  $p= 0.013$ ). No significant differences were observed in the two subgroups in other peri-operative data and post-operative complications between the two groups. Of the 57 cases undergoing LR+RFA, in 29 (50.9%) a single ablation was performed, 15 (26.3%) had two RFA whereas 13 (22.8%) had more than two. A comparison of these three subgroups is given in **Supplementary Table 1**. A propensity-score matching was then performed in order to adjust the analysis to all potentially confounding variables. The new cohort included two homogeneous groups of 57 patients in terms of clinicopathological features and operative strategy (**Table 1 and Table 2**). No difference in operative time, intra-operative blood loss and post-operative morbidity were seen after statistical adjustment in this new model.

#### *Analysis of disease-free and disease specific survival*

Four patients (3.1%, two in each group) experienced systemic progression after hepatic resection in the setting of a “*liver-first*” strategy and before primary tumor surgery and were thus excluded from the survival analysis. Overall median disease-specific survival (DSS) and disease-free survival (DFS) were 69 months (95% CI: 47.3-90.7) and 13 months (95% CI: 10.8-15.2), respectively. In the whole cohort 37 patients (29.8%) died for oncological reasons and 88 (71%) experienced disease recurrence. There was no significant difference in terms of DSS between the two groups ( $p= 0.282$ )

whereas patients undergoing concurrent liver resection and RFA had a higher risk of recurrence (median DFS: 10 months, 95% CI: 8.1-11.9 vs median DFS 14 months, 95% CI: 11.2-16.8 in the resection alone group;  $p=0.028$ ) (**Figure 1A and 1B**). The same survival analysis was conducted to compare LR group and the three subgroups of simultaneous thermal ablation according to number of RFA performed. Cumulative risk of recurrence and survival were comparable among patients undergoing hepatic resection alone and in those cases with one, two or more RFA ( $p=0.096$  and  $p=0.758$ , respectively). In order to assess the prognostic role of the association of thermal ablation with standard resection in liver surgery for CRLM, univariate and multivariate analyses for DFS and DSS were conducted. By univariate analysis, beyond concurrent RFA, factors associated with a higher risk of recurrence were age ( $p=0.039$ ), synchronous or metachronous metastases ( $p=0.006$ ), preoperative chemotherapy ( $p=0.034$ ), presence of 4 or more lesions ( $p=0.002$ ), bilobar tumor distribution ( $p=0.001$ ) and two-stage liver surgery ( $p=0.038$ ) (**Table 3**). Among pathological data, margin status ( $p<0.001$ ) and presence of nodal metastases in the primary site ( $p=0.004$ ) were predictors of disease relapse. At Cox multivariate regression, LR+RFA was not confirmed as a prognostic factor of disease recurrence (HR: 1.48, 95% CI: 0.93-2.35;  $p=0.101$ ). Variables significantly associated with DFS turned out to be tumor size (HR: 1.01, 95% CI: 1-1.02;  $p=0.014$ ), presence of 4 or more CRLM (HR: 1.64, 95% CI: 1.06-2.53;  $p=0.025$ ), margin status during hepatectomy (HR: 3.31, 95% CI: 1.84-5.97;  $p<0.001$ ) and nodal spread of the disease at the primary site (respectively for N1 and N2 stage, HR: 1.92 and 2.64;  $p=0.017$  and  $p=0.004$ ). When analyzing variables associated with DSS (**Table 4**), independent predictors of survival were exclusively site of primary tumor (HR: 0.29 and HR: 0.33,  $p=0.004$  and  $p=0.013$  respectively for left colic and rectal cancer compared to right-sided locations) and RAS/RAF mutations (HR: 2.17,  $p=0.029$ ).

After PSM (**Table 3 and 4**), performing a simultaneous RFA lost his prognostic role in risk of recurrence at univariate analysis ( $p=0.064$ , **Figure 1C**) and, concomitantly, number of RFA remained non significant ( $p=0.192$ ). No modification was seen when analyzing the same

variables in terms of DSS (**Figure 1D**). In the new model, the presence of four or more nodules was no longer an independent prognostic predictor of DFS (HR:1.55, p= 0.064) whereas R status appeared significantly associated with survival (HR: 4.14, p= 0.005).

#### *Association between site of recurrence and surgical strategy*

Of the 88 patients where a disease recurrence was diagnosed during surveillance, 35 (39.8%) had a relapse localized exclusively in the liver whereas the remaining 53 cases (60.2%) presented an extrahepatic or multi-metastatic recurrence (**Table 5**). Median DFS and DSS did not differ according to the specific sites of disease recurrence (p= 0.136 and p= 0.115, respectively). When a binomial logistic regression was performed to assess the risk of extrahepatic recurrence, no significant association was observed in LR+RFA cases (RR: 1.060, 95% CI: 0.450-2.496; p= 0.893), whatever the number of RFA performed. Variables correlated with a systemic relapse were operation for metachronous liver metastasis (RR: 3.013, 95% CI: 1.159-7.836; p= 0.024) and previous primary tumor resection (RR: 4.4, 95% CI: 1.372-14.108; p= 0.013), whereas right-side primary tumor location turned out to be associated with a lower risk of extrahepatic or multi-site recurrence (RR: 0.268, 95% CI: 0.087-0.825; p= 0.022).

## **DISCUSSION**

Parenchymal-sparing hepatectomy is considered as the most appropriate method for the treatment of resectable CRLM, since it is oncologically equivalent to anatomical or major liver resections but leads to fewer postoperative complications and shorter hospital stays. Moreover, this technique does not increase the risk of recurrence in the remnant liver allowing, in case of a localized recurrence, an easier re-hepatectomy.<sup>13,14</sup> RFA represents a valid and safe alternative to liver resection in case of parenchymal-sparing strategy for CRLM. Different series have shown low complications rates and comparable oncologic results<sup>15-17</sup> and international guidelines include this option in the therapeutic algorithm to achieve a complete treatment or to provide an alternative to resection if metastases are inoperable due to patient frailty or challenging anatomical location.<sup>18</sup> However, some issues should be addressed when thermal ablation is performed by the surgeon in combination with

liver resection. The needle is placed under US guidance which lacks tridimensionality and does not always allow optimal visualization, mostly if compared to CT scan or IRM. Once the ablation is launched, its effect on liver parenchyma hinders the evaluation of the treated area. Furthermore, especially in case of high tumor burden or when lesions do not respond to chemotherapy, the risk of peripheral micro-metastases that are not destroyed by RFA is high. This leads to incomplete treatment, equivalent to a surgical positive margin. When more than one lesion is ablated, this risk is multiplied with, as a consequence, potentially impaired long-term outcomes. In this series we reviewed our surgical experience of RFA combined with liver resection for CRLM, by the analysis of a strictly selected group of patients with liver-only metastases in order to assess its prognostic value. Cases with one or more thermal ablations were included in the cohort and separately analyzed to compare recurrence and survival rates according to the number of RFA. Moreover, a propensity-score matching was performed to reduce treatment selection bias.

Most of the data supporting RFA as a curative treatment in resectable CRLM derive from low quality evidence and no prospective studies have been published yet. The EORTC-CLOCC trial, focusing on RFA plus systemic therapy, is exclusively addressed to patients with an unresectable disease.<sup>19</sup> Two interesting multicentric randomized clinical trials, the COLLISION (NCT03088150) and the HELARC (NCT02886104), are currently recruiting with the aim of comparing surgery and local ablation in terms of OS and DFS.<sup>20</sup> A recent meta-analysis found that both RFA and microwave ablation (MWA) in CRLM are superior to cryoablation with better oncological outcomes, but significantly inferior to surgical resection, which still seems to provide the best DFS and OS.<sup>21</sup> Similarly, the group of the M.D. Anderson Cancer Center concluded that RFA can provide a survival benefit over chemotherapy alone but not comparable to surgical resection, although it presented a possible selection bias.<sup>22</sup> Conversely, more recent series found that RFA is a valid option for potentially resectable hepatic diseases, with low recurrence rates and survival similar to surgery.<sup>7,15-17</sup> Our series corroborates these results, with no difference in terms of DFS and DSS between patients undergoing hepatic resection alone and those who benefit from a

simultaneous RFA. A slight significance was observed exclusively when assessing DFS, which was not confirmed by multivariate analysis and mainly after covariate adjusting by PSM.

Indications for thermal ablation in CRLM range from patients with solitary small metastases to unresectable diseases combined with systemic treatment. Recently, a meta-analysis focused on the comparison between liver resection and RFA in unique hepatic lesions, and showed that for lesions < 3cm thermal ablation and surgery result in comparable outcomes.<sup>23</sup> When the tumor burden increases and multiple thermal ablations are necessary, different concurrent variables should be considered. For instance, the Johns Hopkins group demonstrated that surgery is superior to local ablation for low tumor burden, whereas in case of four or more hepatic lesions, an already well-described negative prognostic factor,<sup>24</sup> survival curves do not significantly differ between the two groups, even with multiple ablations.<sup>8</sup> This could be explained by a higher tumor biology which “overcomes” the prognostic meaning of RFA, as it has been demonstrated that surgical margin has no impact on outcomes in high-risk patients with an aggressive disease.<sup>25,26</sup> Similarly, the development of more effective chemotherapy agents over the years could play an important role by reducing the negative effects of a possible incomplete local ablation, and thus increase oncological outcomes.<sup>27</sup> In this context, it is important to evaluate if multiple RFA can be safely performed. De Jong et al. found that this variable did not influence OS in his cohort whereas it was associated with an increased risk of recurrence, although this was not confirmed by multivariate analysis.<sup>28</sup> Our data showed that performing more than one RFA does not influence long-term outcomes, both in the whole cohort and after matching. The homogeneity of the RFA subgroups in terms of tumor burden and preoperative features can partially explain this excellent result, probably in addition to a strict patient selection. Multiple thermal ablations are generally indicated in patients with a high CRLM number and with an aggressive disease, which are probably stronger prognostic factors than performing multiple thermal ablations.

In order to better evaluate the risk of recurrence in patients with CRLM according to the selected treatment, we performed a binomial logistic regression of specific recurrence sites. Liver-only

disease relapse may result from incomplete ablation, as it happens for surgical margins. Assessing recurrence location could therefore provide more information than simple survival curves, in an era of powerful chemotherapies and extensive surgical indications regardless of tumor burden. Previous studies have already reported that simultaneous RFA is not associated with an increased risk of intrahepatic recurrence, whereas ablation of multiple lesions was associated with an increased liver-only relapse.<sup>15,28</sup> When examining our cohort, neither concomitant resection and ablation, nor multiple RFA were associated with a risk of intrahepatic recurrence.

Beyond the above mentioned strengths, this study has some limitations. Its retrospective nature definitely represents the weak point of our conclusions, although the propensity-score model partially solves this issue. Furthermore, some important variables were not always available and could thus not be integrated in the analysis, such as preoperative CEA or specific KRAS/NRAS/BRAF mutations, some of whom are notably associated with a poorer survival. It is worth noting that of the 7 patients excluded from the final survival analysis for hepatic and systemic progression, respectively between the two liver stages and before primitive resection, 6 underwent liver surgery combining resection and at least one RFA. Finally, only RFA were performed in our cohort without resorting to other types of local ablative treatments. Although this definitely represents a strength, conclusions of this study could not be applied to those cases or those groups in which other techniques as MWA or electroporation are used in combination with liver resections. In conclusion, our results confirm that hepatic resection and concomitant RFA is a well-tolerated procedure with similar long-term outcomes compared to liver resection only. Rigorous patient selection is essential when applying thermal ablation and, even in case of multiple treatments, comparable results can be achieved. Furthermore, in our cohort this procedure was not found associated with an increased risk of intrahepatic recurrence.

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## **FIGURE LEGENDS**

**Figure 1.** Kaplan-Meier curves of DFS and DSS in the two groups (liver resection alone vs liver resection + RFA) before (A and B) and after PSM (C and D).

## TABLES

**Table 1.** Clinico-pathological features of the whole cohort (n= 128) and after propensity-score matching (n=114) in the two groups

Variables	Whole cohort			After PSM		
	Liver resection n= 71	Thermal ablation + liver resection n= 57	P	Liver resection n= 57	Thermal ablation + liver resection n= 57	P
	n (%)			n (%)		
Median Age, yrs (range)	64 (26-84)	64.5 (34-84)	0.920	63 (26-84)	64.5 (34-84)	0.781
Gender						
Male	45 (63.4)	39 (68.4)	0.551	35 (61.4)	39 (68.4)	0.556
Female	26 (36.6)	18 (31.6)		22 (38.6)	18 (31.6)	
Median BMI, kg/m <sup>2</sup> (range)	25.4 (18-37.9)	24.9 (14.9-42.3)	0.640	25.4 (18-37.9)	24.9 (14.9-42.3)	0.564
ASA						
I	6 (8.5)	7 (12.3)	0.721	4 (7)	7 (12.3)	0.591
II	37 (52.1)	30 (52.6)		30 (52.6)	30 (52.6)	
III	27 (38)	20 (35.1)		22 (38.6)	20 (35.1)	
IV	1 (1.4)	-		1 (1.8)	-	
Status at diagnosis						
Synchronous	34 (47.9)	43 (75.4)	<b>0.002</b>	34 (59.6)	43 (75.4)	0.110
Metachronous	37 (52.1)	14 (24.6)		23 (40.4)	14 (24.6)	
Site of primary tumor						
Right colon	14 (19.7)	17 (29.8)	0.119	10 (17.5)	17 (29.8)	0.139
Transverse colon	1 (1.4)	3 (5.3)		1 (1.8)	3 (5.3)	
Left colon	36 (50.7)	18 (31.6)		29 (50.9)	18 (31.6)	
Rectum	20 (28.2)	19 (33.3)		17 (29.8)	19 (33.3)	
Previous primary tumor resection						
No	13 (18.3)	14 (24.6)	0.389	13 (22.8)	14 (24.6)	1
Yes	58 (81.7)	43 (75.4)		44 (77.2)	43 (75.4)	
Preoperative Chemotherapy						
No	13 (18.3)	6 (10.5)	0.218	7 (12.3)	6 (10.5)	1
Yes	58 (81.7)	51 (89.5)		50 (87.7)	51 (89.5)	
Number of nodules						
<4	44 (62)	20 (35.1)	<b>0.002</b>	30 (52.6)	20 (35.1)	0.089
≥4	27 (38)	37 (64.9)		27 (47.4)	37 (64.9)	
Distribution						
Unilobar	36 (50.7)	15 (26.3)	<b>0.009</b>	25 (43.9)	15 (26.3)	0.077
Bilobar	35 (49.3)	42 (73.7)		32 (56.1)	42 (73.7)	
Tumor size (largest, mm), median (range)	30 (10-90)	24 (1-95)	0.123	31 (10-90)	24 (1-95)	0.074
R status						
R0	64 (90.1)	47 (82.5)	0.203	51 (89.5)	47 (82.5)	0.419
R1	7 (9.9)	10 (17.5)		6 (10.5)	10 (17.5)	
Primary T status						
0	3 (4.2)	-	0.131	3 (5.3)	-	0.274
1	3 (4.2)	1 (1.8)		1 (1.8)	1 (1.8)	
2	13 (18.3)	4 (7)		9 (15.8)	4 (7)	
3	41 (57.7)	38 (66.7)		34 (59.6)	33 (66.7)	
4	10 (14.1)	11 (19.3)		9 (15.8)	11 (19.3)	
Primary not resected	1 (1.4)	3 (5.3)		1 (1.8)	3 (5.3)	
Primary N status						

0	29 (40.8)	16 (28.1)	0.301	23 (40.4)	16 (28.1)	0.454
1	24 (33.8)	20 (35.1)		17 (29.8)	20 (35.1)	
2	17 (23.9)	18 (31.6)		16 (28.1)	18 (31.6)	
Primary not resected	1 (1.4)	3 (5.3)		1 (1.8)	3 (5.3)	
RAS/RAF mutational status						
Wild-type	49 (69)	36 (63.2)	0.486	40 (70.2)	36 (63.2)	0.551
Mutant	22 (31)	21 (36.8)		17 (29.8)	21 (36.8)	

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*PSM: Propensity-score matching; BMI: Body Mass Index; ASA: American Society of Anesthesiologists.*

**Table 2.** Peri- and post-operative features of the whole cohort (n= 128) and after propensity-score matching (n=114) in the two groups.

Variables	Whole cohort			After PSM		
	Liver resection n= 71	Thermal ablation + liver resection n= 57	P	Liver resection n= 57	Thermal ablation + liver resection n= 57	P
	n (%)			n (%)		
Approach						
Open	50 (70.4)	47 (82.5)	0.240	41 (71.9)	47 (82.5)	0.401
MI	21 (29.6)	10 (17.5)		16 (28.1)	10 (17.5)	
Anatomic Resection						
No	34 (47.9)	35 (61.4)	0.155	28 (49.1)	35 (61.4)	0.187
Yes	37 (52.1)	22 (38.6)		29 (50.9)	22 (38.6)	
Extension of hepatectomy						
Minor	39 (54.9)	33 (57.9)	0.858	28 (49.1)	33 (57.8)	0.348
Major	32 (45.1)	24 (42.1)		29 (50.9)	24 (42.1)	
Two-stage hepatectomy						
No	63 (88.7)	40 (70.2)	<b>0.013</b>	49 (86)	40 (70.2)	0.070
Yes	8 (11.3)	17 (29.8)		8 (14)	17 (29.8)	
Blood loss, ml (range)	225 (0-1700)	200 (0-1000)	0.262	250 (0-1500)	200 (0-1000)	0.627
Operative time, min (range)	240 (31-600)	250 (60-600)	0.740	240 (31-600)	250 (60-600)	0.432
Biliary leak						
No	67 (94.4)	56 (98.2)	0.380	53 (93)	56 (98.2)	0.360
Yes	4 (5.6)	1 (1.8)		4 (7)	1 (1.8)	
Liver Failure						
No	69 (97.2)	54 (94.7)	0.655	55 (96.5)	54 (94.7)	1
Yes	2 (2.8)	3 (5.3)		2 (3.5)	3 (5.3)	
Liver Hemorrhage						
No	70 (98.6)	56 (98.2)	1	57 (100)	56 (98.2)	1
Yes	1 (1.4)	1 (1.8)		-	1 (1.8)	
Clavien-Dindo >2						
No	59 (83.1)	52 (91.2)	0.201	47 (82.5)	52 (91.2)	0.268
Yes	12 (16.9)	5 (8.8)		10 (17.5)	5 (8.8)	

PSM: Propensity-score matching; MI: Minimally-invasive.

**Table 3.** Univariate and Multivariate Cox Regression Analysis of Prognostic Factors for Disease-Free Survival before and after Propensity-Score Matching

Variable	Category	Whole cohort		After PSM	
		Hazard Ratio (95% CI)	P	Hazard Ratio (95% CI)	P
<i>Univariate Analysis</i>					
Age	Continuous data	0.98 (0.97-1)	<b>0.039</b>	0.98 (0.97-1)	0.074
Gender	Female vs Male	0.86 (0.56-1.34)	0.504	0.88 (0.56-1.38)	0.563
BMI	Continuous data	0.99 (0.94-1.04)	0.655	0.98 (0.93-1.03)	0.504
ASA	II vs I	1.18 (0.14-9.6)	0.657	1.35 (0.61-3.01)	0.662
	III-IV vs I	1.76 (0.24-12.9)		1.06 (0.47-2.44)	
Status at diagnosis	Metachronous vs synchronous	0.55 (0.36-0.86)	<b>0.006</b>	0.57 (0.36-0.93)	<b>0.018</b>
Site of primary tumor	Transverse vs right colon	2.47 (0.73-8.35)	0.107	2.2 (0.64-7.49)	0.212
	Left vs right colon	0.78 (0.47-1.3)		0.89 (0.52-1.51)	
	Rectum vs right colon	0.68 (0.38-1.19)		0.66 (0.37-1.2)	
Previous primary tumor resection	Yes vs No	0.94 (0.55-1.63)	0.831	0.82 (0.5-1.36)	0.437
Preoperative Chemotherapy	Yes vs No	1.98 (1.02-3.83)	<b>0.034</b>	1.73 (0.83-3.6)	0.126
Number of nodules	≥4 vs <4	1.89 (1.23-2.88)	<b>0.002</b>	1.82 (1.16-2.86)	<b>0.006</b>
Distribution	Bilobar vs unilobar	1.96 (1.27-3.01)	<b>0.001</b>	1.83 (1.15-2.91)	<b>0.007</b>
Tumor size (largest, mm)	Continuous data	1.01 (1-1.02)	<b>0.017</b>	1.01 (1-1.02)	<b>0.047</b>
RFA performed	Yes vs No	1.58 (1.03-2.4)	<b>0.028</b>	1.49 (0.96-2.32)	0.064
Number of RFA	1 vs 0	1.48 (0.88-2.48)	0.096	1.41 (0.83-2.4)	0.192
	2 vs 0	1.45 (0.77-2.76)		1.37 (0.72-2.63)	
	≥2 vs 0	2.21 (1.04-4.7)		2.07 (0.97-4.46)	
Two-stage hepatectomy	Yes vs No	1.72 (1.01-2.93)	<b>0.038</b>	1.63 (0.95-2.8)	0.065
R status	R1 vs R0	3.84 (2.17-6.82)	<b>&lt;0.001</b>	5.15 (2.75-9.65)	<b>&lt;0.001</b>
Severe post-operative complications (CD ≥2)	Yes vs No	0.87 (0.65-1.16)	0.330	1.07 (0.58-1.97)	0.825
ypT (TNM, 8th ed.)	2 vs 1/CR	0.83 (0.28-2.43)	0.092	0.9 (0.28-2.86)	0.463
	3 vs 1/CR	1.44 (0.57-3.61)		1 (0.36-2.77)	
	4 vs 1/CR	2.15 (0.79-5.85)		1.52 (0.51-4.53)	
ypN (TNM, 8th ed.)	1 vs 0	1.77 (1.06-2.98)	<b>0.004</b>	1.98 (1.14-3.45)	<b>0.007</b>
	2 vs 0	2.41 (1.39-4.16)		2.44 (1.38-4.33)	
RAS/RAF mutational status	Mutant vs Wild-type	1.22 (0.79-1.88)	0.355	1.4 (0.89-2.21)	0.131
<i>Multivariate Analysis</i>					
Age	Continuous data	1 (0.98-1.02)	0.744	-	-
Status at diagnosis	Metachronous vs synchronous	0.73 (0.45-1.18)	0.200	0.71 (0.43-1.18)	0.187
Preoperative Chemotherapy	Yes vs No	1.1 (0.52-2.3)	0.807	-	-
Number of nodules	≥4 vs <4	1.64 (1.06-2.53)	<b>0.025</b>	1.55 (0.97-2.45)	0.064
Distribution	Bilobar vs unilobar	1.11 (0.61-2.02)	<b>0.731</b>	1.02 (0.54-1.9)	0.958
Tumor size (largest, mm)	Continuous data	1.01 (1-1.02)	<b>0.014</b>	1.01 (1-1.02)	<b>0.038</b>
RFA performed	Yes vs No	1.48 (0.93-2.35)	0.101	-	-
Two-stage hepatectomy	Yes vs No	1.03 (0.51-2.08)	0.925	-	-
R status	R1 vs R0	3.31 (1.84-5.97)	<b>&lt;0.001</b>	3.63 (1.91-6.89)	<b>&lt;0.001</b>
ypN (TNM, 8th ed.)	1 vs 0	1.92 (1.12-3.26)	<b>0.017</b>	1.95 (1.09-3.48)	<b>0.024</b>
	2 vs 0	2.64 (1.3-3.94)	<b>0.004</b>	2.23 (1.25-3.99)	<b>0.007</b>

PSM: Propensity-score matching; BMI: Body Mass Index; ASA: American Society of Anesthesiologists; RFA: Radiofrequency Ablation; CD: Clavien-Dindo.

**Table 4.** Univariate and Multivariate Cox Regression Analysis of Prognostic Factors for Disease Specific Survival before and after PSM

Variable	Category	Whole cohort		After PSM	
		Hazard Ratio (95% CI)	P	Hazard Ratio (95% CI)	P
<i>Univariate Analysis</i>					
Age	Continuous data	0.99 (0.97-1.02)	0.652	0.99 (0.96-1.02)	0.418
Gender	Female vs Male	0.56 (0.27-1.2)	0.131	0.62 (0.28-1.38)	0.240
BMI	Continuous data	0.99 (0.91-1.07)	0.777	0.98 (0.9-1.07)	0.727
ASA	II vs I	1.78 (0.53-5.94)	0.418	2.43 (0.57-10.38)	0.204
	III-IV vs I	1.19 (0.33-4.28)		1.34 (0.29-6.2)	
Status at diagnosis	Metachronous vs synchronous	0.79 (0.41-1.54)	0.491	0.69 (0.32-1.46)	0.322
Site of primary tumor	Transverse vs right colon	1.34 (0.31-5.91)	<b>0.005</b>	1.3 (0.29-5.75)	<b>0.003</b>
	Left vs right colon	0.25 (0.11-0.57)		0.2 (0.08-0.49)	
	Rectum vs right colon	0.4 (0.17-0.93)		0.39 (0.16-0.93)	
Previous primary tumor resection	Yes vs No	0.92 (0.36-2.34)	0.865	0.87 (0.33-2.27)	0.776
Preoperative Chemotherapy	Yes vs No	0.93 (0.41-2.13)	0.869	0.97 (0.37-2.53)	0.950
Number of nodules	≥4 vs <4	1.59 (0.83-3.03)	0.157	1.82 (0.9-3.71)	0.091
Distribution	Bilobar vs unilobar	2.25 (1.13-4.47)	<b>0.017</b>	2.28 (1.06-4.88)	<b>0.029</b>
Tumor size (largest, mm)	Continuous data	1.01 (1-1.02)	0.142	1.01 (0.99-1.02)	0.278
RFA performed	Yes vs No	1.42 (0.74-2.71)	0.282	1.6 (0.79-3.24)	0.189
Number of RFA	1 vs 0	1.4 (0.63-3.12)	0.758	1.58 (0.67-3.72)	0.624
	2 vs 0	1.39 (0.58-3.35)		1.56 (0.62-3.92)	
	≥2 vs 0	1.57 (0.46-5.35)		1.73 (0.49-6.12)	
Two-stage hepatectomy	Yes vs No	2.51 (1.16-5.42)	<b>0.015</b>	2.74 (1.23-6.1)	<b>0.010</b>
R status	R1 vs R0	2.32 (0.96-5.65)	<b>0.049</b>	2.87 (1.16-7.12)	<b>0.017</b>
Severe post-operative complications (CD ≥2)	Yes vs No	0.78 (0.53-1.14)	0.191	0.87 (0.6-1.32)	0.504
ypT (TNM, 8th ed.)	2 vs 1/CR	0.47 (0.8-2.8)	0.369	0.23 (0.04-1.39)	0.186
	3 vs 1/CR	1.04 (0.25-4.4)		0.35 (0.08-1.52)	
	4 vs 1/CR	1.6 (0.33-7.79)		0.69 (0.14-3.38)	
ypN (TNM, 8th ed.)	1 vs 0	1.68 (0.76-3.7)	0.356	1.86 (0.77-4.48)	0.276
	2 vs 0	1.74 (0.74-4.09)		2 (0.8-4.97)	
RAS/RAF mutational status	Mutant vs Wild-type	1.94 (1-3.75)	<b>0.045</b>	2.37 (1.17-4.8)	<b>0.013</b>
<i>Multivariate Analysis</i>					
Site of primary tumor	Transverse vs right colon	2.1 (0.46-9.51)	0.338	2.24 (0.48-10.42)	0.305
	Left vs right colon	0.29 (0.13-0.67)	<b>0.003</b>	0.21 (0.08-0.53)	<b>0.001</b>
	Rectum vs right colon	0.4 (0.17-0.95)	<b>0.038</b>	0.37 (0.15-0.9)	<b>0.030</b>
Distribution	Bilobar vs unilobar	1.83 (0.89-3.74)	0.099	1.52 (0.66-3.52)	0.329
Two-stage hepatectomy	Yes vs No	1.75 (0.72-4.27)	0.218	2.14 (0.87-5.27)	0.098
R status	R1 vs R0	2.53 (0.96-6.65)	0.060	4.14 (1.55-11.04)	<b>0.005</b>
RAS/RAF mutational status	Mutant vs Wild-type	2.17 (1.08-4.35)	<b>0.029</b>	2.75 (1.28-5.89)	<b>0.009</b>

PSM: Propensity-score matching; BMI: Body Mass Index; ASA: American Society of Anesthesiologists; RFA: Radiofrequency Ablation; CD: Clavien-Dindo.

**Table 5.** Binomial logistic regression of factors associated with specific-site recurrence (hepatic-only vs extrahepatic/multimetastatic)

Variables	Category	Median months (95% CI)	<i>P</i>	
Median DFS	Liver vs Extrahepatic/multi-site	7 (5.22-8.78) vs 9 (7.41-10.58)	0.136	
Median DSS	Liver vs Extrahepatic/multi-site	Not reached vs 52 (38.3-65.69)	0.115	
		<b>Relative Risk</b>	<b>(95% CI)</b>	<b><i>P</i></b>
Number of nodules	≥4 vs <4	0.569	0.238-1.361	0.205
Site of primary tumor	Transverse vs right colon	-	-	-
	Left vs right colon	0.268	0.087-0.825	<b>0.022</b>
	Rectum vs right colon	0.491	0.142-1.702	0.262
Preoperative Chemotherapy	Yes vs No	1.011	0.264-3.875	0.988
Status at diagnosis	Metachronous vs synchronous	3.013	1.159-7.836	<b>0.024</b>
Previous primary tumor resection	Yes vs No	4.400	1.372 – 14.108	<b>0.013</b>
RFA performed	Yes vs No	1.060	0.450-2.496	0.893
Number of RFA	1 vs 0	2.884	0.839-9.918	0.093
	2 vs 0	0.679	0.190-2.423	0.550
	≥2 vs 0	0.226	0.041-1.242	0.087
R status	R1 vs R0	0.711	0.232-2.177	0.550
RAS/RAF mutational status	Yes vs No	0.698	0.284-1.720	0.435

*DFS: Disease-Free Survival; DSS: Disease Specific Survival; RFA: Radiofrequency Ablation.*