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The impact of additional margin coagulation with radiofrequency in liver resections with subcentimetric margin: can we improve the oncological results? A propensity score matching study

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ABSTRACT

Background: Whereas the usefulness of radiofrequency (RF) energy as haemostatic method in liver surgery has become well established in the last decades, its intentional application on resection margins with the aim of reducing local recurrence is still debatable. Our goal was to compare the impact of an additional application of RF energy on the top of the resection surface, namely additional margin coagulation (AMC), on local recurrence (LR) when subjected to a subcentimeter margin.

Methods: We retrospectively analyzed 185 patients out of a whole cohort of 283 patients who underwent radical hepatic resection with subcentimetric margin. After propensity score adjustment, patients were classified into two balanced groups according to whether RF was applied or not.

Results: No significant differences were observed within groups in baseline characteristics after PSM adjustment. The LR rate was significantly higher in the Control than AMC Group: 12 patients (14.5%) vs. 4 patients (4.8%) ($p = 0.039$). The estimated 1, 3, and 5-year LR-free survival rates of patients in the Control and AMC Group were: 93.5%, 86.0%, 81.0% and 98.8%, 97.2%, 91.9%, respectively ($p = 0.049$). Univariate Cox analyses indicated that the use of the RF applicator was significantly associated with lower LR (HR = 0.29, 95% confidence interval 0.093–0.906, $p = 0.033$). The Control Group showed smaller coagulation widths than the AMC group ($p < 0.001$).

Conclusions: An additional application of RF on the top of the resection surface is associated with less local hepatic recurrence than the use of conventional techniques.

Introduction

Liver resection remains the standard for the curative treatment of most primary and metastatic liver tumors. As the presence of positive margins in the remaining liver after surgical resection is known to be a significant factor correlated with both local recurrence and overall survival [1], surgical margin width often raises concern in surgeons, as being the only factor in which prognosis might be influenced by surgical performance.

Whilst the “1 cm rule” has for some time been considered the state of the art for R0 liver resections [2], some authors advocate accepting the subcentimetric non-positive resection margin (included < 1 mm) as R0. Nowadays, the width of a negative R status is still debatable, varying greatly from one publication to another so that the surgical outcomes yielded in these studies are biased by the lack of a generally agreed definition [3]. It seems

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logical to accept that margin width is directly correlated with the risk of suffering a local recurrence [4] but it might be overly simplistic to assume that an R1 resection is the only factor involved in the patients' overall survival rate, since parameters such as tumour burden and synchronicity are also meant to be independent predictors of poor survival [5–9]. In this context, it seems pretty clear that achieving a >1 cm margin is desirable and should be attempted if possible, as it may produce better oncologic outcomes. However, the optimal width of a subcentimeter margin (0–9 mm), as long as it is negative, is still unclear [1,2,5].

From a practical point of view, since the larger the margin width achieved the better, efforts should be focused on widening the margin but in no case should a doubtful preoperative R0 status preclude a liver resection, if at all feasible. Classical liver transection techniques such as Kelly clamp-crash and suture ligation provide good control of intrahepatic vessels but do little to improve the margin width. However, for the last two decades, hepatobiliary surgeons have increasingly used energy-based sealing systems and haemostatic devices that represent not only an advance in bloodless liver resections [10–12] but also influence oncological outcomes by creating a substantial zone of thermally coagulated tissue at the transection line of the remnant liver [11–13]. Many of the currently employed energy-based systems claim to ablate and increase the tumour-free margin from 2 to 9 mm, based on animal studies [12,14], and have thus shown an effect on local recurrence [6,11]. However none has measured how the depth of the RF coagulation area induced in the remnant liver impacts on local hepatic recurrence in a bias-controlled study. We therefore designed a propensity score matched study to assess the effect of the additional margin coagulation (AMC) on local hepatic recurrence in patients undergoing liver resection, in which the margin width in the pathological specimen was less than 10 mm.

Materials and methods

Study design

A propensity score matched retrospective study was conducted at the tertiary care Hospital del Mar in Barcelona (Spain) after previously obtaining Clinical Research and Ethics Committee approval (Ref: 2020–9397) and following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline [7].

Patient eligibility and data collection

From September 2006 to February 2020, all consecutive patients who presented liver tumors eligible for curative treatment were assessed and discussed at a multidisciplinary tumour board for liver cancer. All the clinical data were obtained from the electronic medical records and checked for completeness by two investigators. Inclusion criteria were:1) age 18 years or older, and 2) diagnosis of hepatocellular carcinoma (HCC), colorectal liver metastases (CLM), intrahepatic cholangiocarcinoma and other liver metastases such as neuroendocrine metastases and gastrointestinal stromal tumour metastases. Patients with a diagnosis of gallbladder adenocarcinoma, perihilar cholangiocarcinoma, sarcoma or cystic tumors were excluded from the analysis, as were all those treated by percutaneous tumour ablation. All the surgical procedures were performed by the same surgeons (F.B., I.P. and P.S.V).

Inclusion criteria considered only patients with a margin width <10 mm. In this subset of patients two study groups were differentiated according to how haemostasis was achieved, using either conventional haemostatic devices (Control Group), or by creating an additional coagulation area by means of an RF-based device (AMC Group) (see Fig. 1). In both groups parenchymal transection was performed with standard devices such as CUSA (Cavitron, Stanford, CT, USA), stapler transection or Ligasure (Valleylab, Boulder, CO, USA) using when possible, parenchyma sparing techniques. Haemostasis was achieved in the Control Group with a combination of stitches, monopolar or bipolar perfused forceps and Ligasure, including sutures or clips. This RF-based device was specifically used to get haemostasis and was selected according to the surgeon preferences and/or availability of the system. In the AMC group, haemostasis was performed with the Coolinside device (initially marketed by Apeiron Medical, Valencia, Spain and lastly by Vecmedical, Montcada i Reixac, Barcelona, Spain under the trademark Coolingbis) whose operating performance has been described in detail elsewhere [8,9,15]. After the completion of liver resection in the AMC Group, RF energy was again used to treat the entire surface for haemostasis to ensure that no bleeding spots were overlooked and to increase the safety margin width (up to 1 cm).

Primary and secondary outcome indicators

The primary endpoint was local recurrence (LR) was defined any growing or enhancing tumour in the margin of hepatic resection specifically reviewed to this aim in a later follow-up imaging [16].

Secondary end-points included disease free survival (DFS), and postoperative complications. The surgical resection margin was defined as the minimum width between the transection plane and tumour measured in millimeters and was evaluated in the histopathological samples in all cases. The total number of nodules was determined by the histopathological study of the liver specimen.

Postoperative morbidity and mortality were graded by Clavien-Dindo classification [17,18]; a minor complication was defined as Clavien-Dindo ≤ 2 and major complication as Clavien-Dindo ≥ 3. The Comprehensive Complication Index (CCI) [18] was used to assess the burden of all combined postoperative complications. All surgery-related complications were recorded at 90 days. Index complications after hepatectomy such as postoperative hepatic failure was defined according to the "50-50 Criteria" on postoperative day 5 [19]. Biliary fistula was defined as total bilirubin level in drainage >3 times the level in serum or bile accumulation in the abdominal cavity [20]. Postoperative mortality was defined as those occurring within 90 days of surgery.

After discharge, all the patients followed a clinical follow-up together with liver imaging within 4–12 weeks after surgery and either an abdominal computed tomography (CT) or magnetic resonance imaging (MRI) was performed every 3 months after surgery in the first year and every 6 months in the second year, according to the standard oncological surveillance protocols of each tumour type.

Measure of AMC size on CT images

Triphasic abdominal CT was performed to define the AMC size within 4–12 weeks after surgery. All measurements were based on the images of the portal venous phase and the measured AMC following the recommendations of MacGahan et al. [21] on studying the coagulation margin after hepatectomy by these new liver transection systems. The AMC was semi-automatically delineated on a representative slice (largest diameter at the approximate midpoint of the attenuation area on the resection surface [21]) from each hepatectomy using the Volume Viewer Software of the Advantage Window workstation (GE Healthcare, Milwaukee, WI, USA). According to this method, any partial or segmental area of necrotic tissue usually found in segmental ischemia is usually

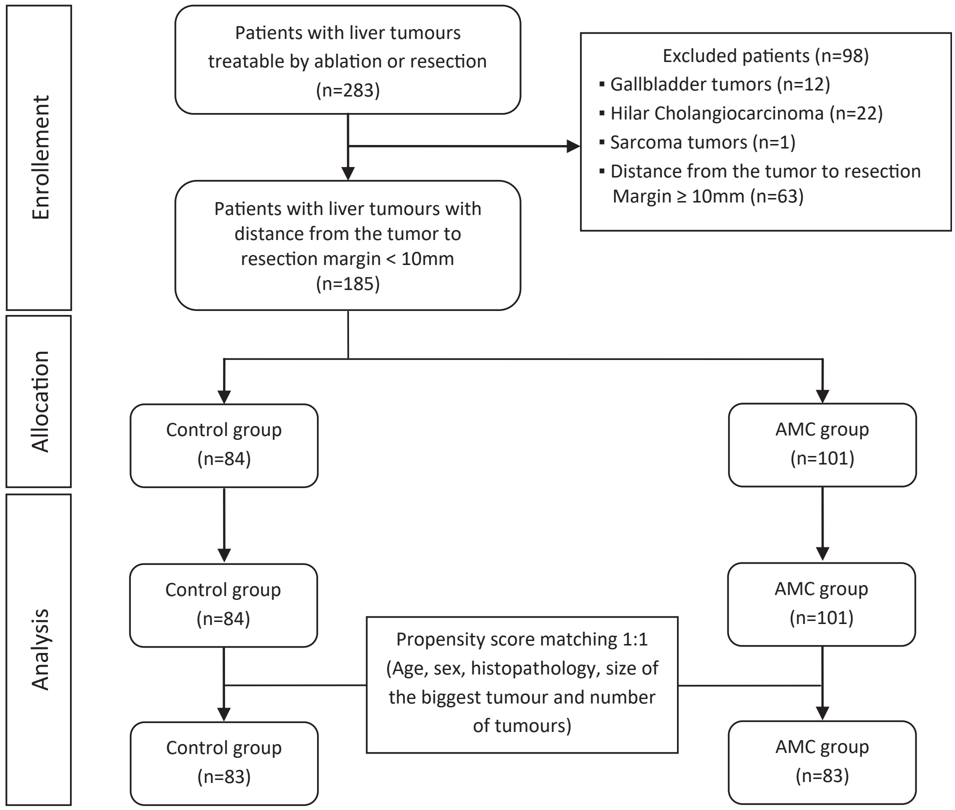

Fig. 1. Flow chart of the study participants and propensity score matching.

recognized, dismissed and not considered in the measurements. This assessment was performed by a consensus of three authors and visually reviewed by an experienced radiologist with more than 10 years of experience in abdominal radiology to ensure the appropriateness of the measurements.

Statistical analysis. Propensity score matching

To balance the baseline clinical variables and control the confounder bias, a propensity score matching (PSM) was applied between groups according to the recommendations by Lonjon et al. who stated that the PSM analysis could produce estimates less biased, more robust and more precise than with multivariate analysis [22]. A set of covariates was selected to estimate the PSM: age, sex, number of tumors, size of the biggest tumour and histological cancer types. Groups were matched in a ratio of 1:1 without replacement. The PSM was calculated using logistic regression and the patients in the AMC Group were matched with those in the Control Group using the nearest neighbour technique with a predefined calliper of 0.3.

The Kolmogorov–Smirnov test was used to check the normality of the data and the Levene test for equality of variances. Continuous variables were expressed as mean and standard deviation (SD) when the distribution was considered normal, and otherwise using the median and interquartile range (IQR). Categorical variables were expressed as absolute numbers and percentages. Baseline continuous variables between groups were analyzed using the Mann–Whitney *U* test or Student's *t*-test before PSM, while the Wilcoxon rank-sum test or paired Student's *t*-test was performed after PSM, depending on the conditions of application. Categorical variables were analyzed using Chi-square test before PSM and McNemar's test after PSM.

LR free-survival and OS were calculated using the Kaplan-Meier method. Differences between groups in LR and OS were tested with the Log-rank test. Hazards ratio (HRs) with 95% confidence intervals was used to measure the association between additional margin coagulation and LR. Univariate Cox regression analyses were used to evaluate the association between LR and age, sex, additional margin coagulation, tumour histology, size of the biggest tumour, number of tumors and distance from the tumour to the resection margin. All the analyses were two-sided, and significance was set at $p < 0.05$. The statistical analysis was carried out on IBM SPSS Statistics for Windows (Version 25.0, IBM, Armonk, NY, USA).

Results

Baseline characteristics

A total of 283 consecutive patients who underwent radical hepatic resection for liver malignancies were retrospectively included from a prospective database and assessed for eligibility for the study (Fig. 1). Ninety eight of the 283 patients did not fulfil the inclusion criteria: 35 (12%) due to a diagnosis other than HCC, CLM or intrahepatic cholangiocarcinoma, and 63 (22%) had a tumour-to-resection margin ≥10 mm. The remaining 185 patients were allocated to the control (n = 84, 45.4%) and AMC groups (n = 101, 54.6%). The final 83 pairs of patients were matched and compared after the propensity score analysis.

Baseline patient demographics before PSM showed significant differences in the operative procedure ($p = 0.037$) and laparoscopic approach ($p = 0.022$) (Table 1). After propensity score-matching, none of these factors differed between the groups, indicating that

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

Baseline Characteristics	Before propensity score-matching			After propensity score-matching		
	Control group (n = 84)	AMC group (n = 101)	P value*	Control group (n = 83)	AMC group (n = 83)	P value**
Male sex	51 (60.7%)	72 (71.3%)	0.129[a]	51 (61.4%)	56 (67.5%)	0.532[d]
Age (years), mean (SD)	67.1 (10.5)	66.7 (11.4)	0.785[b]	67.1 (10.6)	67.7 (10.9)	0.698[e]
Histological cancer types						
Colorectal liver metastases	52 (62%)	65 (64.4%)	0.672[a]	51 (61.5%)	57 (68.7%)	0.447[d]
Hepatocellular carcinoma	19 (22.6%)	17 (16.8%)		19 (22.9%)	14 (16.9%)	
Hilar Cholangiocarcinoma	6 (7.1%)	11 (10.9%)		6 (7.2%)	7 (8.4%)	
Other liver metastases	7 (8.3%)	8 (7.9%)		7 (8.4%)	5 (6.0%)	
Number of metastases						
Solitary tumors	52 (61.9%)	63 (62.4%)	0.915[a]	51 (61.4%)	49 (59.1%)	0.672[d]
2 to 3 tumors	20 (23.8%)	25 (24.8%)		20 (24.2%)	22 (26.5%)	
4 to 5 tumors	8 (9.5%)	7 (6.9%)		8 (9.6%)	6 (7.2%)	
≥ 6 tumors	4 (4.8%)	6 (5.9%)		4 (4.8%)	6 (7.2%)	
Size of the biggest tumour (cm), median (IQR)	3 (2.3–5.0)	3 (1.9–5.0)	0.212[c]	3 (2.3–5.0)	3 (1.7–5.0)	0.209[f]
Distance to resection margin (mm)						
0 mm	28 (33.7%)	45 (44.6%)	0.287[a]	28 (34.1%)	33 (39.8%)	0.768[d]
1–4 mm	36 (43.4%)	34 (33.7%)		35 (42.7%)	29 (34.9%)	
5–9 mm	19 (22.9%)	22 (21.7%)		19 (23.2%)	21 (25.3%)	
Surgical data						
Operative procedure						
Right hepatectomy	17 (20.2%)	7 (6.9%)	**0.037**[a]	16 (19.3%)	6 (7.2%)	0.227[d]
Left hepatectomy	7 (8.3%)	10 (9.9%)		7 (8.4%)	6 (7.2%)	
Segmentectomy/Bisegmentectomy	17 (20.2%)	14 (13.9%)		17 (20.5%)	12 (14.5%)	
Atypical resection	42 (50.1%)	67 (66.3%)		42 (50.6%)	56 (67.5%)	
Other liver resection	1 (1.2%)	3 (3.0%)		1 (1.2%)	3 (3.6%)	
Laparoscopic approach	34 (40.5%)	58 (57.4%)	**0.022**[a]	34 (41.0%)	43 (51.8%)	0.137[d]
Pringle maneuver (min), median (IQR)	0 (0.0–14.3)	0 (0.0–10.8)	0.743[c]	0 (0.0–14.5)	0 (0.0–12.0)	0.907[f]

AMC additional margin coagulation, IQR interquartile range, SD standard deviation.
*P- value for the difference between Control group and AMC 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 AMC group after propensity score-matching. d:McNemar test; e: Paired Samples Student's *t*-test; f: Wilcoxon test.
Differences in variables were considered to be significant at a threshold of $P < 0.05$. Bold values indicate statistically significant.
Cumulative length of Pringle maneuver (min).

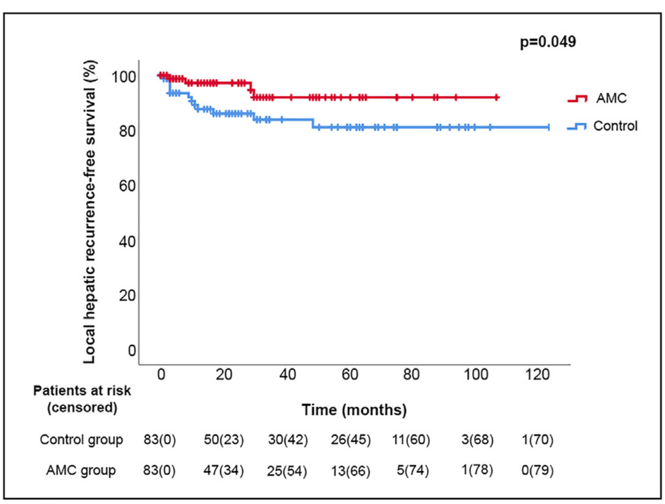

Fig. 2. Kaplan-Meier curve of local hepatic recurrence-free survival in patients with liver tumors with distance from the tumour to resection margin <10 mm (Log-rank test p = 0.049).

the clinical baseline characteristics of the two groups had been successfully balanced (Table 1).

Primary endpoint: local recurrence analysis

Regarding the primary end-point, 16 (9.6%) out of 166 developed an LR. The local recurrence rate was significantly higher in the Control than AMC Group [12 (14.5%) *vs* 4 (4.8%) patients, p = 0.039] after a median follow-up period of 65 months (IQR 42–88 months). The estimated 1-, 3-, and 5-year LR free survival of the control and AMC group patients were 93.5%, 86.0%, 81.0% and 98.8%, 97.2%, 91.9% respectively (p = 0.049) (Fig. 2). The AMC Group was significantly associated with reduced LR (HR = 0.29, 95%CI 0.093–0.906, p = 0.033).

On the other hand, a supplementary analysis of the subset with a tumour-to-resection margin ≥10 mm, revealed similar LR probabilities in both groups (p = 0.796) (see Supplementary Fig. 1).

Secondary end-points: postoperative outcomes and disease free survival analysis

No significant differences were found between groups in mortality (Table 2) and the patients in the AMC Group had significantly fewer severe postoperative complications than the Control Group (Table 2). No differences were found in index postoperative complications between both groups such as liver failure, bile leak or abdominal abscesses. Hospital stay was significantly shorter in the AMC than Control Group (median, 8 vs. 5 days, p = 0.015). The readmission rate was the same for the 2 study groups.

Forty-one of 83 (49.4%) patients in the Control Group and 19 of 83 (22.7%) in the AMC Group had died after a median follow-up period of 65 months (IQR 42–88 months). The estimated 1-, 3-, and 5-year global cumulative DFS were 70.4%, 43.8% and 34.6% in the Control Group and 68.9%, 44.1%, 42.0% in the AMC Group (p = 0.422).

Measurement of AMC size on CT images

A total of 92 patients (46 patients in AMC and Control group) presented an available CT imaging in the follow-up. The statistical analyses of maximal AMC size (cm) of central ablation zone for the

Table 2
Mortality and morbidity in Propensity Score–Matched Patients.

Complications	Control group (n = 83)	AMC group (n = 83)	Total	P value
Morbility	29 (34.9%)	19 (22.9%)	48 (28.9%)	0.144[a]
Abscess	12 (14.5%)	9 (10.8%)	21 (12.7%)	0.648[a]
Biliary leak	1 (1.2%)	5 (6.0%)	6 (3.6%)	0.219[a]
Hemoperitoneum	0 (0.0%)	1 (1.2%)	1 (0.6%)	1.000[a]
Liver failure	3 (3.6%)	5 (6.0%)	8 (4.8%)	0.727[a]
Wound infection	5 (6.0%)	3 (3.6%)	8 (4.8%)	0.727[a]
Pneumonia	0 (0.0%)	1 (1.2%)	1 (0.6%)	1.000[a]
Other complications	21 (25.3%)	12 (14.5%)	33 (19.9%)	0.124[a]
Blood transfusion	10 (12.0%)	5 (6.0%)	15 (9.0%)	0.227[a]
Red packed cells transfusion, median (IQR)	0 (0–0)	0 (0–0)		0.321[b]
Clavien-Dindo grades*				
No	50 (60.2%)	61 (73.5%)		0.015[a]
I-II	13 (15.7%)	7 (8.4%)		
III-V	20 (24.1%)	15 (18.1%)		
CCI score, median (IQR)	26.2 (0–36)	19.1 (0–40)		0.306[b]
Reoperation[c]	6 (7.2%)	4 (4.8%)	10 (6.0%)	0.754[a]
Length of stay (days), median (IQR)	8 (4–9)	5 (4–8)		0.015[b]
90-d mortality	2 (2.4%)	1 (1.2%)	3 (1.8%)	1.000[a]

AMC additional margin coagulation, IQR interquartile range, CCI Comprehensive Complication Index.
Data as absolute numbers and percentages in parenthesis unless otherwise stated.
[a] McNemar test.
[b] Wilcoxon test. Statistical differences were considered to be significant at a threshold of $p < 0.05$. Bold values indicate statistically significant.
[c] Within 90 days.

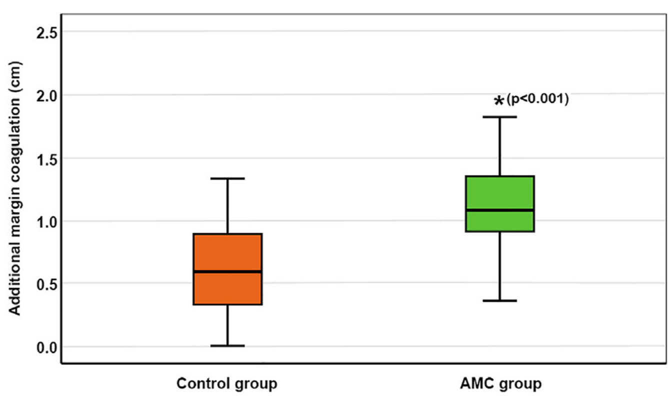

Fig. 3. Boxplot of maximal additional margin coagulation size (in cm) of central ablation zone of additional margin coagulation (AMC) Group compared with Control Group.Boxplot illustrates changes of median AMC of Control Group compared to AMC Group (*$p < 0.001$).

Control and AMC Groups are shown in Fig. 3. Control group had significantly smaller ablation zone widths than the AMC Group ($p < 0.001$, Wilcoxon signed-rank test). Mean ablation zone width was 0.5 ± 0.4 cm in Control and 1.14 ± 0.45 cm in AMC. A sample case of AMC size measurement on CT images is depicted in Fig. 4.

Discussion

Local recurrence is a common cause of early liver tumour recurrence after an hepatectomy due to the persistence of tumour cells close to the resection margin, which could subsequently favour the tumour recurrence and somehow challenge the quality of surgical performance. LR incidence in the literature ranges from 7 to 17% or even higher when non-anatomical resections are performed and is usually linked with a positive margin during hepatectomy, with a risk-ratio of over 10% [6].

On the basis of the argument that these remaining malignant cells in the hepatic remnant are responsible for tumour relapse, we aimed to demonstrate that additional coagulation of the hepatic

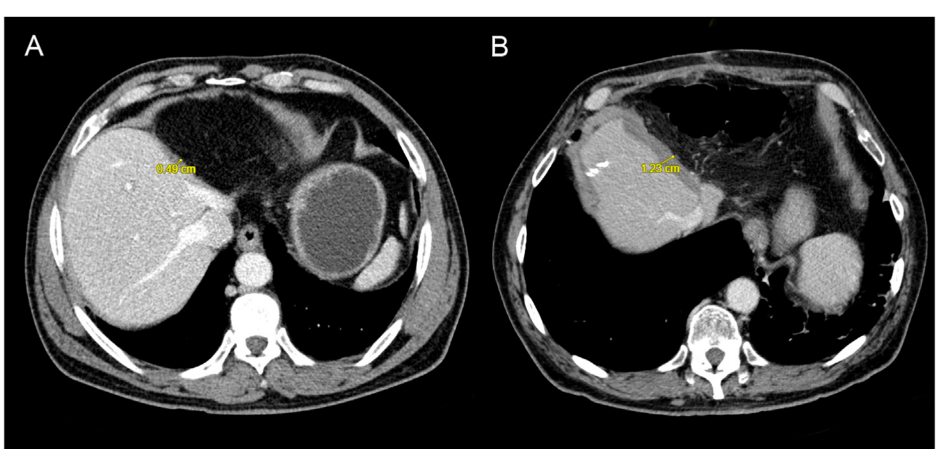

Fig. 4. Axial CT scans obtained 1-month after surgery from two different patients who had undergone left hepatectomy in Control Group (A), and additional margin coagulation (AMC) Group (B). Maximal AMC size of central ablation zone was 0.49 cm in Control Group and 1.23 cm in AMC group.

surface with an efficient RF-based device not only successfully achieved hemostasis but also had a favorable effect on local recurrence. In this bias-controlled population of 185 patients who underwent liver resection with a subcentimetric margin it was shown that LR was significantly lower in the AMC than in the Control Group. Interestingly, in a supplementary analysis (Supplementary Fig. 1) of the subset of patients with a tumour-to-resection margin $\geq$10 mm this beneficial effect seems to fade away with similar LR rates. These data are consistent with the fact that margin coagulation size measured by CT in our patients following a validated method is precisely around 10 mm (see Figs. 3 and 4) [21] and because the presence of microsatellite lesions beyond the 1 cm margin width is progressively reduced, so that its impact on LR is thus irrelevant. Taking into account, for instance the fact that, in the specific case of HCC, 94% of the micrometastasis in tumors <30 mm are found within 3 mm, this suggests that AMC seems to be more efficient in the first millimeters of the margin.

The effect of heat during liver resection to actually kill residual cells in situ margins is by no means new. This effect has been studied experimentally in animal models [12,14]and clinically [6,11]in both R1 and R0 resections and has been found to be related to lower LR because in situ margins can contain tumour cells, satellite nodules, or both, even after an apparently R0 resections [12]. In our study this heat effect in the remnant liver was pragmatically studied taking into account the smaller attenuation area on the resection surface and excluding any partial or segmental ischemia. This is especially relevant since partial or segmental ischemia, usually due to unintentional damage to a segment's inflow or outflow vessel, can impair perfusion and has been associated with other postoperative complications and even early recurrence and poor survival rates, at least in patients with hepatocellular carcinoma [23,24]. It therefore seems that some heat coagulation in the margin may be beneficial for avoiding LR as long as technical refinements are used to avoid any remnant liver ischemia. With the ever-increasing complexity of liver surgery [25], the presence of positive margins to preserve vital structures has become more usual since it enables hazardous resections that would otherwise be impossible. In this precise scenario in which a portal pedicle or a hepatic vein might jeopardize the margin status, AMC may be a useful tool in the surgeon's armamentarium even though in our study we were not able to correlate close-to-vessel margins with actual local recurrences. In any case, in this application, the utmost care must be taken to avoid segmental ischemia. This could be valid for the vast array of transection methods that employ heat to achieve coagulation during liver resection.

The present study still has some limitations. First, although we used PSM to mitigate the confounding factors, the retrospective design of the study has inherent limitations and biases could still be present in the patient enrollment and also in the availability of postoperative imaging in the follow-up. Second, despite applying standardized surgical techniques, different individual surgical experiences and habits could also be confounding factors and introduce certain variability among the surgical procedures. Finally, the fact of including different tumour types in the analysis might be considered a limitation because different tumour biology may affect the requirement for different margins to be attained, but it also strengthens the hypothesis of the oncological benefit of using an additional margin coagulation no matter which tumour we are handling.

In conclusion, our results provide evidence to support the use of additional RF-induced coagulation in scenarios in which the surgeon suspects a narrow margin and anatomical constraints will hinder expanding the resection in order to achieve an acceptable margin. These results should be taken into consideration in pre-op decision-making, especially with the recent introduction of two-stage, volume-manipulating and parenchyma-sparing hepatectomies.

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CRediT authorship contribution statement

María Villamonte: Conceptualization, Data curation, Investigation, Methodology, Formal analysis, Writing – original draft, Manuscript review. **Fernando Burdío:** Investigation, Methodology, Manuscript review. **Eva Pueyo:** Conceptualization, Formal analysis, Manuscript review. **Ana Andaluz:** Conceptualization, Data curation, Investigation, Methodology, Formal analysis, Manuscript review. **Xavier Moll:** Data curation, Investigation, Methodology. **Enrique Berjano:** Data curation, Investigation, Methodology, Manuscript review. **Aleksander Radosevic:** Data curation, Investigation, Methodology, Manuscript review. **Luís Grande:** Conceptualization, Investigation, Methodology, Formal analysis, Manuscript review. **Miguel Pera:** Manuscript review. **Benedetto Ielpo:** Investigation, Methodology, Manuscript review. **Patricia Sánchez-Velázquez:** Conceptualization, Investigation, Methodology, Formal analysis, Manuscript review.

Declaration of competing interest

FB declares that he is co-inventor of the US Patent 8.303.584 which corresponds to Coolinside and Coolingbis devices employed in the AMC Group. The other authors have no conflict of interests or financial ties to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2021.06.008

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