

Margin Size is an Independent Predictor of Local Tumor Progression After Ablation of Colon Cancer Liver Metastases

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Received: 24 December 2011 / Accepted: 15 March 2012 / Published online: 26 April 2012

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Abstract

Purpose This study was designed to evaluate the relationship between the minimal margin size and local tumor progression (LTP) following CT-guided radiofrequency ablation (RFA) of colorectal cancer liver metastases (CLM).

Methods An institutional review board-approved, HIP-PA-compliant review identified 73 patients with 94 previously untreated CLM that underwent RFA between March 2003 and May 2010, resulting in an ablation zone completely covering the tumor 4–8 weeks after RFA dynamic

CT. Comparing the pre- with the post-RFA CT, the minimal margin size was categorized to 0, 1–5, 6–10, and 11–15 mm. Follow-up included CT every 2–4 months. Kaplan–Meier methodology and Cox regression analysis were used to evaluate the effect of the minimal margin size, tumor location, size, and proximity to a vessel on LTP.

Results Forty-five of 94 (47.9 %) CLM progressed locally. Median LTP-free survival (LPFS) was 16 months. Two-year LPFS rates for ablated CLM with minimal margin of 0, 1–5 mm, 6–10 mm, 11–15 mm were 26, 46, 74, and 80 % ($p < 0.011$). Minimal margin ($p = 0.002$) and tumor size ($p = 0.028$) were independent risk factors for LTP. The risk for LTP decreased by 46 % for each 5-mm increase in minimal margin size, whereas each additional 5-mm increase in tumor size increased the risk of LTP by 22 %.

Conclusions An ablation zone with a minimal margin uniformly larger than 5 mm 4–8 weeks postablation CT is associated with the best local tumor control.

Abstract was presented to CIRSE Meeting 2011.

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Keywords Ablation · Radiofrequency ablation · Minimal margin · Local tumor progression · Colon cancer liver metastasis · Image guided · CT guided · Ablation margin evaluation method

Introduction

Radiofrequency ablation (RFA) has been used increasingly for the treatment of hepatic malignancies in selected unresectable patients [1–4]. Several studies have analyzed risk factors and patterns of local tumor progression (LTP) in an effort to improve local disease control and oncologic outcomes after RFA [1, 5–7]. The ablation margin is

considered one of the key factors associated with local tumor control [6, 8–12].

Although current societal guidelines for liver tumor ablation provide a general definition of the ablation margin [13, 14], there is still no universally accepted definition of the ablation margin. Some authors defined the postablation margin as the difference between the maximum diameter of the postablation zone and the maximum pretreatment tumor diameter divided by 2 [11]. This metric assumes a centrally located tumor within the ablation zone and does not consider a possible eccentric spatial relationship between the two. Efforts have been made to characterize the minimal ablation margin, but inadequate description of the methodology makes the reproducibility of these techniques questionable [6, 9, 10]. Most previous publications have evaluated the minimal margin after ablation of primary liver tumors, in particular HCC [6, 8–11, 15, 16]. A small, previous series demonstrated no advantage in 3D volumetric evaluation of the ablation defect compared with traditional CT for the detection of LTP after CLM RFA [12]. Another study showed that incomplete ablation defect margin on immediate post-RFA CT was associated with LTP after treatment of CLM [17]. A recent publication evaluated the feasibility of a new technique for registration of post- to preablation CT images for the assessment of the margin after RFA [18]. This method requires dedicated registration software and the technique was only applied to selected patients with HCC tumors treated with RFA.

The goals of this study are: 1) the explicit description of a method to measure the minimal margin after thermal ablation using anatomical landmarks on pre- and postablation CT; and 2) the correlation of the minimal ablation margin size to local tumor progression (LTP) after RFA of CLM.

Materials and Methods

Subjects

Institutional review board waiver was obtained for retrospective review. All patients signed informed consent for ablation before treatment. A retrospective review of our prospectively created HIPAA registered RFA database identified 171 consecutive colorectal hepatic metastases (CLM) in 116 patients treated by percutaneous RFA between March 2003 and May 2010. Ninety-four tumors with largest diameter ranging between 0.5 to 4 (median, 1.75) cm in 73 patients (39 males, 34 females; mean age, 60.86 ± 13) were deemed eligible for enrollment in this study using the following inclusion criteria: 1) well-defined CLM with no previous locoregional treatment by ablation, embolization, or resection; and 2) CT evidence of effective

ablation: ablation defect completely covering the target CLM on 4–8 weeks after RFA contrast enhanced CT [19].

Seventy-seven of 171 tumors were excluded from this study, including 17 previously ablated lesions, 8 complex, fused or irregular lesions, 1 lesion involving the abdominal wall, 3 lesions with incomplete ablation, and 48 lesions with pre- or postablation follow-up imaging that did not meet the inclusion criteria (baseline or first follow-up imaging only by MRI or PET or first follow-up CT beyond the 8-week window).

In our department, CT-guided RF ablation for CLM is generally offered to patients with up to three metastatic liver tumors (≤ 5 cm in diameter) with limited or no extrahepatic disease. The decision to perform ablation rather than resection or radiotherapy is made by a multidisciplinary colon cancer or hepatobiliary disease management team on an individual basis to provide the best possible treatment for each patient.

Treatments

All tumors were treated by percutaneous CT-guided RFA under general anesthesia. A prophylactic antibiotic (1 g Ancef, GlaxoSmithKline, Research Triangle Park, NC) was administered intravenously immediately before the procedure. RFA was performed with the Radiotherapeutics LeVeen ($n = 33$), the RITA ($n = 26$), or the Covidien/Valley Lab/Radionics ($n = 35$) device. RF device choice was based on tumor size, shape, and location as well as the operator's preference. The goal of each treatment was to create a zone of ablation at least 1 cm larger than the tumor's largest diameter to achieve a minimum ablation margin of at least 5 mm uniformly all around the tumor. We applied and completed the manufacturer's recommended protocol in all cases. Overlapping ablations were performed whenever needed to provide the desired minimal margin as previously described [5, 8].

Imaging Protocol

Portal venous phase contrast-enhanced CT (with 5-mm axial slices) was used for treatment planning and was available within 6 weeks from the RFA. In general, at our institution we do not offer ablation for lesions situated less than 5 mm to a vessel measuring more than 7 mm in diameter. Index tumors were characterized according to the size, subcapsular location (< 5 mm from the liver capsule), and proximity (within 10 mm) to any measurable vessel (3–6 mm).

The first post-RFA CT was performed within 4–8 weeks and was used according to SIR guidelines for the evaluation of treatment efficacy [19]. An ablation defect completely covering the target CLM was considered a complete

and technically effective RFA. Irregular peripheral or nodular enhancement within 1 cm of the ablated area on this postprocedure CT was considered untreated (residual) tumor and a technical failure [19–21].

Subsequent radiologic follow-up continued at 2–4-month intervals for at least 1 year and was used to evaluate LTP. Evidence of irregular or nodular enhancement within 1 cm of the previously treated tumor was considered LTP [19, 20].

Description of semiquantitative evaluation of the minimal margin based on CT anatomic landmarks

Using a PACS workstation with split monitor capabilities, the pre- and postablation portal venous phase CT images were reviewed side by side to compare the index tumor and the ablation zone/defect. Anatomic landmarks present on both pre- and postablation CT images were classified into four categories according to their reliability and reproducibility (Table 1; Fig. 1).

The landmark choice in each case was based on the following criteria: 1) higher level reliability landmark was

Table 1 Landmarks choice according to level of reproducibility/reliability

Category level	landmarks
I	Point of intrahepatic vessel bifurcations
II	Intrahepatic smooth vessel segment; small benign lesions (calcification, cyst, etc.)
III	Indentation or bulge points of liver capsula or ligament; surgical staples
IV	Smooth portion of liver capsula or ligament

preferred over lower level landmark; and 2) the nearest landmark to the tumor contour was preferred over a distant landmark.

On the basis of selected landmarks at the same CT axial image level, the distance values “ a_n ” between the selected “ n ” landmarks and the periphery of the ablation defect in at least four directions (medial, lateral, anterior, and posterior) were measured. Similarly, the distance values “ b_n ” between the same “ n ” landmark and the periphery of the tumor in the same directions were recorded. Subtracting the corresponding value of a_n from b_n yields m_n , the margin measurements for the specific landmark. The minimal margin (M) for each ablated CLM is the minimum value of m_n set or margins (Fig. 2). To determine the margin at the cranio-caudal aspects of the tumor, the CT slice position with identified defect above and below the CLM were counted.

The clock position of the minimal margins locations was recorded [8]. Given the limited spatial resolution of CT image and the potential error in subcentimeter calculations, the minimal margin measurements were stratified into four groups: 0; 1–5; 6–10; 11–15 mm. In cases in which one or more areas of the margin were <5 mm, we categorized the margin(s) as “close.” We subsequently categorized the close margin into multiple or single as defined in Table 2. The site concordance between the minimal margin location and the site of LTP was recorded as defined in Table 2.

The minimal margins were evaluated individually by two experienced radiologists who were blinded to the oncologic outcomes.

Statistical Analysis

The LTP-free survival (LPFS) probabilities were estimated by using Kaplan-Meier survival methodology and compared by using the log-rank test. Factors considered

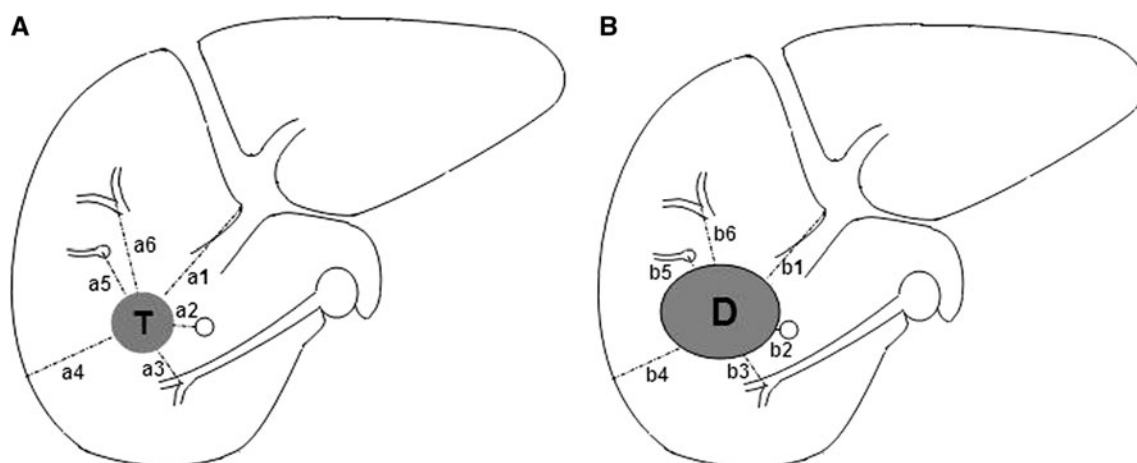


Fig. 1 Minimal margin evaluation method. Minimal margin (M) is the minimum of n margin values (m): $m_1 = a_1 - b_1$, $a_2 - b_2$, $a_3 - b_3$, etc. In this demonstrated case, “ $a_3 - b_3$ ” represents the minimal margin

Fig. 2 Landmark classifications according to reliability

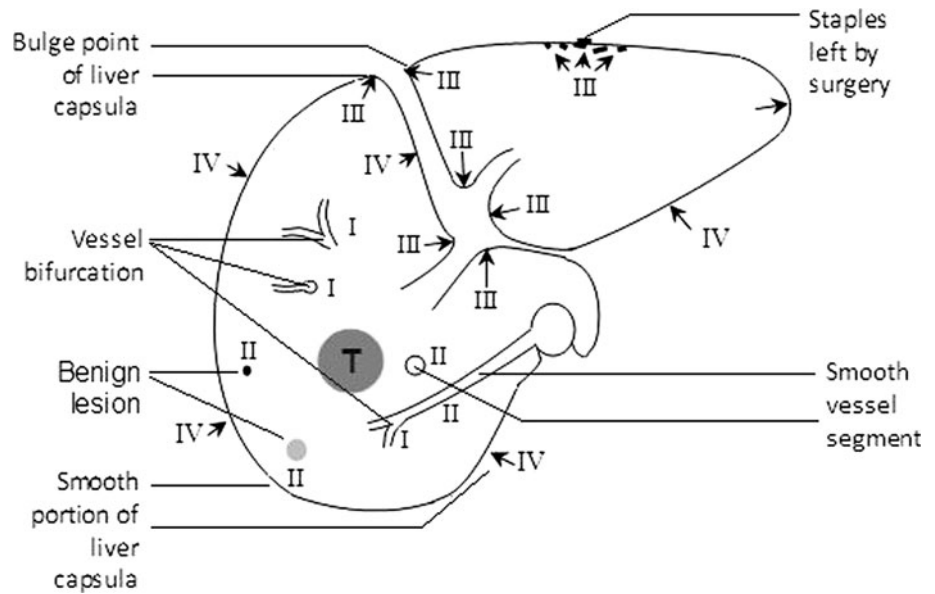


Table 2 Definitions related to minimal margin

Margin terms	Definitions
Margin size	0, 1–5, 6–10, 11–15 mm
Single close margin (<5 mm)	Margin extending less than four consecutive hour points
Multiple close margin (<5 mm)	At least two noncontinuous parts of the margin or one consecutive margin extending for more than four consecutive hour points
The site concordance	The concordance of at least one hour point on the "round the clock" coordination system between the minimal margin and the LTP site

included the size of the minimal margin, the tumor size and location, the patient’s age and sex, and the time interval between the primary tumor resection to the development of liver metastases (DFI1), the time interval from initial diagnosis of liver metastasis to ablation (DFI2), previous chemotherapy for liver metastasis, previous hepatectomy, and multiplicity of the minimal margin. Multivariate analysis was conducted using Cox’s regression, including those risk factors that were found to be significant on univariate analysis. Chi-square test was used to compare the site concordance rate of LTP between different margin sizes. Two-sided $p < 0.05$ was considered significant.

Results

Local Tumor Progression

The median follow-up period was 20 (range, 2–87) months. Overall 45 of 94 (47.9 %) tumors progressed. Median hepatic local tumor progression free survival (LPFS) was 16 months (95 % confidence interval (CI), 6.6–25.41 months; Fig. 3).

The 1-, 2-, and 3-year cumulative LPFS rates were 59, 46, and 38 %, respectively.

Minimal Margin and LTP

Of the 94 ablated CLM, the minimal margin as evaluated at the 4–8 weeks after RFA CT was 0 in 30 (31.9 %), 1–5 mm in 41 (43.6 %), 6–10 mm in 15 (16 %), and 11–15 mm in 8 (8.5 %) tumors, respectively. Two-year recurrence rate for tumors with 0, 1–5, 6–10, or 11–15 mm minimal margin were 74, 54, 26, and 20 %, respectively ($p = 0.011$; Figs. 4, 5, 6). The corresponding site concordance rates for LTP were 21/21 (100 %), 16/19 (84.2 %), 1/4 (25 %), and 0/1 (0 %) for 0, 1–5, 6–10, and 11–15 minimal margin category ($p < 0.001$), respectively (Table 3) Fig. 5.

Seventy-one of 94 (75.5 %) CLM had a close margin (<5 mm). Of those, 35 of 71 (49.3 %) tumors had a single close margin and 36 of 71 (50.7 %) tumors had multiple close margins (Fig. 7). The presence of multiple close margins was associated with a higher risk for LTP compared with a single close margin, with median LPFS of 9 (95 % CI,

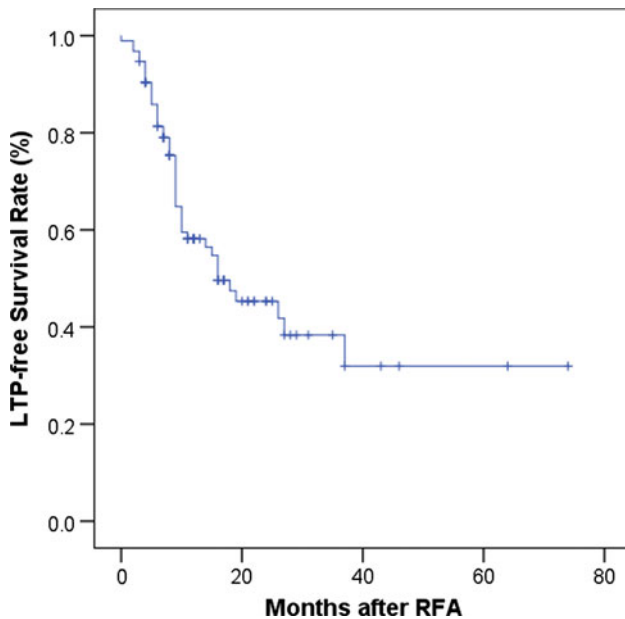


Fig. 3 Total local tumor progression-free survival after ablation

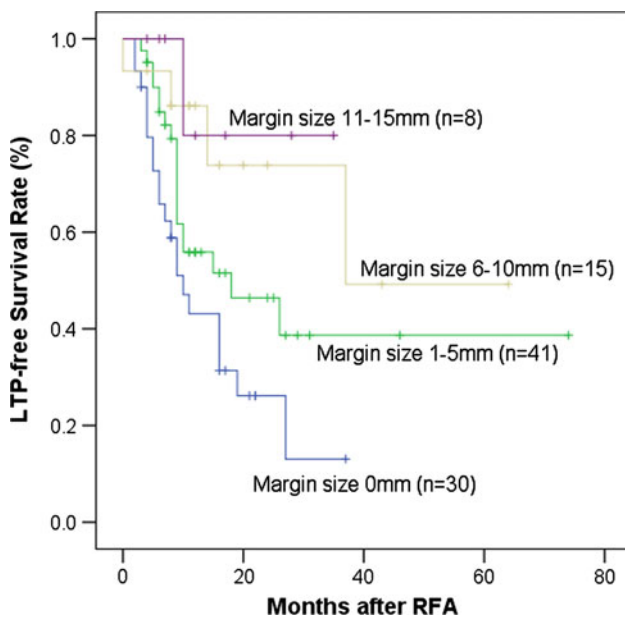


Fig. 4 LTP-free survival curves for different minimal margin

7.27–10.73) versus 19 months (95 % CI, 13.52–24.48), respectively ($p = 0.03$; Fig. 8).

Univariate and multivariate analysis of factors associated with local tumor progression

In the univariate analysis, minimal margin ($p = 0.011$), tumor size ($p = 0.023$), and multiple close margins ($p = 0.03$) were significant risk factors associated with LTP. Age, sex, subcapsular tumor location, proximity to

measurable vessel (3–6 mm), DFI1, DFI2, previous chemotherapy, and previous hepatectomy were not statistically significant predictors of LTP (Table 4).

Significant factors from the univariate analysis (tumor size, margin size, and multiplicity) were used in multivariate analysis. Multiple margins was not significant ($p = 0.18$) and was removed, resulting in the final model presented in Table 5.

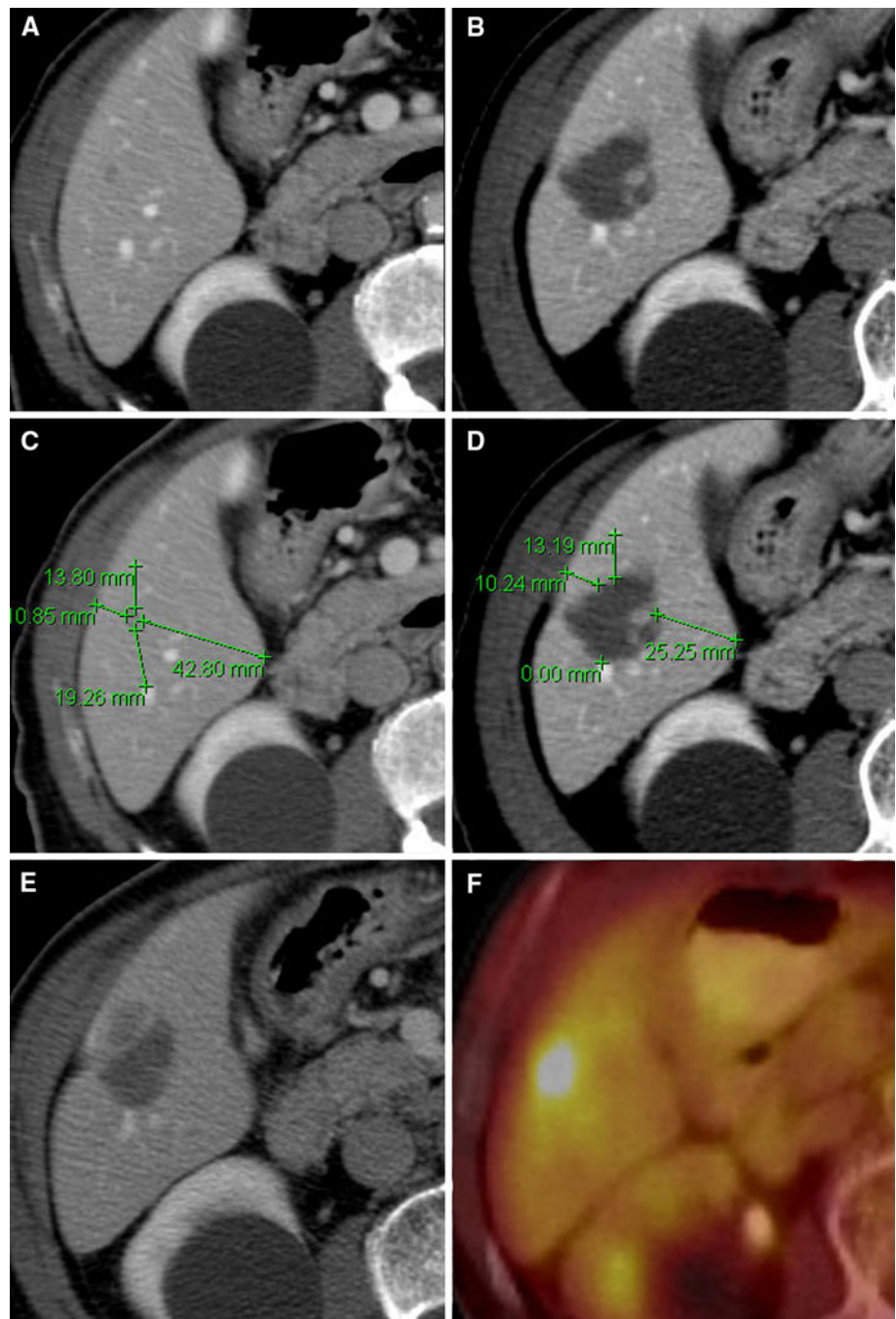
The risk of LTP decreased by 46 % for each 5-mm increase in margin size. Each additional 5 mm in tumor size increased the risk of local recurrence by 22 %.

Discussion

Factors associated with relatively lower recurrence rates after surgical resection of malignant liver tumors include absence of extrahepatic disease, small number of resected tumors, and the ability to achieve a tumor-free resection margin [22, 23]. RFA has been used increasingly as an alternative locoregional treatment for primary and secondary hepatic malignancies and has been frequently used in patients who are poor candidates for surgery or deemed unresectable [1–4, 24]. Local tumor control of ablation for CLM varies significantly between published series, with local tumor recurrence rates of 2–60 % [4, 25–34].

Several studies have analyzed risk factors and patterns of LTP in an effort to improve local disease control and oncologic outcomes after RFA [1, 5–7]. Like the surgical margin [35–37], the ablation margin is one of the factors associated with local tumor control [6, 8–12] after ablation. The minimal surgical margin represents the thickness of normal tissue interposed between the tumor edge and the margin of the resected tissue. Unlike the resected specimen, the evaluation of the ablation zone and corresponding margin is very challenging when it depends solely on imaging. To overcome the limitations of standard CT imaging, Kim et al. used fused CT imaging to quantitate the ablation margin size after RFA of HCC [8]. Although this technique allows for the direct assessment of margin size, it has several limitations: the minimal margin is calculated from measurements of the distance of the ablation defect periphery from the edge of the tumor. The method presumes that the ablation zone represents coagulation necrosis. Accurate fusion based on tumor center is questionable, and up to 18 % of cases could not be analyzed due to architectural distortion and displacement, patient position, and respiratory phase difference. Moreover, the fusion workstation is not widely available and thus cannot be proposed as a standard technique for margin evaluation after ablation. We described a method for the evaluation of the ablation margin, based on anatomic landmarks on contrast-enhanced CT imaging. As such, this methodology

Fig. 5 LTP of CLM after ablation from the site of the minimal margin (82-year-old male). **A** Preablation CT scan shows a small tumor located in the *right hepatic lobe*. **B** Postablation CT shows the expected changes within the ablation zone. **C** Measuring the distance between the tumor edge and nearest reliable landmark in different directions on pre-CT. **D** Measuring the distance between the above same landmarks and ablation defect on post-CT; minimal margin was acquired to be 1–5 mm located at approximately 11 o'clock. **E**, **F** Five months later, CT and PET all showed local tumor progression at the site of this minimal margin



can be performed in any center that has CT and PACS workstations.

The surgical margin after resection of CLM has been associated with LTP and overall survival [35–37]. It was shown that all 10-year survivors after resection of CLM were those patients where a surgical margin of at least 10 mm was achieved [38]. Our study has similar results. Multivariate analysis showed that the minimal margin ($p = 0.002$) was an independent risk factor for LTP. A 46 % decrease in risk of LTP was achieved for each 5-mm increase in margin. This finding is consistent with the

theory that LTP is attributed to the growth of microscopic viable tumor at the site of ablation [5, 8]. This is supported by previous work, which showed that tumor cells may be detected on the RF electrode by pathologic examinations and that detection of proliferation or viability in these tumor cells was a strong independent predictor of LTP after hepatic malignant tumor ablation [5, 39–41]. As a matter of fact in a recent publication [42], Ki67 + tumor cells adherent on the electrode were a strong independent predictor of patient survival after liver tumor ablation. In addition, the site concordance rate decreased as the margin

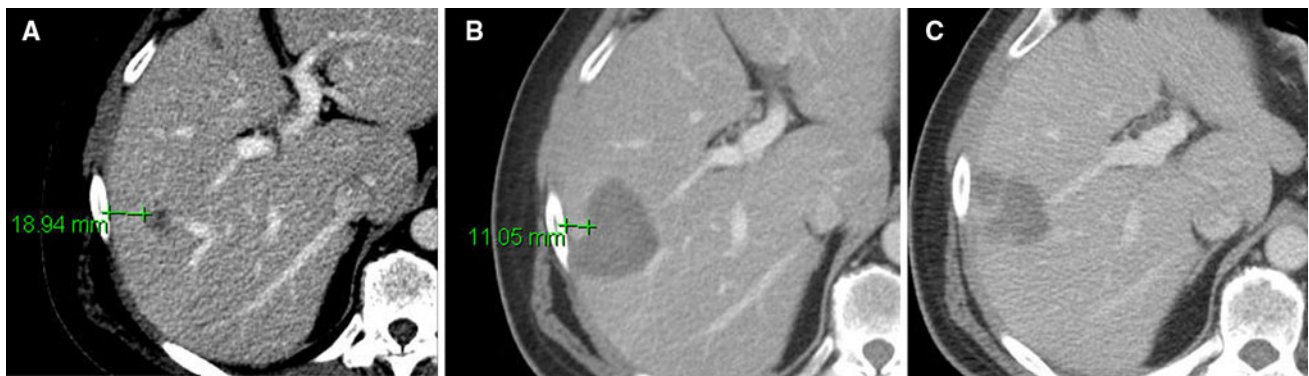


Fig. 6 Concordant LTP of CLM after ablation at the site of minimal margin (55-year-old male). **A** Preablation CT scan showed a tumor located in *right lobe*. **B** Postablation CT showed the expected changes

within the ablation zone; minimal margin was calculated as 6–10 mm located at approximately 9 o'clock. **C** Eight months later, concordant LTP occurred at the site of minimal margin

Table 3 Local tumor recurrence and site concordance for different margin size

Margin size (mm)	No.	No. with LTP	2-yr LTP rate (%)	Site concordance (%)
0	30	21	74	21/21 (100)
1–5	41	19	54	16/19 (84.2)
6–10	15	4	26	1/4 (25)
11–15	8	1	20	0/1 (0)

size increased ($p < 0.001$) in the current study, which supports the hypothesis that when the ablation margin is adequate, progression is probably the result of de novo growth of another lesion rather than proliferation of residual viable cancer cells that remained in the ablation zone.

As previously shown, we found that tumor size was associated with LTP [1, 4, 6, 7, 10, 11]. The influence of a nearby vessel on the ablation margin and the effectiveness of RFA due to the “heat-sink effect” has been described [1, 6, 7, 10, 19, 43]. This study did not detect any

significant difference of LTP for tumor adjacent to a 3–6-mm vessel. This disparity may be in part attributed to the overall small tumor size in this cohort and our exclusion of tumors incompletely treated with residual disease at the first post ablation CT.

An irregular ablation defect eccentrically located around the tumor resulting in a small minimal margin was identified as a risk factor in univariate analysis, highlighting the importance of accurate electrode positioning and necessity of overlapping ablations to create an adequate margin all around the tumor.

This study showed that a close margin (<5 mm) can result from a relatively small ablation zone or the eccentric location of the ablation zone in relation to the tumor center. Description of the ablation zone using maximum/effective diameter, defect/tumor diameter ratio volume, defect/tumor volume ratio, or ablation margin calculated as the difference between the maximum defect and tumor diameter divided by 2 does not take into account the nonellipsoid tumor geometry or eccentric ablation zone [11, 12, 44]. This study demonstrated that the creation of a uniform margin >5 mm all around the tumor in every direction is



Fig. 7 LTP associated with multiple margin after RFA (69-year-old man). **A, B** Multiple “0” margin (*arrow*) based on 1-month follow-up CT was demonstrated. **C** Seven-month follow-up CT showed concordant LTP at the site of the minimal margin

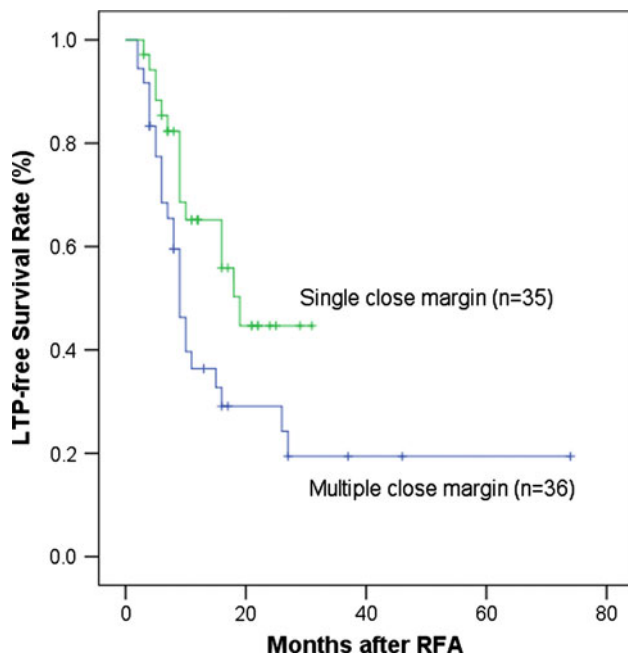


Fig. 8 LTP-free survival curves for single and multiple close margin (<5 mm)

essential to achieve local tumor control. Another point of interest in our work is the fact that despite technical efforts to achieve a margin >5 mm homogeneously around the tumor, this was frequently not evident on the first postablation CT, 4–8 weeks later. Although it is conceivable that the margin immediately after ablation was larger than the one we calculated 4–8 weeks later, it is clear that an accurate estimation of the margin on CT landmarks is time-consuming and may not be possible to accurately estimate visually during the ablation procedure. To that effect, the development and application of image registration and fusion software that can superimpose the ablation zone on the target tumor and calculate the margin immediately after ablation is necessary and may dramatically improve outcomes of tumor ablation [45]. We also recommend that ablation margins evaluated on the day of ablation exceed the 5-mm threshold and be at least 10 mm all around the target tumor, whenever this is safe.

Our methodology for the assessment of minimal margins relies on the choice of anatomic landmarks that can be used as fiducials in the pre- and postablation imaging. Based on our experience, the bifurcation of intrahepatic vessel was the most reliable landmark, because the vessel bifurcation is a 3D fixed point in the liver. In contrast, a smooth vessel segment is a 2D fixed segment and more points on the same vessel can be chosen potentially as landmarks, increasing variability between observers and diminishing reproducibility. Surgical clips serve as a less reliable landmark than other radiodense or radiolucent lesions in the liver (such as tiny calcifications and cysts).

Table 4 Univariate analysis of local tumor recurrence risk factors

Variable	Total	No. LTP	<i>p</i> value
Gender			0.722
Male	51	21	
Female	43	24	
Age (yr)			0.414
<60	53	27	
>60	41	18	
DFI1			0.904
<12 M	80	38	
>12 M	14	7	
DFI2			0.916
<12 M	19	9	
>12 M	75	36	
Tumor size (cm)			0.023
<2.5	70	29	
≥2.5	23	16	
Subcapsular			0.454
No	50	26	
Yes	44	19	
Adjacent to vessel			0.432
No	63	30	
Yes	31	15	
Prior chemo for liver mets			0.712
No	7	4	
Yes	87	41	
Prior hepatectomy			0.948
No	28	14	
Yes	66	31	
Minimal margin (mm)			0.011
0	30	21	
0–5	41	19	
5–10	15	4	
10–15	8	1	
Single vs. Multiple close margin			0.03
Single	35	15	
Multiple	36	25	

This is due to possible shift of staples or clips over time as a result of scarring and healing after resection. The smooth portion of the liver capsule or the ligament are the least reliable landmarks, because they are extremely variable and shift with respiration and positioning.

There are several limitations of this study. Our study used a CT examination 4–8 weeks after the ablation, because these were available for all patients enrolled in the study and because published series and reporting standards guidelines recommend this first postprocedure imaging as a universally accepted time point for the evaluation of ablation effectiveness [19]. This evaluation however has its

Table 5 Multivariate Cox regression analysis of factors related to LTP*

Variable	Hazard ratio	95 % Confidence interval	<i>p</i> value
Size (for each 5-mm increase)	1.22	1.02–1.49	0.028
Margin (for each 5-mm increase)	0.54	0.36–0.79	0.002

* Tumor size, margin size, and multiplicity of close margin were included in the initial multivariate analysis; multiple close margin lost its significance ($p = 0.18$) and therefore was removed, resulting in this “final” model

limitations, because the margin calculated at 4–8 weeks postablation does not represent the margin on the day of the ablation, which is probably larger. Our methodology has limitations similar to other techniques, such as the changes in measurements that can be attributed to different patient positions and variations on the respiratory phases during pre- and postablation imaging. Another limitation of our methodology is the semiquantitative evaluation of the margin due to the relatively limited z-axis CT spatial resolution, the tissue structural changes after ablation and the inconspicuous nature of tumor and/or ablation defect periphery in certain cases. Also, all of our work is based on the evaluation of the ablation margin by CT without any pathological assessment for confirmation. Another limitation is that this cohort included only tumors that were considered completely treated by CT at 4–8 weeks postablation. As such, it is possible that lesions not completely ablated, with residual tumor at the site of ablation due to the heat-sink phenomenon, were excluded from this cohort. A final limitation is that ablation margin measurement is a time-consuming process, which requires a comparative and meticulous review of the images between prior and posts CT on several “same levels” and calculations in several directions based on the optimal and carefully chosen landmarks for each ablated tumor. This last limitation is however at the same time an advantage of the presented methodology, because it demonstrated how to evaluate the ablation margin only by landmarks identified in CT. This allows the application of this methodology anywhere in the world where CT is used. This is particularly important in less fortunate places in the world where dedicated fusion and registration software or even PACS are not available.

In conclusion, the minimal margin size estimated using anatomic landmarks on contrast-enhanced CT is an independent imaging surrogate biomarker of LPFS after RFA of CLM. A minimal margin >5 mm in all directions around the target CLM on the 4–8 weeks post-RFA CT is associated with improved local tumor control and prolonged LPFS. Accounting for the possible decrease of the ablation zone within the 4–8-week period since RFA and based on the surgical data, a margin of 10 mm all around the tumor is recommended whenever safe and feasible.

Acknowledgments This work was supported in part by NIH Grant No. 5R21CA131763.

Conflict of interest Authors Xiaodong Wang, Constantinos T. Sofocleous, Joseph P. Erinjeri, Elena N. Petre, Mithat Gonen, Kinh G. Do, Karen T. Brown, Anne M. Covey, Lynn A. Brody, William Alago, Raymond H. Thornton, and Kemeny NE have no conflict of interest to declare. Stephen B. Solomon—consultant for Covidien (Mansfield, MA) and Johnson and Johnson (Piscataway, NJ) and has a research contract with GE Healthcare (Milwaukee, WI).

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