

Incidental Ring-hyperenhancing Liver Micronodules at CT Hepatic Arteriography–guided Percutaneous Thermal Ablation of Colorectal Liver Metastases

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CT during hepatic arteriography (CTHA) is a highly sensitive imaging method for detecting colorectal liver metastases (CLMs), which supports its use during percutaneous thermal liver ablation. In contrast to its high sensitivity, its specificity for incidental small CLMs not detected at preablation cross-sectional imaging is believed to be low given the absence of specific imaging signatures and the common presence of pseudolesions. In this retrospective study of 22 patients (mean age, 55 years \pm 10.6 [SD]; 63.6% male, 36.4% female) with CLMs undergoing CTHA-guided microwave percutaneous thermal ablation between November 2017 and October 2022, the authors provided a definition of incidental ring-hyperenhancing liver micronodules (RHLMs) and investigated whether there is a correlation of RHLMs with histologic analysis or intrahepatic tumor progression at imaging follow-up after applying a biomechanical deformable image registration method. The analysis revealed 25 incidental RHLMs in 41.7% (10 of 24) of the CTHA images from the respective guided ablation sessions. Of those, four RHLMs were ablated. Among the remaining 21 RHLMs, 71.4% (15 of 21) were confirmed to be CLM with either histology ($n = 3$) or imaging follow-up ($n = 12$). The remaining 28.6% (six of 21) of RHLMs were not observed at follow-up imaging. This suggests that RHLMs at CTHA may be an early indicator of incidental small CLMs.

Supplemental material is available for this article.

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Image-guided thermal ablation is commonly used to treat colorectal liver metastases (CLMs). It has been used for nonsurgical patients and in combination with surgery, including patients with oligometastatic disease, as long as all visible disease is treated (1–3). Its success depends on precise tumor identification, targeting, and ablation with appropriate margins. Intra-procedural administration of intravenous contrast medium before and after ablation can help reduce the incidence of residual tumor and minimize the risk of incomplete ablation (1,4). CT during hepatic arteriography (CTHA) has also been demonstrated as a useful imaging tool during percutaneous ablation because CTHA facilitates tumor depiction, accurate planning of probe placement, and assessment of ablative margins (5,6). In this approach, contrast medium is injected intra-arterially into the common or proper hepatic artery. CTHA offers several advantages, such as the ability to perform repeated imaging throughout the procedure with small aliquots of contrast medium, which allows for near-real-time monitoring of the size and shape of the ablation zone (5,7).

The optimal signal-to-noise imaging ratio of CTHA enables effective identification of CLMs during percutaneous ablation procedures. However, this characteristic also results in the detection of nontumorous

perfusion abnormalities that can appear as pseudolesions (8), making it difficult to differentiate them from incidental small CLMs not initially observed on preprocedural images. This difficulty in differentiation hampers the optimal management of such incidental lesions. In this retrospective study, we provided a definition of incidental ring-hyperenhancing liver micronodules (RHLMs) and investigated their correlation with histologic analysis or intrahepatic tumor progression at imaging follow-up by applying a biomechanical deformable image registration (DIR) method.

Materials and Methods

Patient Selection

This retrospective study was approved by the institutional review board with a waiver of informed consent, in compliance with the Health Insurance Portability and Accountability Act. Between November 2017 and October 2022, 29 consecutive patients with CLMs undergoing CTHA-guided microwave percutaneous thermal ablation were reviewed for enrollment in this study. Patients eligible for percutaneous thermal ablation presented with up to five CLMs, each measuring less than or equal to 5 cm, and limited oligometastatic disease (up to three extrahepatic sites of disease). Seven patients

Abbreviations

CLM = colorectal liver metastasis, CTHA = CT during hepatic arteriography, DIR = deformable image registration, RHLM = ring-hyperenhancing liver micronodule

Summary

The presence of incidental ring-hyperenhancing liver micronodules at CT during hepatic arteriography may be an early indicator of incidental small colorectal liver metastasis, potentially impacting patient treatment.

Key Points

- In a retrospective study of 22 consecutive patients with colorectal liver metastases (CLMs) undergoing CT hepatic arteriography-guided percutaneous ablation, 25 incidental ring-hyperenhancing liver micronodules (RHLMs) were detected that were not present at preablation imaging.
- Fifteen RHLMs were confirmed to be CLMs, either with histologic findings or imaging follow-up after applying a biomechanical deformable image registration method, suggesting RHLMs as a potential early indicator of CLMs.

Keywords

Colorectal Neoplasms, Liver, Angiography, CT, Incidental Findings, Ablation

were excluded because they did not undergo preprocedural CTHA for tumor identification. A total of 22 patients with CLMs who underwent 24 sessions of CTHA-guided percutaneous thermal ablation were included in this study.

CTHA Imaging Protocol

All patients underwent microwave ablation (NeuWave; Ethicon) while under general anesthesia. The CTHA images were acquired before and after the ablation for tumor targeting and ablation outcome assessment, respectively. After obtaining arterial access via the right common femoral artery and selecting the common or proper hepatic artery with a 5F catheter, digital subtraction angiography was conducted. CTHA was performed during a dual-phase (early and late arterial) acquisition with undiluted contrast medium (Omnipaque 350; GE HealthCare), with a total volume of 20 mL injected at a rate of 2 mL/sec and an acquisition delay of 8 (early arterial) and 10 (late arterial) seconds using a power injector.

RHLM Definition

The acquired preablation CTHA image data were transferred to Syngo.via VB30 (Siemens Healthineers) for evaluation of the presence of RHLMs (Fig 1). Incidental RHLM was defined as a micronodule with a continuous ring of enhancement on CTHA images that could not be identified on preablation diagnostic cross-sectional and functional images (CT, PET/CT, and/or MRI), using venous contrast medium. Baseline imaging examination protocols adhered to the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (version 2.2023) (2). RHLMs were to be identified on three orthogonal planes in the late arterial phase of CTHA, with the average Hounsfield

units being at least two times higher than the adjacent liver parenchyma (7). Two trained radiologists (J.A. and Y.M.L., with 5 and 7 years of abdominal imaging experience, respectively) independently reviewed the images, initially blinded to nature of incidental RHLMs. After initial evaluation, they collectively analyzed suspected RHLMs based on definition criteria, resolving disagreements by consensus.

Correlative Analysis of RHLM Nature

The nature of incidental RHLMs was disclosed by the histologic confirmation. For incidental RHLMs without tissue biopsy, follow-up images were reviewed for intrahepatic progression. Follow-up was defined as the time between the first procedure and the last cross-sectional imaging examination or death. When intrahepatic progression was observed on follow-up images, a biomechanical DIR method was used to map the RHLMs detected on intraprocedural CTHA images onto the initial follow-up CT images (RayStation version 11B; RaySearch Laboratories) (9). The RHLM contour was expanded by 5 mm to reduce the impact of segmentation variability. We considered the incidental RHLMs as CLMs if their mapped contours overlapped with those of intrahepatic progression (Fig 2). Intrahepatic progression was assessed according to the Response Evaluation Criteria in Solid Tumors version 1.1.

Statistical Analysis

Interobserver agreement between the two independent readers in identifying incidental RHLMs was assessed by using the Cohen κ . The level of agreement for κ statistics was classified as follows: less than or equal to 0.20, no to slight agreement; 0.21–0.40, fair agreement; 0.41–0.60, moderate agreement; 0.61–0.80, substantial agreement; and greater than 0.80, almost perfect agreement (10). Each incidental RHLM was considered an independent event. Frequencies with percentages are summarized for categorical data and means \pm SDs or medians with IQRs for quantitative data, as appropriate. Statistical analyses were performed using R version 3.4.1 (R Foundation for Statistical Computing) by a biomedical engineer with 6 years of biomedical liver imaging experience (I.P.).

Results

Patient Characteristics

Among 22 consecutive patients (mean age, 55 years \pm 10.6 [SD]; 63.6% male, 36.4% female) with CLMs who underwent 24 sessions of CTHA-guided percutaneous thermal ablation, 41 CLMs were treated and the median number of ablated tumors per session was two (IQR, one to two). Of those, all patients underwent contrast-enhanced cross-sectional imaging and/or functional imaging at a mean of 29.4 days \pm 19.1 before the ablation. Seven of these patients underwent an MRI examination with gadoteric acid, and one of these seven patients also underwent a PET/CT examination. Detailed patient characteristics are summarized in Table 1.

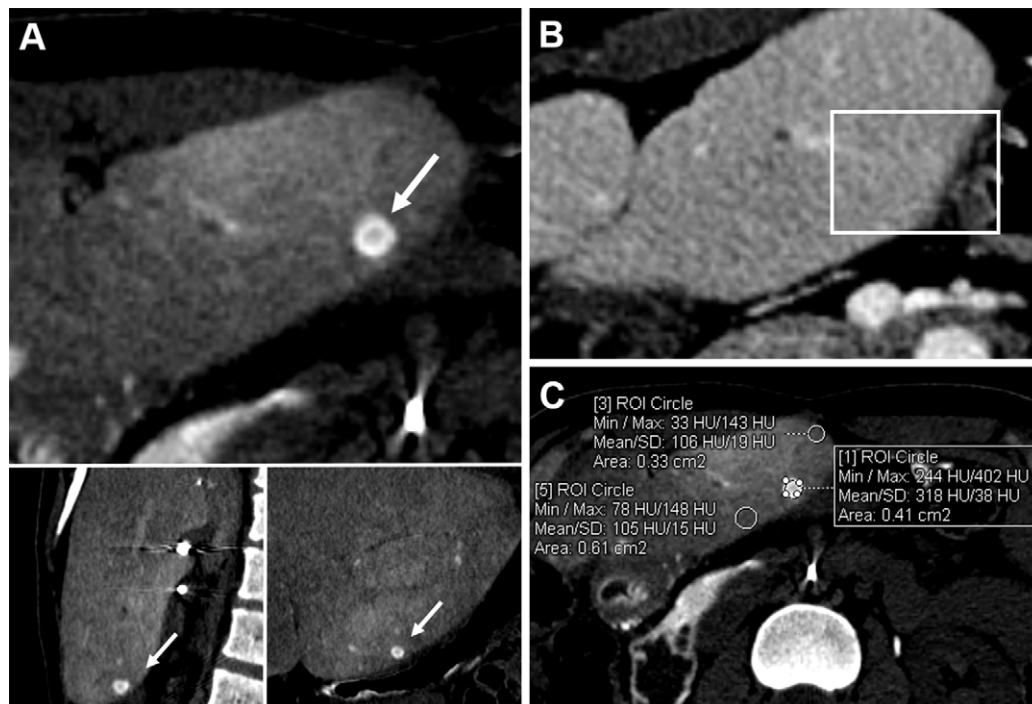


Figure 1: Images in a 42-year-old woman who underwent ablation for colorectal liver metastases with an incidental RHLM (size: 8 mm). **(A)** Axial CTHA image shows the incidental RHLM (arrows), which is also visible in the other two orthogonal planes (insets). **(B)** Incidental RHLM was not detected on baseline axial CT image during portal venous phase obtained 9 days prior to procedure (inset). **(C)** Axial CTHA image exemplifies ROI-based quantitative analysis. The image shows ROI_{Tumor} (circle with higher attenuation) with a mean Hounsfield unit of more than two times higher (318 vs 105.5 HU) than the ROI_{liverparenchyma} (circles with low attenuation). CTHA = CT during hepatic arteriography, HU = Hounsfield units, RHLM = ring-hyperenhancing liver micronodule, ROI = region of interest.

RHLM Incidence

Among the 22 patients, a total of 25 incidental RHLMs were identified on 10 of 24 (41%) preablation CTHA images from the respective guided ablation sessions. Detailed RHLM characteristics are summarized in Table 2. The level of agreement on the identification of incidental RHLMs was almost perfect between the two observers ($\kappa = 0.91$). The median number of incidental RHLMs per session was two (IQR, one to three), with a mean largest diameter of 0.8 cm (range, 0.3–1.7). RHLMs were identified on the right liver in 19 of 25 (76%) cases, and three of 25 (12%) incidental RHLMs were perivascular and seven of 25 (28%) subcapsular.

RHLM Nature

Of the 25 incidental RHLMs, four were ablated during the ablation session by the operating physician given their similarity to targeted CLMs. Among the remaining 21 RHLMs, 15 (71%) were indicated as CLMs, with three confirmed with histologic findings and 12 confirmed at imaging follow-up with a biomechanical DIR method at a mean time of 52 days \pm 27.8 after the ablation (9). Six of the 21 (29%) tumors had unknown nature, and no intrahepatic progression of these RHLMs was observed on follow-up imaging surveillance following a course of chemotherapy at a mean time of 275.3 days \pm 195.9.

Specifically, in three incidental RHLMs with tissue biopsy, one (in patient 8) was biopsied during the ablation

session given the low specificity of an incidental RHLM finding (8,11), confirming its metastatic nature. Two other RHLMs were noted in patient 2 during the ablation session. They were not biopsied given the assessment challenges because the interventionist considered the risk–benefit ratio unjustifiable. Following the ablation session, the patient underwent additional chemotherapy and surgical resection for these two RHLMs, which confirmed their metastatic nature (Fig 3).

Among the 12 RHLMs confirmed to be CLMs using a biomechanical DIR method, with a mean largest diameter of 0.8 cm (range, 0.4–1.4), seven RHLMs were detected in patient 5, who underwent two ablation sessions. However, the second-stage ablation was aborted because of the presence of multiple RHLMs, which were confirmed to be CLMs at follow-up imaging (Fig S1).

Discussion

Several studies have reported that CTHA is a highly sensitive modality for detecting CLMs, which typically appear as nodules with ring enhancement (12). While incidental lesions at CTHA have been reported in patients with CLMs, their clinical significance remains uncertain because their nature has not been determined (7). In this retrospective study, we proposed that small CLMs may appear as RHLMs. We defined an RHLM as a micronodule with a continuous ring of enhancement on CTHA images in three orthogonal

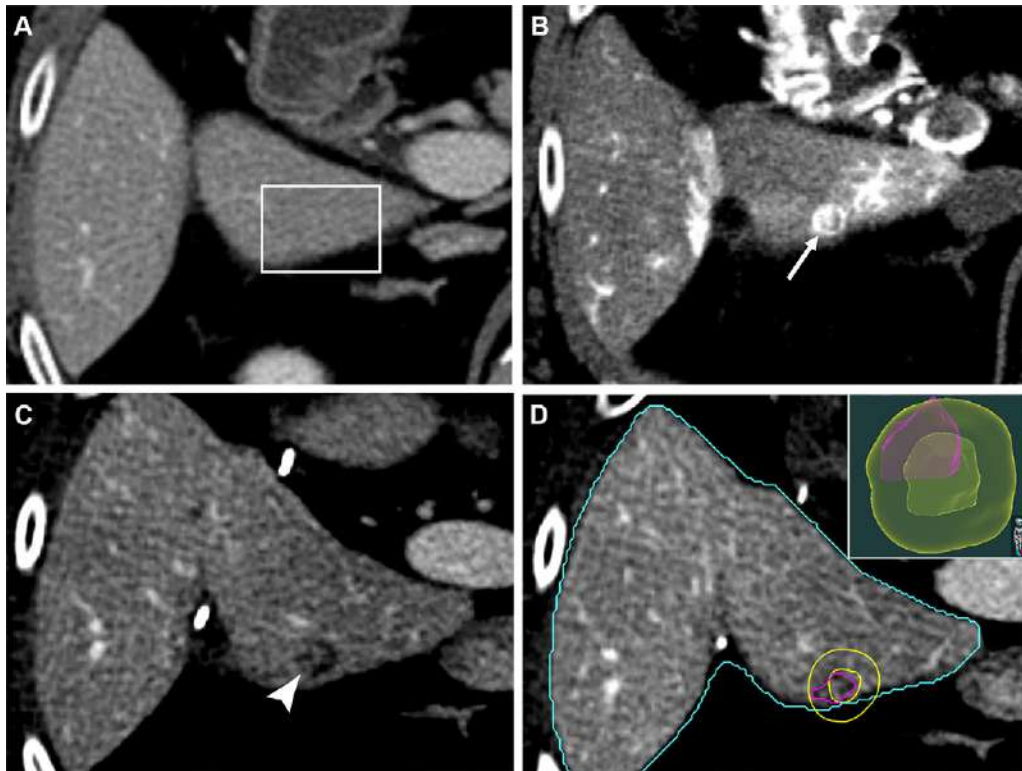


Figure 2: Images in a 50-year-old man who presented with an incidental RHLM (size: 9 mm), which was confirmed to be colorectal liver metastasis at follow-up imaging. **(A)** Axial CT image during portal venous phase obtained 19 days before the procedure shows no lesion on segment VI (inset). **(B)** Preablation axial CTHA image in late arterial phase shows one incidental RHLM (arrow). **(C)** Axial CT image in portal venous phase obtained at first follow-up demonstrates a new hypovascular nodule (arrowhead). A biomechanical deformable image registration method was performed to register and map the incidental RHLM from CTHA to follow-up CT. **(D)** Axial CTHA image with segmentation shows the liver, incidental RHLM with 5-mm expanded margins, and new hypovascular nodule contours (blue, yellow, and pink, respectively). The new nodule overlaps with the incidental RHLM, which was computed on images with three-dimensional volume rendering (inset). CTHA = CT during hepatic arteriography, RHLM = ring-hyperenhancing liver micronodule.

planes, demonstrating twice the Hounsfield units of normal liver parenchyma.

In our study, 25 incidental RHLMs were found on 10 of 24 (42%) preablation CTHA images from the respective guided ablation sessions; these RHLMs were not identified on diagnostic cross-sectional and functional images before ablation. Among these incidental RHLMs, 15 were confirmed to be CLMs by histologic confirmation and by follow-up images with a biomechanical DIR method.

CTHA has been shown to be a sensitive imaging technique for detecting hepatic neoplasms. In 1979, Prando et al (13) introduced CTHA as a method for evaluating hepatic neoplasms, including CLMs. Subsequent studies have demonstrated significantly high sensitivity of this method in detecting metastatic lesions, particularly small tumors (14). For instance, van Ooijen et al (15) showed better detection rates of CLMs with CTHA (94%) compared with intravenous contrast-enhanced CT (52%) and transabdominal US (48%). However, the specificity of CTHA in detecting small tumors is low as a result of nontumorous perfusion abnormalities, as was also demonstrated by a false-positive rate of 38% per patient (15).

The low specificity of CTHA may be the result of perfusional abnormalities, including arterioportal shunts and inflammatory changes, which can mimic liver lesions. Aberrant

portal venous supply from third hepatic inflow tracts can appear as perfusion defects, as well. Furthermore, CTHA may have limited usefulness in detecting hepatic neoplasms in advanced cirrhosis and Budd-Chiari syndrome given the changes in hepatic blood flow dynamics (16). Interestingly, ring enhancement is not observed in such perfusional abnormalities, which can help differentiate them from hepatic malignancies (17). Despite being hypovascular, CLMs show ring enhancement during the hepatic arterial phase because of multiple factors, including tumor compression, neoangiogenesis, arterioportal shunts, and histopathologic alterations (12). In our study, 71.4% of RHLMs were confirmed to be CLMs by our definition, suggesting RHLMs as a potential specific marker for CLMs at CTHA. Further studies are needed to confirm this finding and to explore the underlying mechanisms, progression, and clinical implications in RHLM diagnosis and treatment.

Among the 15 RHLMs confirmed to be CLMs, the metastatic nature was confirmed in 80% of those tumors using imaging follow-up with a biomechanical DIR method. Recently, Lin et al (18) validated this method to correlate the location of tissue at risk for tumor progression at post-ablation CT with subsequent intrahepatic progression on follow-up CT images. In our study, the same biomechanical

Table 1: Demographic and Clinical Data of Study Patients

Characteristic	Patients with RHLMs (<i>n</i> = 9)	Patients RHLM-free (<i>n</i> = 13)
Age (y)	49.1 ± 18.1	55.8 ± 11.6
Sex		
Male	7 (78)	7 (54)
Female	2 (22)	6 (46)
Primary tumor		
Colon	4 (44)	9 (69)
Rectum	5 (56)	4 (31)
Liver metastasis		
Synchronous	5 (56)	9 (69)
Metachronous	4 (44)	4 (31)
No. of tumors ablated per procedure*	2 (1–3.25)	1 (1–2)
Extrahepatic metastasis prior ablation	4 (44)	9 (69)
Liver steatosis	5 (56)	4 (31)
Liver cirrhosis	1 (11)	0 (0)
Chemotherapy prior to ablation	9 (100)	13 (100)
RAS mutation status		
Mutant	3 (33)	8 (61)
Wild-type	1 (11)	4 (31)
No available data	5 (56)	1 (8)
Time interval between baseline examination [†] to CTHA (d)	23.5 ± 12.2	31.5 ± 20.5

Note.—Data are means ± SDs, and numbers of patients with percentages in parentheses unless otherwise indicated. CTHA = CT during hepatic arteriography, RHLM = ring-hyperenhancing liver micronodule.

* Data are medians with IQRs in parentheses.

[†] PET/CT, CT, and/or MRI with venous contrast medium.

DIR method was applied to correlate the location of RHLMs on CTHA images with intrahepatic progression on follow-up images. Unlike two-dimensional visual inspection using images side-by-side, which can be subjective and biased by operator interpretation, the biomechanical DIR method is more accurate because it registers CTHA and follow-up CT or MR images in three dimensions and also considers inherent liver and ablation biomechanical properties (1,9). This method has shown promising results in localizing RHLMs and subsequent intrahepatic progression, which can be useful for guiding treatment decisions.

The main limitation of this study was the small sample size due to limited CTHA accessibility, which restricted detailed analysis to individual RHLMs rather than a per-patient assessment. Second, it was a retrospective study, potentially introducing selection bias. Third, a relatively short follow-up period limited the evaluation of incidental RHLMs' impact on patient oncologic outcomes. Fourth, the absence of pseudolesion analysis precluded the assessment of specificity and positive predictive values. Finally, a minority of patients had a final histopathologic RHLM diagnosis, which could have improved correlation with the biomechanical DIR method.

In conclusion, incidental RHLMs were demonstrated as an early indicator of incidental small CLMs, supported by histologic confirmation and biomechanical DIR-based

imaging follow-up analysis. Further investigations with a larger patient sample and longer follow-up are warranted to evaluate the relevance of such small incidental RHLMs given that resection is the only potentially curative treatment option for liver-limited CLMs (19).

Author contributions: Guarantors of integrity of entire study, J.A., J.N.V., B.C.O.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; agree to ensure any questions related to the work are appropriately resolved, all authors; literature research, J.A., K.K.B., B.C.O.; clinical studies, J.A., C.S.O., C.W.T., J.N.V., K.K.B., B.C.O.; statistical analysis, J.A., Y.M.L., I.P.; and manuscript editing, J.A., Y.M.L., I.P., C.W.T., J.N.V., K.K.B., B.C.O.

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Table 2: Ring-hyperenhancing Liver Micronodule Data of Study Patients

Patient No.	CTHA No.	Incidental RHLM		Perivascular		Subcapsular		Liver Parenchyma		Incidental RHLM Size (mm)	Confirmed as CLM*	Incidental RHLM Size at FU (mm)	Intrahepatic Progression at FU†
		per CTHA	No.	No.	No.	Right Liver	Left Liver	RHLM (HU)	(HU)				
1	1	1	1	No	No	Yes	No	190	95	8	No	NA	No
		1	2	No	Yes	Yes	No	176	88	9	Yes	NA	
		2	3	No	Yes	Yes	No	178	88	7	Yes	NA	
2	2	3	4	No	Yes	Yes	No	311	125	5	No	NA	No
		4	5	No	Yes	No	Yes	342	110	8	No	NA	
		5	6	No	No	No	Yes	289	98	8	—	NA	
		6	7	No	No	No	Yes	235	104	5	No	NA	
3	3	1	8	No	No	Yes	No	168	73	6	No	NA	No
		2	9	No	No	Yes	No	140	72	9	No	NA	
4	4	1	10	No	No	Yes	No	146	72	13	Yes	6	No
		5	11	Yes	Yes	Yes	No	209	91	17	Yes	12	Yes
5	5	2	12	No	No	Yes	No	122	60	9	Yes	11	
		3	13	No	No	Yes	No	189	89	6	Yes	8	
		4	14	No	No	No	Yes	171	83	14	Yes	14	
		1	15	Yes	Yes	Yes	No	166	81	9	Yes	1	
5	6	2	16	No	No	Yes	No	170	82	8	Yes	11	No
		3	17	No	No	No	Yes	149	72	11	Yes	11	
6	7	1	18	No	No	Yes	No	186	77	6	Yes	13	No
		1	19	No	No	Yes	No	165	73	6	—	NA	
7	8	2	20	No	No	Yes	No	167	69	8	—	NA	No
		3	21	No	No	Yes	No	103	51	9	—	NA	
8	9	1	22	No	Yes	Yes	No	140	58	6	Yes	4	No
		2	23	Yes	No	Yes	No	180	87	3	Yes	4	
9	10	1	24	No	No	Yes	No	135	65	65	Yes	6	Yes
		2	25	No	No	No	Yes	142	66	66	Yes	9	

Note.—CLM = colorectal liver metastasis, CTHA = computed tomography during hepatic arteriography, FU = follow-up, HU = Hounsfield units, NA = not applicable, RHLM = ring-hyperenhancing liver micronodule.

* RHLM indicated to be CLM by either histologic confirmation or using a biomechanical deformable image registration method with CTHA and follow-up images. Four RHLMs ablated during the procedure have no confirmation of their nature.

† New CLM that did not geographically correlate with RHLM.

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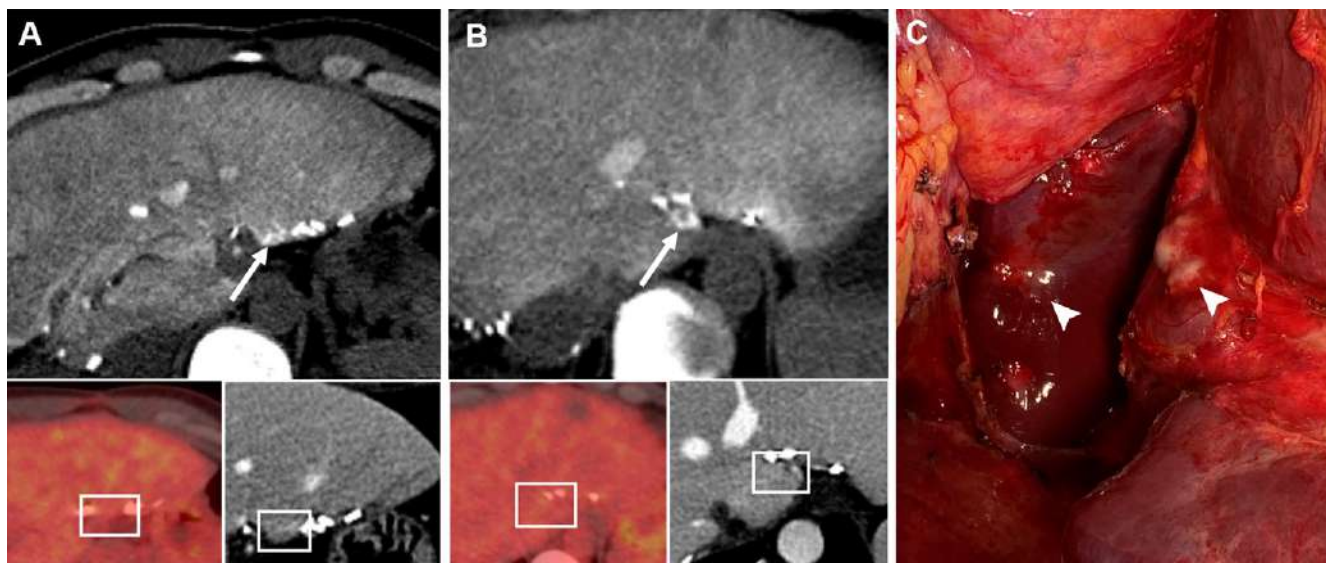


Figure 3: Images in a 42-year-old woman who presented with two small incidental RHLMs (both sizes: 5 mm) found at CTHA during ablation; the RHLMs were confirmed to be colorectal liver metastases by subsequent surgery. **(A, B)** Preprocedural axial CTHA images in late arterial phase show two incidental RHLMs (arrows), near the surgical clips, which were not detected at PET/CT and axial CT in portal venous phase performed 1 day and 9 days before the ablation, respectively (insets). **(C)** Intraoperative image shows two necrotic tumors in correspondence with the incidental RHLMs (arrowheads). CTHA = CT during hepatic arteriography, RHLM = ring-hyperenhancing liver micronodule.

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