



# Post radiofrequency ablation assessment of colorectal cancer liver metastases—does post ablation biopsy really matter?

Hanping Wu, Agata A. Exner, Sidhartha Tavri

Department of Radiology, Case Western Reserve University, University Hospitals Cleveland Medical Center, Cleveland, OH, USA

*Correspondence to:* Sidhartha Tavri, MBBS, Assistant Professor. Vascular and Interventional Radiology, University Hospitals/CWRU School of Medicine, 11100 Euclid Ave, BSH 5056 Cleveland, OH 44106, USA. Email: Sidhartha.Tavri@UHhospitals.org.

*Comment on:* Sotirchos VS, Petrovic LM, Gönen M, *et al.* Colorectal Cancer Liver Metastases: Biopsy of the Ablation Zone and Margins Can Be Used to Predict Oncologic Outcome. *Radiology* 2016;280:949-59.

Submitted Jul 29, 2016. Accepted for publication Aug 09, 2016.

doi: 10.21037/tcr.2016.08.28

View this article at: <http://dx.doi.org/10.21037/tcr.2016.08.28>

Colorectal cancer is the third most common malignancy in the United States among both men and women and second leading cause of cancer death in the United States. There are about 135,000 estimated new cases of colorectal cancer in 2016 and about 50,000 deaths, however death rates have fallen by about 2.7% each year over the past 10 years (1). In fact, nearly 50% of patients with colorectal cancer develop hepatic metastases at some point during the course of their disease. Patients with untreated colorectal cancer liver metastases (CLM) have a median survival time of approximately 5 months with poor 5-year survival rates. Hepatic resection is the first choice treatment for the resectable cases and results in long-term survival for approximately 40% of patients. The perioperative mortality of hepatectomy is now less than 5%. In highly selected patients, the 5-year survival rates of hepatectomy is 22–40% (2). Radiofrequency (RF) ablation is a common, minimally-invasive interventional procedure for treatment of primary and secondary liver lesions with a low complication rate of about 1.3–2.2% (3,4). This treatment modality has been increasingly used in the treatment of CLM. Although many techniques have been invented to improve the ablation efficacy, RF ablation for unresectable CLM has shown wide variability in the reported 5-year overall survival rates (14–50%) and local tumor recurrent rate (3.6–60%) (3,5). Local tumor progression (LTP) and/or recurrence due to factors such as large tumor size (>3 cm), insufficient margin, irregular lesion contours, and heterogeneous blood supply, continues to be the primary cause of treatment failure (6,7).

Early detection of residual or locally recurrent tumor

after RF ablation is critical and can facilitate successful retreatment at an early stage. The International Working Group on Image-Guided Tumor Ablation recommended a baseline study that may perform in the first week or, at the latest, no more than 4 weeks after RF ablation. Subsequent routine follow-ups are then recommended every 3 to 4 months thereafter (8). Early re-intervention is needed to achieve optimal primary tumor ablation success. Contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI) are currently used to evaluate RF ablation efficacy. Pathologic studies have shown that the best correlation of necrotic tissue is defined by the zone of non-enhancement on cross-sectional studies. Ultrasound (US) is arguably the simplest, most widely available, and cost-effective. Recently, contrast enhanced ultrasound (CEUS) was tested in the planning, guiding and post-ablation assessment of RF ablation. Results indicate that CEUS is able to not only monitor the procedure in real time but also accurately show the treatment response at the end of the procedure, and performs equally to CT and MRI in the detection of tumor recurrence post RF ablation (9). Pathologic cell viability studies have shown that it needs at least 48 hours for the RF ablated tissue to undergo complete coagulation (10,11). Therefore, contrast enhanced imaging follow-up should be performed after 48 hours to accurately evaluate the coagulation zone. However, CEUS may also accurately evaluate the area of coagulation as early as 2 hours after ablation, as evaluated in a prior study (10).

Overall, follow-up imaging after thermal ablation interventions using primarily anatomic imaging procedures, such as CT or MRI, has been challenging.

The accuracy of assessment is often limited because of the presence of an ablation-induced hyperemic rim around the margin of ablated tissue which appears as early as 10–12 min after treatment and remains for 2–6 months (12). Previous clinical imaging and pathology correlation studies showed that this inflammatory rim presents benign periablational enhancement (BPE), usually uniform in thickness. In contrast, viable residual or recurrent tumor showed focal irregular peripheral enhancement on contrast enhanced CT or MR images (13,14). However, it is difficult to detect viable tumor in early stage solely based on these morphological findings. Dromain *et al.* (15) reported that CT and MR imaging may at earliest depict tumor recurrence at 4 months after RF ablation since the peripheral rim disappeared with time and was present in only 8% of the RF-ablated areas at this time point. The overall sensitivity to detect residual tumor after RF ablation when assessed with CT or MRI ranges between 44% and 89% (15,16). Since early detection of residual tumor allows initiation of additional treatment with potential benefits for patient survival (17–19), improved or novel imaging methods are needed for early detection of residual tumor and accurate follow-up of local tumor ablation.

Functional imaging was used in the differentiation of local tumor regression from BPE. Fluorine 18 fluorodeoxyglucose (FDG) positron emission tomography (PET) is a functional imaging modality that can be used to study the effects and efficacy of RF ablation. FDG-avid tumor becomes completely photopenic immediately after complete ablation. Focal areas of increased FDG uptake within the ablated zone are suggestive of residual disease. Reactive tissue changes in the periphery of the ablated lesion show a uniform low-grade FDG uptake, while residual tumor appears focal, nodular intense uptake. Several articles reported that PET/CT demonstrated good sensitivity in detection of early tumor recurrence after RF ablation compared with CT alone. To decrease the false positive rate induced by inflammatory response to the ablation, Khandani *et al.* did a pilot study to perform PET/CT within 2 days after RF ablation (20). They found that there is infrequent inflammatory uptake at the RF ablation site of liver metastases on 18F-FDG PET if scanning is performed within 2 days after ablation. They concluded that early PET has the potential to evaluate the efficacy of an RF ablation procedure by indicating macroscopic tumor-free margin as total photopenia and macroscopic residual tumor as focal uptake. However, how PET/CT should be incorporated into the routine postablation follow-up

imaging algorithm remains unclear.

Perfusion imaging has been used in early differentiation residual tumor from BPE in animal study. Using a rat subcutaneous tumor model, our group analyzed the perfusion of CEUS first-pass dynamic enhancement (FPDE) and microflow imaging (MFI) in residual tumor and BPE region before ablation and immediately, 1, 4 and 7 days after ablation. We found that blood volume in BPE was significantly higher than that in residual tumor in both FPDE imaging and MFI on days 0, 4 and 7 after ablation. Significantly greater blood flow was seen in BPE compared with residual tumor tissue in FPDE on day 7 and in MFI on day 4 (21). Furthermore, research has shown that tumor vessels are immature, lack normal smooth muscle and pericyte structure, and do not react to vasoactive drugs. The perfusion in BPE inflammatory tissue and viable residual tumor surrounding an ablated zone would change differently in response to vasoactive drugs. Using a subcutaneous tumor model and CT perfusion, our group found that phenylephrine markedly decreased blood flow in the BPE of ablated tumor but had little effect on the untreated viable tumor on days 2, 7 and 14 post RF ablation (22). Our study implies that perfusion imaging has the potential in early differentiation of residual tumor from BPE.

The presence of residual viable tumor has been proved to be related with local recurrence. Although more advanced imaging has been developed and is being used in post-ablation assessment, imaging is still not as accurate as pathology. Sofocleous *et al.* (23) studied the relation of histopathologic features of tissue adherent to electrodes after RF ablation of 68 liver tumors less than 5cm in size. Histopathological analysis of the tissue specimen adherent to RF electrodes revealed that 55 of 68 (81%) specimens demonstrated coagulation necrosis. However, on the first post-RF ablation contrast-enhanced CT scan (25–42 days post procedure), successful treatment (no enhancement) was suggested in 64 of 68 (94%) ablated tumors. In the viable group, local tumor progression (LTP) occurred in 12 of the 13 (92%) specimens; however, in coagulation necrosis group, LTP occurred in 16 of 55 (29%) specimens. The 1-year LTP-free rates were 0% and 74%, respectively ( $P < 0.001$ ). This indicated that contrast-enhanced imaging overestimates the treatment efficacy and possesses a false negative rate of about 13%, and the presence of viable tumor of the tissue attached to the ablation electrode highly predicts LTP.

Furthermore, in a recent published paper, Sotirchos *et al.* not only analyzed the pathology findings of the tissues attached to the RF ablation electrode, but also performed the

image-guided biopsy immediately after each RF ablation (24). They treated 67 CLM in the liver with RF ablation. The mean tumor size was 2.1 cm (range 0.6–4.3 cm). Tissue adherent to the RF electrode was present in 35 of 67 ablations. Biopsy tissue samples were obtained from the center of all of 67 ablated tumors and the margin of 61 of 67 ablated tumors. 24 tissue samples from 16 (24%) of 67 ablation zones were classified as viable tumor. Among them, 3 were from ablation electrodes, 12 were from ablated center, and 9 from the margin of the ablation zone. This indicated that biopsy can reveal more viable residual tumor cells compared to the tissue sample attached to the electrode alone. After a median follow-up period of 29 months, LTP occurred in 11 (69%) of 16 lesions classified as viable and in 10 (20%) of 51 lesions classified as necrotic ( $P < 0.001$ ). Interestingly, no significant correlation existed between the biopsy site (center versus margin) and the presence of tumor cells. Univariate analysis in this study showed that PET/CT ablation guidance was not a significant predictor of time to LTP. Multivariate analysis showed that a positive post ablation biopsy (hazard ratio = 3.4;  $P = 0.008$ ) and a minimal ablation margin size ( $< 5$  mm) (hazard ratio 6.7;  $P < 0.0001$ ) were independent predictors of shorter time to LTP. This study further confirmed that viable tumor may be present within the ablation zone, even when post ablation imaging displays sufficient ablation margins, and therefore pathologic assessment of tissue is an objective tool to assess ablation effectiveness. They also concluded that a minimum ablation margin of 5 mm and R0 surgical resections for CLM have comparable time to LTP outcomes.

The utilization of biopsy in the post ablation assessment is still challenging. First, it is an additional invasive procedure which increases the risk of complication. Second, there is an inherent disadvantage of a sampling error with the ablation zone. Third, in the absence of experienced tumor pathologists, routine standard hematoxylin-eosin staining is not sensitive and accurate to evaluate viable tumor immediately after ablation, due to no presence of the classic manifestations of coagulative necrosis in specimens obtained immediately after ablation (14). More advanced immunohistochemistry staining, such as Ki-67 (proliferative potential marker), OxPhos antibody (mitochondrial viability marker) are needed (24,25). This also has additional cost burden.

In summary, post-ablation assessment of liver tumor RF ablation remains challenging. While traditional cross-sectional and metabolic imaging have shown significant potential in predicting recurrence, there is a concern for underestimation of residual disease. Although post ablation

tissue sampling is invasive and costly at this time, it appears to provide an objective and more accurate assessment of residual viable tumor. Whether it will be incorporated into routine practice by interventional radiologists will depend on various different factors, including technical advances in ablation techniques to improve ablation margins and advances in functional and perfusion imaging techniques for early detection of residual malignancies.

## Acknowledgments

*Funding:* None.

## Footnote

*Provenance and Peer Review:* This article was commissioned and reviewed by the Section Editor Mu-xing Li, MD [Department of Abdominal Surgical Oncology, Cancer Hospital, Chinese Academy of Medical Sciences (CAMS) and Peking Union Medical College (PUMC), Beijing, China].

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr.2016.08.28>). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

*Open Access Statement:* This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: <https://creativecommons.org/licenses/by-nc-nd/4.0/>.

## References

1. SEER Stat Fact Sheets: Colon and Rectum Cancer. Available online: <http://seer.cancer.gov/statfacts/html/colorect.html>
2. Wong SL, Mangu PB, Choti MA, et al. American Society of Clinical Oncology 2009 clinical evidence review on

- radiofrequency ablation of hepatic metastases from colorectal cancer. *J Clin Oncol* 2010;28:493-508.
3. Solbiati L, Ahmed M, Cova L, et al. Small liver colorectal metastases treated with percutaneous radiofrequency ablation: local response rate and long-term survival with up to 10-year follow-up. *Radiology* 2012;265:958-68.
  4. Livraghi T, Solbiati L, Meloni MF, et al. Treatment of focal liver tumors with percutaneous radio-frequency ablation: complications encountered in a multicenter study. *Radiology* 2003;226:441-51.
  5. Van Tilborg AA, Meijerink MR, Sietses C, et al. Long-term results of radiofrequency ablation for unresectable colorectal liver metastases: a potentially curative intervention. *Br J Radiol* 2011;84:556-65.
  6. Curley SA. Radiofrequency ablation versus resection for resectable colorectal liver metastases: time for a randomized trial? *Ann Surg Oncol* 2008;15:11-3.
  7. Harrison LE, Koneru B, Baramipour P, et al. Locoregional recurrences are frequent after radiofrequency ablation for hepatocellular carcinoma. *J Am Coll Surg* 2003;197:759-64.
  8. Ahmed M, Solbiati L, Brace CL, et al. Image-guided tumor ablation: standardization of terminology and reporting criteria--a 10-year update. *J Vasc Interv Radiol* 2014;25:1691-705.e4.
  9. Frieser M, Kiesel J, Lindner A, et al. Efficacy of contrast-enhanced US versus CT or MRI for the therapeutic control of percutaneous radiofrequency ablation in the case of hepatic malignancies. *Ultraschall Med* 2011;32:148-53.
  10. Wu H, Wilkins LR, Ziats NP, et al. Real-time monitoring of radiofrequency ablation and postablation assessment: accuracy of contrast-enhanced US in experimental rat liver model. *Radiology* 2014;270:107-16.
  11. Goldberg SN, Girnan GD, Lukyanov AN, et al. Percutaneous tumor ablation: increased necrosis with combined radio-frequency ablation and intravenous liposomal doxorubicin in a rat breast tumor model. *Radiology* 2002;222:797-804.
  12. Rutherford EE, Cast JE, Breen DJ. Immediate and long-term CT appearances following radiofrequency ablation of renal tumours. *Clin Radiol* 2008;63:220-30.
  13. Hsu CP, Razavi MK, So SK, et al. Liver tumor gross margin identification and ablation monitoring during liver radiofrequency treatment. *J Vasc Interv Radiol* 2005;16:1473-8.
  14. Goldberg SN, Gazelle GS, Compton CC, et al. Treatment of intrahepatic malignancy with radiofrequency ablation: radiologic-pathologic correlation. *Cancer* 2000;88:2452-63.
  15. Dromain C, de Baere T, Elias D, et al. Hepatic tumors treated with percutaneous radio-frequency ablation: CT and MR imaging follow-up. *Radiology* 2002;223:255-62.
  16. Blokhuis TJ, van der Schaaf MC, van den Tol MP, et al. Results of radio frequency ablation of primary and secondary liver tumors: long-term follow-up with computed tomography and positron emission tomography-18F-deoxyfluoroglucose scanning. *Scand J Gastroenterol Suppl* 2004;(241):93-7.
  17. Curley SA. Radiofrequency ablation of malignant liver tumors. *Oncologist* 2001;6:14-23.
  18. Izzo F, Barnett CC Jr, Curley SA. Radiofrequency ablation of primary and metastatic malignant liver tumors. *Adv Surg* 2001;35:225-50.
  19. Veit P, Antoch G, Stergar H, et al. Detection of residual tumor after radiofrequency ablation of liver metastasis with dual-modality PET/CT: initial results. *Eur Radiol* 2006;16:80-7.
  20. Khandani AH, Calvo BF, O'Neil BH, et al. A pilot study of early 18F-FDG PET to evaluate the effectiveness of radiofrequency ablation of liver metastases. *AJR Am J Roentgenol* 2007;189:1199-202.
  21. Wu H, Patel RB, Zheng Y, et al. Differentiation of benign periablational enhancement from residual tumor following radio-frequency ablation using contrast-enhanced ultrasonography in a rat subcutaneous colon cancer model. *Ultrasound Med Biol* 2012;38:443-53.
  22. Wu H, Exner AA, Krupka TM, et al. Radiofrequency ablation: post-ablation assessment using CT perfusion with pharmacological modulation in a rat subcutaneous tumor model. *Acad Radiol* 2009;16:321-31.
  23. Sofocleous CT, Nascimento RG, Petrovic LM, et al. Histopathologic and immunohistochemical features of tissue adherent to multitined electrodes after RF ablation of liver malignancies can help predict local tumor progression: initial results. *Radiology* 2008;249:364-74.
  24. Sotirchos VS, Petrovic LM, Gönen M, et al. Colorectal Cancer Liver Metastases: Biopsy of the Ablation Zone and Margins Can Be Used to Predict Oncologic Outcome. *Radiology* 2016;280:949-59.
  25. Sofocleous CT, Garg S, Petrovic LM, et al. Ki-67 is a prognostic biomarker of survival after radiofrequency ablation of liver malignancies. *Ann Surg Oncol* 2012;19:4262-9.

**Cite this article as:** Wu H, Exner AA, Tavri S. Post radiofrequency ablation assessment of colorectal cancer liver metastases—does post ablation biopsy really matter? *Transl Cancer Res* 2016;5(S3):S411-S414. doi: 10.21037/tcr.2016.08.28