Viewpoint

Thermal ablation in colorectal liver metastases—the paradox of equipoise

Nalinie Joharatnam-Hogan[1,2], Khurum Khan[1,3,4]

[1]Department of Gastrointestinal Oncology, University College London Hospitals NHS Foundation Trust, London, UK; [2]MRC Clinical Trials Unit at UCL, London, UK; [3]UCL Cancer Institute, London, UK; [4]Department of Gastrointestinal Oncology, North Middlesex University Hospital, London, UK

Correspondence to: Dr Khurum Khan, MD (Res), MRCP (UK) (Medical Oncology), Dip Oncology, Honorary Associate Professor and Consultant Medical Oncologist, Gastrointestinal Oncology Service, Cancer of Unknown Primary Service, University College London Hospital; Research Lead North Middlesex University Hospital; GI Research Lead North London Cancer Research Network, UCL Cancer Institute and North Middlesex University Hospital, London, UK. Email: nalinie.joharatnam@nhs.net.

Comment on: Takahashi H, Berber E. Role of thermal ablation in the management of colorectal liver metastasis. Hepatobiliary Surg Nutr 2020;9:49-58.

Submitted Jan 01, 2021. Accepted for publication Jan 21, 2021.
doi: 10.21037/hbsn-21-1
View this article at: http://dx.doi.org/10.21037/hbsn-21-1

Approximately 25% of individuals with colorectal cancer (CRC) present with metastatic disease, and it is estimated that throughout the course of the disease, up to 50% of individuals may develop liver metastases, the majority of which are unresectable (1). However, thermal ablation is a treatment modality increasingly used to manage individuals with liver metastases. Recently Takahashi *et al*. published a comprehensive review of the various approaches to thermal ablation and summarised the recent evidence demonstrating an associated survival benefit supporting its use in the management of metastatic CRC (mCRC) (2). It is however critical to analyse the studies evaluated to ensure the strength of the evidence presented.

Takahashi *et al*. highlight the various approaches to thermal ablation, of which there are three main methods: open, laparoscopic and percutaneous (2). Of the three approaches, laparoscopy provides the visual benefits of open, with better evaluation of occult liver tumours on imaging and less morbidity, but also the percutaneous benefits of a minimally invasive approach. Additionally, simultaneous staging of other sites of peritoneal and hepatic disease not previously visualised may prevent avoidable or unnecessary procedures. The laparoscopic approach has been demonstrated to be non-inferior to the surgical approach measured by the rate of ablation sites recurrence (3). A multicentre study of 450 patients undergoing microwave ablation (MWA) showed no significant difference in morbidity by approach, although median hospital stay was prolonged with the open approach (4).

Microwave thermal ablation (MTA), the newest of ablative techniques is suggested to have superiority over radiofrequency ablation (RFA) based on its more predictable, faster and homogenous ablative zones. In Takahashi's study of 51 patients undergoing MTA, both total ablative time and local recurrence rates were significantly improved over those undergoing RFA (n=54) (5).

There has however been only one randomised trial published of 119 patients with unresectable colorectal liver metastases (CRLM), with no other sites of disease, evaluating RFA compared to systemic treatment alone in those with unresectable CRLM (6). Unfortunately, due to slow accrual, the study was amended from phase III to a randomised phase II trial. However after almost 10 years of follow up the combined modality arm of RFA and systemic treatment demonstrated a significantly improved overall survival (OS) [hazard ratio (HR) =0.58, 95% confidence interval (CI) = 0.38 to 0.88, P=0.01] and progression free survival (PFS) compared to systemic therapy alone, the first randomised study to show that aggressive local treatment is associated with a survival benefit (6). Those in the combined arm had a median of four liver metastases, and 26 out of 60 patients in the combined arm also underwent resection, the majority using the open approach. Nonetheless further phase III randomised trials need to be

conducted with a larger sample size to have true confidence in the potential survival advantage of ablative therapies, as well as an evaluation of the other modalities of ablation. Two randomised trials COLLISION (NCT03088150) and LAVA (ISRCTN52040363) comparing liver resection with thermal ablation for CRLM are currently ongoing hoping to answer these questions.

There are however multiple observational studies evaluating the survival benefit of RFA and/or MWA, with OS ranging from 24 to 57 months (2). Of the studies evaluating the influence of tumour size on efficacy, highlighted in Takahashi *et al*.'s review, in univariate and multivariate analysis all five consistently demonstrated tumour size to be an independent predictor of recurrence and survival, with 3cm or more predicting for poorer outcomes (2,4,7-10). The largest of these by Siperstein *et al*. prospectively evaluated 234 individuals receiving RFA (7). Strong predictors for survival were number of lesions, less than three versus more than three lesions (27 *vs*. 17 months, P=0.0018); dominant lesion size, less than 3 cm versus more than 3cm; and preoperative carcinoembryonic antigen value (7).

Although the literature in the randomised setting remains limited at present, Takahashi *et al*. present a reasonably broad criteria for consideration of ablation, including unresectable CRLM with fewer than eight lesions and the dominant lesion less than 4 cm (2). A multidisciplinary approach to treatment decisions for individuals with CRLM is crucial to ensure that where appropriate, liver surgery remains the gold standard for those with resectable disease, taking into account patient fitness, comorbidity, extent of disease, patient preference, but also goals of treatment (11). However, the association of ablation with less morbidity and a more rapid recovery makes it a desirable option in selected patients with unresectable disease, with multidisciplinary input still essential to assess suitability for ablation.

The evidence presented thus far remains positive for use of thermal ablation in the management of CRLM, and therefore can be considered both feasible in addition to systemic therapy, but also as a combined approach with surgery in unresectable disease, perhaps allowing interruption or discontinuation of systemic therapy. However as always, until phase III randomised evidence is available, these data should be interpreted with caution. In summary, we feel that a multidisciplinary approach taking into pertinent clinical, molecular, and biological features of the tumour is warranted in order to offer personalised and appropriate decision making.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office of *Hepatobiliary Surgery and Nutrition*. The article did not undergo external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/hbsn-21-1). 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.

References

1. Abdalla EK, Vauthey JN, Ellis LM, et al. Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases. Ann Surg 2004;239:818-25; discussion 825-7.
2. Takahashi H, Berber E. Role of thermal ablation in the management of colorectal liver metastasis. Hepatobiliary Surg Nutr 2020;9:49-58.
3. Giglio MC, Logghe B, Garofalo E, et al. Laparoscopic Versus Open Thermal Ablation of Colorectal Liver Metastases: A Propensity Score-Based Analysis of Local Control of the Ablated Tumors. Ann Surg Oncol 2020;27:2370-80.
4. Groeschl RT, Pilgrim CH, Hanna EM, et al. Microwave

ablation for hepatic malignancies: a multiinstitutional analysis. Ann Surg 2014;259:1195-200.
5. Takahashi H, Kahramangil B, Kose E, et al. A comparison of microwave thermosphere versus radiofrequency thermal ablation in the treatment of colorectal liver metastases. HPB (Oxford) 2018;20:1157-62.
6. Ruers T, Van Coevorden F, Punt CJA, et al. Local Treatment of Unresectable Colorectal Liver Metastases: Results of a Randomized Phase II Trial. J Natl Cancer Inst 2017;109:djx015.
7. Siperstein AE, Berber E, Ballem N, et al. Survival after radiofrequency ablation of colorectal liver metastases: 10-year experience. Ann Surg 2007;246:559-65; discussion 565-7.
8. Shady W, Petre EN, Gonen M, et al. Percutaneous Radiofrequency Ablation of Colorectal Cancer Liver Metastases: Factors Affecting Outcomes--A 10-year Experience at a Single Center. Radiology 2016;278:601-11.
9. Leung U, Kuk D, D'Angelica MI, et al. Long-term outcomes following microwave ablation for liver malignancies. Br J Surg 2015;102:85-91.
10. Kennedy TJ, Cassera MA, Khajanchee YS, et al. Laparoscopic radiofrequency ablation for the management of colorectal liver metastases: 10-year experience. J Surg Oncol 2013;107:324-8.
11. Van Cutsem E, Cervantes A, Adam R, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol 2016;27:1386-422.

Cite this article as: Joharatnam-Hogan N, Khan K. Thermal ablation in colorectal liver metastases—the paradox of equipoise. HepatoBiliary Surg Nutr 2021;10(2):276-278. doi: 10.21037/hbsn-21-1

