



# Utility of liver resection for breast cancer liver metastases, time for action

**Karan Rangarajan, Zaed Z. R. Hamady**

Department of Surgery, University Hospital Southampton NHSFT, University of Southampton, Human Development and Health, Camberley, UK  
*Correspondence to:* Karan Rangarajan. Department of Surgery, University Hospital Southampton NHSFT, University of Southampton, Human Development and Health, Camberley, UK. Email: [karan.rangarajan@gmail.com](mailto:karan.rangarajan@gmail.com).

*Comment on:* Grazi GL. Renewed considerations on the utility (or the futility) of hepatic resections for breast cancer liver metastases. *Hepatobiliary Surg Nutr* 2021;10:49-58.

Submitted Apr 07, 2022. Accepted for publication Apr 17, 2022.

doi: [10.21037/hbsn-22-131](https://doi.org/10.21037/hbsn-22-131)

View this article at: <https://dx.doi.org/10.21037/hbsn-22-131>

Breast cancer is the most common cancer in women with approximately 25–40% of these cases eventually develop metastases; the majority of which will be multi-site and include the liver (BCLM) exclusively in approximately 5% of patients with metastatic disease (1). The management and treatment of BCLM requires a multi-disciplinary approach with the current standard approach “with or without extrahepatic disease” being systemic chemotherapy and/or hormonal therapy, depending on tumour hormone receptor status (2). This is associated with a median survival time of 14.3 months (95% CI: 13.5–15.5 months) (3). Loco-regional treatment to BCLM has not been accepted as treatment strategy despite encouraging results from multiple case series.

In *HBSN*, Grazi *et al.* summarises the possible treatment options in line with the current literature suggesting that in contrast to colorectal liver metastases, the role of surgical treatment of BCLM is still a matter of debate (4). In addition, Grazi *et al.* provided a comprehensive breakdown of recent reviews pertaining to liver resection in BCLM; suggesting that majority of these reviews are limited by including case series often with low case numbers. Secondly, they note the heterogeneity of reported data, lack of defined selection criteria and randomised controlled studies. Furthermore, due to the scarcity of surgical procedures performed for this indication, the data collection periods for these studies are usually very long, thus introducing historical bias as well as bias in terms of staging and surgical technique. Despite the published data, proposing the safety

of surgical resection in BCLM, there remains a lack of level I evidence on long term outcome.

In one retrospective comparative study, 51 medically treated patients were matched to 49 surgically treated patients with BCLM, demonstrating significantly better survival in the surgical treated group (5). Two further comparative studies, one investigating 38 patients treated with chemotherapy over a 7-year period compared to 26 patients with isolated BCLM that received liver-directed therapies and another study including 61 patients with isolated BCLM; of which 23 were treated with surgery, 11 with percutaneous radiofrequency ablation and 27 with chemotherapy alone; both studies showed that locoregional approached to the liver demonstrated better overall survival than a systemic approach (6,7).

Grazi *et al.* also included one cost utility analysis (8), where liver resection followed by adjuvant systemic therapy in patients with BCLM proved to be cost-effective when compared with systemic therapy alone, particularly in oestrogen receptor-positive tumours.

In the end, the authors concluded that liver resection is an effective treatment for BCLM indeed this may be tied to the progress achieved in the field of liver surgery in recent years, particularly in terms of safety, excellent port operative survival, enhanced post-operative recovery and the introduction of minimally invasive technology with associated short recovery time. This is in stark contrast to colorectal liver metastases for example, where Liver resection is becoming the standard of care with patients

reaching 5-year survivals of >40% (9), and neuroendocrine neoplasms with a reported 5-year survival of 60–80% for curative resection of liver metastases (10).

However, not all BCLM patients are candidates for liver resection. There are well-described clinical characteristics of BCLM that predict a positive response to liver resection, as summarized by Golse and Adam (11). These characteristics include small liver metastases (<4–5 cm), positive hormone receptor status, radical resection, stable disease, and greater than 1–2 years between primary and secondary lesions. It is worth pointing out that bony metastasis is not a contraindication for surgery for BCLM. There have been significant improvements in breast cancer therapy in recent years and more patients are living longer with bony metastases with the use of modern chemotherapy, radiation and hormonal therapy to reduce the incidence and morbidity of metastasis.

Interestingly, although the current gold standard treatment for BCLM is systemic chemotherapy and/or hormonal therapy; our own recently published meta-analysis sought to compare survival outcomes for available systemic and local treatments, focusing on surgical resection and radiofrequency ablation (3). We extracted data from 54 studies and algorithmically reconstructing individual patient-level data from published Kaplan-Meier survival curves. Subsequent analysis of the reconstructed data demonstrated apparent 5 years survival advantage for the surgical group (53%) compared to chemotherapy group (14%) ( $P < 0.0001$ ). Our analysis suggests that local therapeutic interventions such as liver resection and radiofrequency ablation are effective treatments for BCLM, particularly in patients with metastatic disease localised to the liver.

Although current limited evidence has data to support the effectiveness of surgical resection for BCLM, further prospective studies for managing oligometastatic breast cancer disease are required.

### Difficulty in setting up randomised studies on BCLM

It appears there is unexplained difficulty to set up studies on BCLM treatment strategies with high powered randomised controlled trials, despite many attempts both in Europe and the UK. Understandably the role of surgical intervention is based on the proposed hypotheses of metastases which may vary depending on the organ. For example, it is suggested that the mechanism of metastatic spread in colorectal liver metastases (CRLM) occurs via the portal circulation, resulting

in liver limited metastases. By contrast BCLM implies a systemic spread, which may limit local therapy options.

Further to this, one inherent limitation of a proposed trial relates to current guidelines which don't recommend routine use of staging in early breast cancers. NCCN guideline recommend Staging investigations to include bone scans and staging CTs in stage I and II diseases only if patient have symptoms or abnormal liver function tests. In stage III breast cancers, staging CT may be considered routinely. Indeed, Canadian guidelines recommends liver ultra sound scan in stage II diseases only if more than 4 nodes are found to be involved (12). Therefore, we may be missing a significant proportion of liver metastases by not including staging investigations early in the course of breast cancer diagnosis. We believe that staging of breast cancer with CT scan should be considered, in similar way to colorectal cancer staging.

Despite metastasis being the main cause of breast cancer death, currently there is no surveillance abdominal imaging in the follow up protocols. In a Cochrane review by Rojas *et al.* (13) included 3,055 women, there was no difference in overall or disease-free survival rates for patients who underwent laboratory and imaging surveillance compared to those managed with clinical visits and mammography. Similar results were observed in two multicentric randomized surveillance studies performed in Italy in asymptomatic breast cancer patients (14,15). In both studies patients were randomized to intensive follow-up, including bone scintigraphy, chest X-ray, and liver ultrasound, whereas the control group was clinical review only. In both studies intensive surveillance found more metastases; however, no significant difference seen in the overall survival between the two groups. It is worth noting, that these surveillance studies did not offer active loco-regional treatment approach when metastases were diagnosed, therefore, not surprisingly that survival benefit was not seen. Given the morbidity and mortality of metastatic recurrence, we suspect a renewed interest in investigating the role of targeted abdominal imaging as surveillance in high-risk patients.

In summary, prospective randomised controlled trials comparing the outcomes between hepatic resection and best current treatment in oligometastatic BCLM, are urgently required.

### Acknowledgments

*Funding:* None.

## Footnote

*Provenance and Peer Review:* This article was commissioned by the editorial office, *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 <https://hbsn.amegroupp.com/article/view/10.21037/hbsn-22-131/coif>). 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

- Guarneri V, Conte P. Metastatic breast cancer: therapeutic options according to molecular subtypes and prior adjuvant therapy. *Oncologist* 2009;14:645-56.
- Singletary SE, Walsh G, Vauthey JN, et al. A role for curative surgery in the treatment of selected patients with metastatic breast cancer. *Oncologist* 2003;8:241-51.
- Rangarajan K, Lazzereschi L, Votano D, et al. Breast cancer liver metastases: systematic review and time to event meta-analysis with comparison between available treatments. *Ann R Coll Surg Engl* 2022. [Epub ahead of print]. doi: 10.1308/rcsann.2021.0308.
- Grazi GL. Renewed considerations on the utility (or the futility) of hepatic resections for breast cancer liver metastases. *Hepatobiliary Surg Nutr* 2021;10:49-58.
- Mariani P, Servois V, De Rycke Y, et al. Liver metastases from breast cancer: Surgical resection or not? A case-matched control study in highly selected patients. *Eur J Surg Oncol* 2013;39:1377-83.
- Polistina F, Costantin G, Febbraro A, et al. Aggressive treatment for hepatic metastases from breast cancer: results from a single center. *World J Surg* 2013;37:1322-32.
- Abbas H, Erridge S, Sodergren MH, et al. Breast cancer liver metastases in a UK tertiary centre: Outcomes following referral to tumour board meeting. *Int J Surg* 2017;44:152-9.
- Spolverato G, Vitale A, Bagante F, et al. Liver Resection for Breast Cancer Liver Metastases: A Cost-utility Analysis. *Ann Surg* 2017;265:792-9.
- Abbas S, Lam V, Hollands M. Ten-year survival after liver resection for colorectal metastases: systematic review and meta-analysis. *ISRN Oncol* 2011;2011:763245.
- Fairweather M, Swanson R, Wang J, et al. Management of Neuroendocrine Tumor Liver Metastases: Long-Term Outcomes and Prognostic Factors from a Large Prospective Database. *Ann Surg Oncol* 2017;24:2319-25.
- Golse N, Adam R. Liver Metastases From Breast Cancer: What Role for Surgery? Indications and Results. *Clin Breast Cancer* 2017;17:256-65.
- Myers RE, Johnston M, Pritchard K, et al. Baseline staging tests in primary breast cancer: a practice guideline. *CMAJ* 2001;164:1439-44.
- Rojas MP, Telaro E, Russo A, et al. Follow-up strategies for women treated for early breast cancer. *Cochrane Database Syst Rev* 2000;(4):CD001768.
- Rosselli Del Turco M, Palli D, Cariddi A, et al. Intensive diagnostic follow-up after treatment of primary breast cancer. A randomized trial. National Research Council Project on Breast Cancer follow-up. *JAMA* 1994;271:1593-7.
- Impact of follow-up testing on survival and health-related quality of life in breast cancer patients. A multicenter randomized controlled trial. The GIVIO Investigators. *JAMA* 1994;271:1587-92.

**Cite this article as:** Rangarajan K, Hamady ZZR. Utility of liver resection for breast cancer liver metastases, time for action. *HepatoBiliary Surg Nutr* 2022;11(3):446-448. doi: 10.21037/hbsn-22-131