Editorial

Breast cancer liver metastasis: time to resection and criteria

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A manuscript recently published by Grazi pools outcomes from data on patients undergoing surgical resection for breast cancer liver metastases (BCLMs). In the manuscript, Grazi shows no definitive proof of liver resections (LR) effectiveness for BCLM. However, the author suggests surgery may be possible in selected patients (1-3). Several retrospective case series have been published evaluating patients' survival following resection for BCLM, reporting results for 5-year overall and disease-free survivals. Grazi tries to make recommendations based on the data that show which patients have a good prognosis following liver surgery. However, the conclusion that surgical treatment is an option with a survival advantage for selected patients is not evident in the current literature as the criteria for surgery are not well established. In the article, those criteria have been identified in radical surgery (margins R0) and saving at least 30% of the liver parenchyma that are general rules of thumb for LR in oncological diseases (1). Also, the stable skeletal disease could not be a contraindication to resection (1,4), and the only identified prognostic criterion is the interval treatment in metachronous hepatic disease (>24 months) (1,3,4). Some considerations in a complex and systemic disease such as BC should be made when treating this patient subgroup. Notably, the decreased mortality rate and overall survival in BC are due to earlier tumour detection and treatment improvement (e.g., chemotherapy and target therapy) (1,5). Furthermore, tumour biology has been better clarified in the last decade. New drugs have increased the chance of survival in patients with metastatic disease. The gold standard for treating BCLM is a systemic therapy which remains the first line of treatment (4). Several protocols are available based on the expression of BC molecular phenotypes (endocrine-responsive metastatic breast cancer, HER2-positive metastatic breast cancer, and metastatic triple-negative breast cancer) (*Table 1*) (5-9).

Non-systemic alternatives for metastatic breast cancer include local therapies related to the tumour burden (2,10). Therefore, radical therapy could aim to debulk the tumour load after systemic therapy and improve the outcomes. An emergent field comprises oligometastatic disease treatment (up to five metastases) (5). That subgroup of patients can be treated by various local therapeutic approaches, including surgery and radiotherapy, with palliative, radical, and even curative intentions. However, discrepancies in results considering several prognostic factors stress the need for clear definitions and open different questions (e.g., how score stable bone metastasis and oligometastatic disease? How do we define synchronicity? How do we define long and short intervals between primary and BCLM? What are the cut-offs for multiple liver lesions? What are the cut-offs for BCLM size?) (*Table 2*) (4). Therefore, the lack of consensus about definitions reflects the limitations to planning further studies and add a significant selection bias to the already published studies.

Nevertheless, the leading cause of mortality for breast cancer is metastatic spread, and the liver is the third most frequent metastatic site of BC after lymph nodes and lungs (1). Advance in techniques and management of patients after LR have made liver surgery safe, effective with a low mortality rate and an acceptable complication rate. In addition, the studies have been published from a broad time interval with vast differences in medical and surgical treatment and a consequential impact on

Table 1 Systemic treatment in metastatic breast cancer

Molecular phenotypes BC	Treatment
Endocrine responsive BC (luminal A-luminal B ER+ HER2–)	CDK 4/6 inhibitor + endocrine therapy (fulvestrant or tamoxifen)
Endocrine-responsive BC PIK3 mutation	PIK3 inhibitor (alpelisib) + fulvestrant or mTor inhibitor (everolimus) + exemestane or abemaciclib
Endocrine responsive BC with BRCA1 or BRCA2 mutation	PARP inhibitors (Olaparib or Talazoparib)
HER2+ metastatic BC	First line: Dual HER2 blockade (trastuzumab plus pertuzumab) + chemotherapy (taxanes)
	Second-line: trastuzumab emtansine or trastuzumab + any chemotherapy agent. or trastuzumab + lapatinib
	Further line: neratinib + capecitabine or the highly selective anti-HER2 tyrosine kinase inhibitor (tucatinib) + capecitabine + trastuzumab
Metastatic TNBC (expressing more than 1%PD-L1)	Atezolizumab (immune checkpoint inhibitor) + Nab-paclitaxel or pembrolizumab + nabpaclitaxel or paclitaxel, or carboplatin-gemcitabine
Metastatic TNBC with germline BRCA or BRCA2-mutation	Veliparib + paclitaxel + carboplatin

BC, breast cancer; TNBC, triple-negative breast cancer.

Table 2 Prognostic factors in BCLM underwent surgery

Factors	Hazard ratio (95% CI)
Positivity of axillary lymph node	1.74 (1.25–2.41)
Number of liver metastasis	1.16 (1.09–1.24)
Size of liver metastasis	1.59 (1.26–2.01)
R1/2	2.64 (1.28–5.42
Interval between BC and diagnosis of liver metastasis (<24 months)	2.36 (1.14–4.89)
Extra-hepatic disease	1.64 (1.31–2.04)
The burden of the systemic disease (oligometastatic disease)	Not assessed
Receptor status (ER–)	2.09 (1.40–3.12)

BCLM, breast cancer liver metastasis.

the results (3,4). Most resections (parenchyma sparing *vs.* anatomical resection) provide free margins (1,4). In a recent meta-analysis, six comparative studies (surgical *vs.* systemic treatment) did not show any difference in survival for patients with BCLM highlighting the significant heterogeneity and lack of robust conclusions. The causes of the heterogeneity among studies were mainly due to the retrospective design of the studies, the selection bias among inclusion criteria, the lack of survival data about patients with BCLM resected included in "non-colorectal" or "non-neuroendocrine" reports, and the prolonged time interval between the selected studies, which complicated the comparison of results (1). Therefore, prospective studies with subgroup analysis are needed to improve the results and decrease the high level of heterogeneity.

Furthermore, there are no randomized controlled trials (RCTs) comparing surgery *vs.* other treatments in BCLM, and only overviews from retrospective studies are available. That weak evidence could explain the contrasting outcomes across studies. Another limitation in the published literature is the lack of time-to-event analysis, including intervention effects as the hazard ratio of the included studies (1,4). Another consideration regards the absence of comparison between various subgroups [e.g., no extra-hepatic disease *vs.* skeletal disease *vs.* other metastatic sites in early *vs.* late intervals (e.g., last ten years)]. Notably, the number of candidate patients for upfront surgery is minimal, with clear implications in planning any trial. To further complicate the picture, there are studies focused on other treatment adjuncts (e.g., locoregional and ablative techniques) that could represent promising and less invasive alternatives. An article comparing liver-directed therapies didn't show any benefits of ablation over medical therapy, although surgical treatment provided a temporary free-of-disease status (11). However, following this pathway the patients could interval the chemotherapy avoiding the drug toxicity. This strategy has been already applied in another type of cancer (e.g., colorectal). Therefore, we are still far in defining the best pathway to treat BCLM.

Surgery could be an ideal treatment for isolated BCLM downstaged or stable after the first line of systemic treatment. A comparative study by Wen *et al.* showed that the patients with low tumour burden, who are potential candidates for LR or local ablative therapies, had similar progression-free survival (PFS) with patients only receiving systemic therapy, indicating that hepatic surgical intervention could not provide survival benefits for all BCLM patients (3). Remarkably, BCLM patients who gained clinical benefit from the first-line endocrine or chemotherapy had a better PFS than those with progressive disease who underwent hepatic resection, and the patients only received systemic treatment (12).

In conclusion, according to the recent literature liver surgery may be performed in patients with BCLM after systemic treatment without progressive disease and in the context of oligometastatic diseases. However, further study should clarify definitions and clinical outcomes in this sub-group of patients.

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