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ORIGINAL ARTICLE

The role of liver-directed surgery in patients with hepatic metastasis from primary breast cancer: a multi-institutional analysis

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Abstract

Background: Data on surgical management of breast liver metastasis are limited. We sought to determine the safety and long-term outcome of patients undergoing hepatic resection of breast cancer liver metastases (BCLM).

Methods: Using a multi-institutional, international database, 131 patients who underwent surgery for BCLM between 1980 and 2014 were identified. Clinicopathologic and outcome data were collected and analyzed.

Results: Median tumor size of the primary breast cancer was 2.5 cm (IQR: 2.0–3.2); 58 (59.8%) patients had primary tumor nodal metastasis. The median time from diagnosis of breast cancer to metastasectomy was 34 months (IQR: 16.8–61.3). The mean size of the largest liver lesion was 3.0 cm (2.0–5.0); half of patients (52.0%) had a solitary metastasis. An R0 resection was achieved in most cases (90.8%). Postoperative morbidity and mortality were 22.8% and 0%, respectively. Median and 3-year overall-survival was 53.4 months and 75.2%, respectively. On multivariable analysis, positive surgical margin (HR 3.57, 95% CI 1.40–9.16; p = 0.008) and diameter of the BCLM (HR 1.03, 95% CI 1.01–1.06; p = 0.002) remained associated with worse OS.

Discussion: In selected patients, resection of breast cancer liver metastases can be done safely and a subset of patients may derive a relatively long survival, especially from a margin negative resection.

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Introduction

Breast cancer is the most frequently diagnosed cancer in the Western world and in the United States more than 40,000 patients are estimated to have died from breast cancer in 2014 alone.[1–4] Approximately 30% of patients with breast cancer will develop distant metastases at some point during their disease course.[5] While liver is the third most frequent site of metastatic spread, only 5–25% of patients will have isolated breast cancer liver metastases (BCLM) and will, in turn, be eligible for liver-directed surgery.[6] For these patients, a recent meta-analysis reported a 5-year survival of 39% following curative intent liver resection of BCLM.[7] Furthermore, median perioperative morbidity and mortality after liver resection of BCLM was reported to be 13% and 0.3%, respectively.[7] While the FDA has

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approved over 25 oncology drugs to treat breast cancer, there are disparate response rates with systemic chemotherapy.[8] Specifically, while up to 90% of primary tumors may respond to chemotherapy, systemic therapy is less effective for metastatic lesions, as only about 50% of metastatic lesions will respond.[8] The lower response rate for metastatic breast cancer may be due to a higher likelihood of acquired therapeutic resistance during the course of treatment.[9,10] In addition, among those patients with metastatic breast tumors that lose estrogen and progesterone receptor positivity, the effectiveness of hormonal treatments is even more limited.[11]

Given that BCLM is a systemic disease, surgeons have historically been less enthusiastic about operating on these patients.[12] As a result, most data on surgical management of BCLM have come from small, retrospective studies.[7,13,14] In fact, only a handful of single-institution studies had sufficient sample size to report on clinicopathologic prognostic factors in multivariable analysis.[7,15–18] As such, data on selection of patients with BCLM who might potentially benefit from a liver resection are lacking. The aim of the current study was to define the long-term outcomes of a select group of patients who underwent resection of BCLM, as well as identify which factors were associated with prognosis using a large international, multicenter collaborative database.

Methods

Data sources and patient population

Patients undergoing surgery for BCLM between January 1, 1980, and December 31, 2014 were identified using data collected at eight participating, international institutions (Johns Hopkins University, Baltimore, Maryland; Emory University, Atlanta, Georgia; Stanford University, Stanford, California; Curry Cabral Hospital, Lisbon, Portugal; Mauriziano Hospital, Turin, Italy; Medical College of Wisconsin, Milwaukee, Wisconsin; San Raffaele Hospital, Milan, Italy; University of Virginia Health System, Charlottesville, Virginia). Only patients undergoing surgery who presented with a histologically confirmed diagnosis of BCLM were included in the final study population. The study was approved by the Institutional Review Boards of each participating institution.

For each patient, sociodemographic data were collected including age, gender, race. Clinicopathological data on the primary tumor including TNM stage, presence of nodal disease, final resection margin, focality, localization, hormone receptor status, and type of surgery, as well as information on the BCLM, presence of extrahepatic metastases and receipt of adjuvant therapy were collected. Using the final pathology report, the presence of disease at the resection margin (R0: no disease at resected margin, R1: presence of disease at the resected surgical margin, R2: presence of macroscopic disease at the resection margin) and the presence of lymph node metastases were determined. Surgery specific information was also collected including the extent of surgery (minor, <3 Couinaud segments vs. major, ≥3 Couinaud segments) was determined, as well as the receipt of hormonal/systemic therapy. Complications with a Clavien-Dindo grade ≥3 were considered major complications.

Statistical analysis

Categorical variables were described as whole numbers and percentages, while continuous variables were reported as medians with interquartile (IQR) range. The primary outcome of the study was OS, which was defined as the time from the date of surgery to the date of death or date of last available follow-up, as appropriate. OS was estimated using the Kaplan–Meier method and compared between patient groups using the log-rank test. Cox proportional hazards regression analysis was utilized to identify potential risk factors associated with a worse OS. Specifically, associations between OS and margin status after BCLM surgery, as well as BCLM size were evaluated. Results from the Cox proportional hazards regression analysis were reported as hazard ratios (HR) with corresponding 95% confidence intervals (95% CI). Factors with a $p < 0.10$ were included into the multivariable analysis. All analyses were performed using SPSS 22.0 (IBM, New York). All tests were two-tailed and a $p < 0.05$ was used to define statistical significance.

Results

Demographic and clinicopathologic characteristics

A total of 131 patients underwent a resection for BCLM and met inclusion criteria (Table 1). Median patient age was 54.9 years (IQR 46–66); all patients were female. Over ninety percent of patients were Caucasian (n = 121, 92.4%); 10 were African–American (7.6%). Most primary tumors were unifocal (n = 92, 89.3%) with primary tumors being roughly equally distributed in the right (n = 54, 48.6%) and left (n = 53, 47.7%) breasts; 4 (3.6%) patients had bilateral primary tumors. Surgery for the primary breast tumor largely consisted either of a partial mastectomy (n = 53, 46.5%) or a modified radical mastectomy (n = 42, 36.8%). On final pathology, the majority of primary breast tumors were classified as either T1 or T2 (n = 81, 89.0%); however, a small number of patients (n = 10, 11%) had an advanced T3 or T4 primary breast cancer. Most patients (n = 58, 59.8%) had associated lymph node metastases; in contrast, only 5 (5.1%) patients had a positive surgical margin. Regarding hormonal receptor status, 79 (76.7%) patients had an estrogen positive tumor, while 74 (74%) women had a progesterone positive tumor; 54 (54.5%) patients had a HER2/neu positive tumor and 9 patients had a Ki-67 > 14%. After diagnosis of BCLM, 39 patients received chemotherapy, 51 patients received hormonal therapy and 35 received biological therapy. 55 (69.6%) patients who received neoadjuvant therapy had a measurable response.

Data pertaining to BCLM are included in Table 2. BLCM were diagnosed at a median of 34.0 months from the time of surgery for the primary breast tumor. The median time that elapsed between diagnosis and surgical treatment of BCLM was 2.2 months (IQR

Table 1 Clinicopathological characteristics of primary breast cancer

Characteristic	n = 131
Age, yr, median (IQR)	54.9 (46.0–66.0)
Sex	
Female	131 (100.0)
Race	
White	121 (92.4)
Black	10 (7.6)
BMI, median (IQR)	25.9 (23.0–28.5)
T stage primary tumor	
T1–T2	81 (89.0%)
T3–T4	10 (11.0%)
N stage primary tumor	
N0	39 (40.2%)
N+	58 (59.8%)
Margin primary tumor	
R0	93 (94.9%)
R1	4 (4.1%)
R2	1 (1.0%)
Primary tumor surgery	
Partial mastectomy	53 (46.5%)
Modified radical mastectomy	42 (36.8%)
Radical mastectomy	18 (15.8%)
Focality	
Monofocal	92 (89.3%)
Multifocal	11 (10.7%)
Localization	
Right mamma	54 (48.6%)
Left mamma	53 (47.7%)
Bilateral	4 (3.6%)
Receptor status primary tumor	
Estrogen positive	79 (76.7%)
Progesterone positive	74 (74.0%)
C-erb B2 positive	54 (54.5%)
Ki 67 > 14%	9 (69.2%)
Adjuvant therapy	90 (85.7%)
Disease free survival, mo (IQR)	34.0 (16.8–61.3)

Table 2 Clinicopathological characteristics of breast cancer liver metastases

Characteristic	n = 131
Reason for diagnosis	
Follow up	99 (87.6%)
Symptomatic disease	14 (12.4%)
Neoadjuvant chemotherapy	39 (75%)
Neoadjuvant hormonal treatment	51 (49.0%)
Neoadjuvant biological therapy	35 (40.2%)
Response to neoadjuvant therapy	
No	24 (30.4%)
Yes	55 (69.6%)
Diameter of BCLM, mm (IQR)	30.0 (20.0–50.0)
Number of tumors (IQR)	1 (1–3)
Distribution of BCLM	
Unilobar	95 (75.4%)
Bilobar	31 (24.6%)
BCLM surgery	
Minor surgery	73 (62.9%)
Major surgery	43 (37.1%)
Curative intent	
No	12 (9.2%)
Yes	119 (90.8%)
ER BCLM	
Negative	24 (26.7%)
Positive	66 (73.3%)
PR BCLM	
Negative	36 (40.4%)
Positive	53 (59.6%)
Margin BCLM	
R0	108 (90.8%)
R1	10 (8.4%)
R2	1 (0.8%)
Extrahepatic disease	
No	103 (86.6%)
Yes	16 (13.4%)
Adjuvant chemotherapy	41 (51.9%)
Adjuvant hormonal treatment	43 (47.8%)
Adjuvant biological therapy	21 (27.3%)

0–12.7). At the time of surgery for BCLM, roughly one-third of resections (n = 43, 37.1%) involved ≥3 Couinaud segments. On final histopathology, a negative microscopic margin (R0) was obtained in 90.8% (n = 108) of patients; 8.4% (n = 10) of patients had a microscopically positive margin (R1). Median tumor size was 3.0 cm (IQR, 2.0–5.0). At the time of BCLM resection, 66 (73.3%) patients had a tumor with positive estrogen receptor status, while 53 (59.6%) patients had a tumor with positive progesterone receptor status. Regarding extrahepatic disease, 16 patients (13.3%) had distant metastases at the time of surgery.

There were no procedure-related deaths within 90-days, however almost one quarter (n = 29, 22.8%) of patients experienced a complication. Among patients who had a complication 12 (41.3%) had a minor complication, while 17 (58.6%) had a major complication. Postoperatively 41 (51.9%) patients received cytotoxic systemic chemotherapy while 43 (47.8%) women received hormonal therapy.

Long-term clinical outcomes

At a median follow-up of 23.8 months (IQR, 10.2–53.6), median, 1- and 3-year OS was 53.4 months, 98.8%, and 75.2%, respectively. At the time of data analysis, 45 patients were alive without evidence of disease with a median follow-up of 18 months (IQR: 3–43.9). Following resection, recurrence occurred in 61 (51.7%) cases with a median disease-free survival of 24.0 months. Among patients who recurred following hepatectomy, 33.3% had an intrahepatic recurrence, 52.6% had an extrahepatic recurrence, and 14.0% had both an intra- and extra-hepatic recurrence. Recurrence outside the liver occurred in the lungs (45.2%), bones (12.9%), lymph nodes (19.4%), brain (12.9%) or in other locations (9.7%). Of these recurrences, 9 were treated with re-resection, 24 were treated with chemotherapy and 4 were treated in another manner (e.g. radiation, ablation).

On univariate analysis, BCLM tumor size (HR 1.03; 95% CI 1.01–1.05; $p < 0.001$) and a positive resection margin (HR 4.39; 95% CI 1.86–10.35; $p < 0.001$) were associated with worse overall survival (Supplemental Table 1). Specifically, the median survival of patients with tumors <3.0 cm was 58.8 months versus 53.3 months for patients with tumors ≥3.0 cm ($p = 0.041$) (Fig. 1). Similarly, patients who underwent an R0 resection had a median survival of 58.8 months, whereas median survival among patients who had an R1 resection was only 28.2 months ($p < 0.001$) (Fig. 2). Of note, extrahepatic disease and estrogen/progesterone receptor status were not associated with long-term survival (both $p > 0.05$). On multivariable analysis, after adjusting for other clinicopathologic factors, BCLM tumor size (HR 1.03, 95% CI 1.01–1.06; $p = 0.002$) and positive surgical margin status (HR 3.57, 95% CI 1.40–9.16; $p = 0.008$) remained associated with OS among patients with BCLM.

Discussion

Because metastatic breast cancer is largely a systemic disease, surgery has traditionally had a limited role in the treatment of these patients. While many centers employ hepatic resection for well-selected BCLM patients, empiric data to support surgical management is still lacking as most data come from small, single center studies.[12] In turn, in clinical practice cytotoxic chemotherapy and hormonal manipulation have been preferred to treat patients with BCLM. There has been a growing interest, however, in employing surgical approaches for patients with non-neuroendocrine, non-colorectal liver metastasis.[12] In fact, Adam and colleagues have noted that the dogma that surgical therapy has no role in the treatment of cancer patients with systemic disease might no longer be valid.[16] To this end, over the last several decades there has been increased reports of liver resection for BCLM. Specifically, while only one study on liver resection for BCLM was published prior to 1990, four reports were published between 1990 and 2000, and 23 have been published since 2000.[19] Most of these studies, however, were small, single center studies and the use of resection for BCLM remains controversial. As a result, there is an ongoing debate about the benefit of surgical resection. The current study is important because, using one of the largest, multi-institutional cohorts to date, we demonstrated that well-selected patients with BCLM can have a relatively long-term survival after surgical resection. Specifically, following resection of BCLM, median and 3-year OS were 53.4 months and 75.2%, respectively. Of note, most patients were diagnosed during regular follow up (87.6%) with a relatively long disease-free period (median, 34.0 months). In addition, those patients with small tumors and who had an R0 resection benefited the most (Figs 1 and 2). As such, our recommendation is that surgery of BCLM should largely be reserved for women with metachronous disease who have had a long-disease free-period in which the metastatic disease burden is low (i.e. small tumors) and in which all disease can be resected with a negative surgical margin.

Prior to the current study, Adam *et al.* had reported the largest study to date (n = 85) of patients undergoing liver resection for BCLM.[16] In that study, the authors reported a median survival of 38 months with a 5-year OS of 37% following resection of BCLM.[16] In a separate more recent study, Sadot *et al.* reported a

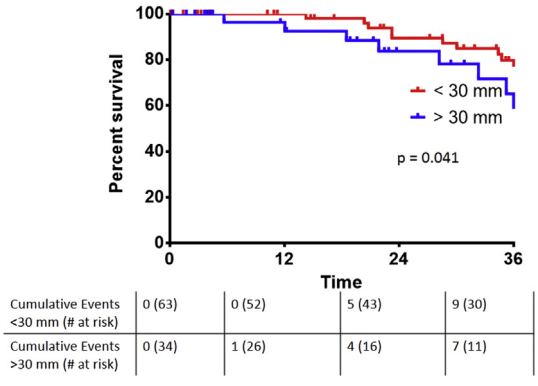

Figure 1 Overall survival stratified by diameter of the largest breast cancer liver metastases

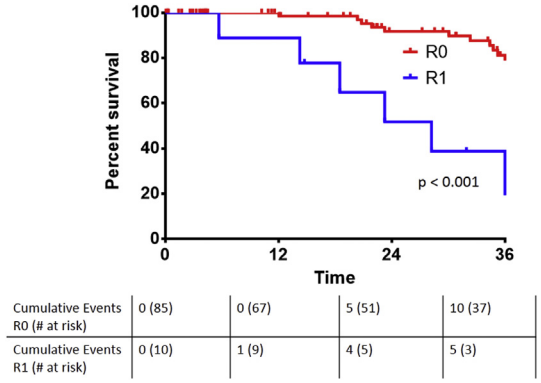

Figure 2 Overall survival stratified by final margin status of the breast cancer liver metastases resection

median survival of 50 months and a 5-year OS of 38% for patients with BCLM who had undergone liver resection.[20] Interestingly, some authors have reported a 5-year OS even as high as 61%.[21] Of note, these surprisingly high survival rates might be the result of very careful patient selection. As such, they might not reflect the survival noted in overall clinical practice. In the current study, using a multi-center database, 3-year OS following liver resection for BCLM was 75.2%. Selection of patients for surgery should, however, be discriminating in order to achieve these results. For example, previous data on surgery for BCLM have largely included patients with small, solitary lesions.[7] In one study that compared a medically treated group of patients versus a matched surgically treated cohort, patients had a median number of one liver metastasis (IQR, 1–2) and a median tumor size of 3 cm (IQR, 2–5).[20] Similarly, in the current study, the majority of patients had only one liver metastasis that was relatively small in size. In fact, metastatic tumor size was associated with long-term outcomes (HR 1.03, 95% CI 1.01–1.06; p = 0.002). These data were consistent with a previous report by Groeschl and colleagues who similarly noted that BCLM tumor size was an independent predictor of worse survival.[15]

A recent study from Memorial Sloan Kettering Cancer Center questioned the benefit associated with surgical treatment of BCLM.[20] In this study, the authors reported a similar survival when matched cohorts of surgically and medically treated patients were compared.[20] Among 69 patients who underwent surgery/ablation for BCLM, the median recurrence-free interval was 28.5 months and there was no significant difference in OS between the surgical and medical cohorts. In turn, the authors concluded that, while hepatic resection and/or ablation was not associated with a survival advantage, significant recurrence-free intervals could be accomplished with surgical treatment. In a separate study by Spolverato *et al.* the authors estimated the cost-effectiveness of liver resection followed by adjuvant systemic therapy relative to systemic therapy alone for patients with BCLM using a decision-analytic Markov model.[1]

Interestingly, the net health benefit of hepatic resection was 10.9 quality adjusted life months (QALMS) with letrozole as systemic therapy and only 0.3 QALMs when docetaxel + trastuzumab were used as systemic therapy. Furthermore, the addition of newer biological agents significantly decreased the cost-effectiveness of conventional systemic therapy alone relative to hepatic resection. As such, liver resection in patients with BCLM was determined to be cost-effective when compared to systemic therapy alone, particularly in ER + tumors or when modern agents were used. Collectively, the data would therefore strongly suggest that surgical intervention should be considered in highly selected patients with the goal of providing time off of systemic chemotherapy.[1,20]

The current study had several limitations that should be considered when interpreting the results. Given its retrospective nature, selection bias in how patients were chosen for surgical therapy was likely. The non-random selection of patients for liver resection of BCLM versus systemic treatment should not, however, have affected our underlying hypothesis, which was focused on determining the long-term outcomes of surgery in a select subset of patients with BCLM. However, the "true" benefit of surgery could not be estimated, as an appropriate control group of patients who received modern systemic chemotherapy alone was not available. Due to the rarity of resection of BCLM, the study also spanned a long period of time during which adjuvant treatments undoubtedly varied. Finally, although the study combined data from eight major hepatobiliary centers and is the largest cohort of surgically resected BCLM reported to date, the overall sample size was still relatively small. As such, some statistical analyses were limited and causal inferences should be considered in light of this limitation.

In conclusion, patients with small tumors that were resected with a negative surgical margin had reasonable long-term outcomes following surgical intervention. As such, in conjunction with increasingly efficacious chemotherapy for BCLM, surgical resection of BCLM may be appropriate as part of a multimodality, multi-disciplinary approach to patients who suffer from this disease.

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Conflicts of interest

None to declare.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.hpb.2016.05.014.