

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.

Received 3 April 2016; accepted 30 May 2016

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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

This study was presented as an oral presentation at the 12th International Hepato-Pancreato-Biliary Association (IHPBA) World Congress, April 20–23, 2016, Sao Paulo, Brazil.

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alone.<sup>1–4</sup> Approximately 30% of patients with breast cancer will develop distant metastases at some point during their disease course.<sup>5</sup> 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.<sup>6</sup> For these patients, a recent meta-analysis reported a 5-year survival of 39% following curative intent liver resection of BCLM.<sup>7</sup> Furthermore, median perioperative morbidity and mortality after liver resection of BCLM was reported to be 13% and 0.3%, respectively.<sup>7</sup> While the FDA has

approved over 25 oncology drugs to treat breast cancer, there are disparate response rates with systemic chemotherapy.<sup>8</sup> 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.<sup>8</sup> The lower response rate for metastatic breast cancer may be due to a higher likelihood of acquired therapeutic resistance during the course of treatment.<sup>9,10</sup> 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.<sup>11</sup>

Given that BCLM is a systemic disease, surgeons have historically been less enthusiastic about operating on these patients.<sup>12</sup> As a result, most data on surgical management of BCLM have come from small, retrospective studies.<sup>7,13,14</sup> In fact, only a handful of single-institution studies had sufficient sample size to report on clinicopathologic prognostic factors in multivariable analysis.<sup>7,15–18</sup> 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. Clinicopathologic 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,  $\geq 3$  Couinaud segments) was determined, as well as the receipt of hormonal/systemic therapy. Complications with a Clavien-Dindo grade  $\geq 3$  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. BCLM 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

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