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Review

Hepatic resection for metastatic breast cancer: A systematic review

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ABSTRACT

Background: Systemic chemotherapy is the mainstay of treatment for metastatic breast cancer with the role of surgery being strictly limited for palliation of metastatic complications or locoregional relapse. An increasing number of studies examining the role of therapeutic hepatic metastasectomy show encouraging survival results. A systematic review was undertaken to define its safety, efficacy and to identify prognostic factors associated with survival. **Methods:** Electronic search of the MEDLINE and PubMed databases (January 2000–January 2011) to identify studies reporting outcomes of hepatectomy for breast cancer liver metastases (BCLM) with hepatectomy was undertaken. Two reviewers independently appraised each study using a predetermined protocol. Safety and clinical efficacy was synthesised through a narrative review with full tabulation of results of all included studies.

Results: Nineteen studies were examined. This comprised of 553 patients. Hepatectomy for BCLM was performed at a rate of 1.8 (range, 0.7–7.7) cases per year in reported series. The median time to liver metastases occurred at a median of 40 (range, 23–77) months. The median mortality and complication rate were 0% (range, 0–6%) and 21% (range, 0–44%), respectively. The median overall survival was 40 (range, 15–74) months and median 5-year survival rate was 40% (range, 21–80%). Potential prognostic factors associated with a poorer overall survival include a positive liver surgical margin and hormone refractory disease.

Conclusion: Hepatectomy is rarely performed for BCLM but the studies described in this review indicate consistent results with superior 5-year survival for selected patients with isolated liver metastases and in those with well controlled minimal extrahepatic disease. To evaluate its efficacy and control for selection bias, a randomised trial of standard chemotherapy with or without hepatectomy for BCLM is warranted.

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1. Introduction

It is estimated that in the United States, 207,090 was diagnosed with breast cancer of whom 39,840 died from meta-

static disease in the year 2010.¹ The mortality rate has decreased over the years and 5-year survival of patients with stage IV disease is approximately 23%.¹ In a cohort study examining the survival trends of patients with recurrent

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breast cancer treated at the MD Anderson Cancer Centre between 1974 and 2000, the survival of 834 women when divided over five consecutive groups based on year of recurrence indicate a median survival and 5-year survival rate that improved from 15 months and 10% to 58 months and 44% in the latest time period.² Likewise in a meta-analysis of 1361 patients' data collected from randomised and non-randomised clinical trials by the Hellenic Oncology Cooperative Group between 1991 and 2006 stratified according to four of each 4 year time periods, the median survival and 3-year survival rate improved from 15 months and 18% to 31 months and 42%, respectively.³ Therefore, if an assumption that the natural history of this disease has not changed, the survival trends reported in the metastatic setting could be attributed to the improved prognosis gained from therapeutic advances in its palliative management.

Metastatic breast cancer commonly involves the bones, liver, lung and brain. Current management commonly involves systemic therapy with radiotherapy for local control of bone or brain metastases. In a large cohort study of 1038 patients from the Centre Antoine Lacassagne, Nice, survival by site of disease revealed a median survival of 43 months for lymph node and skin metastases, 33 months for bone metastases, 22 months for lung metastases, 12 months for liver metastases, 9 months for multiple metastatic sites and 3 months for brain metastases.⁴ Surgery was previously rarely employed in the metastatic setting.

In recent years, there has been an increased in the number of hepatic resectional procedures performed.⁵ Indications for hepatic resections have also expanded along with its technology. Colorectal liver metastases are the most commonly resected liver metastases and the indications for non-colorectal and non-neuroendocrine resections are less well defined. With advancement in modern chemotherapeutics for metastatic breast cancer, the prolongation in survival may be further maximised through surgery. In view of the safety of liver surgery and the availability of effective systemic therapies, a systematic review of hepatic resection of breast cancer liver metastases was undertaken to define the safety, efficacy and to identify prognostic factors associated with survival.

2. Patients and methods

2.1. Literature search strategy

Original studies published on hepatectomy for liver metastases from breast cancer were identified by searching the MEDLINE database (January 2000–January 2011) and PubMed (January 2000–January 2011) using the key words; 'breast cancer', 'liver metastases', and 'surgery'. The searches were limited to human articles published in the English language. The reference lists of all retrieved articles were manually reviewed to further identify potentially relevant studies. All relevant articles identified were assessed with application of a predetermined selection criterion.

2.2. Selection criteria

The safety and clinical efficacy of hepatectomy for breast cancer liver metastases was evaluated. Outcomes measures of

interest include the mortality, morbidity, median overall survival, 5-year survival rates and prognostic factors associated with survival. Studies were selected for inclusion if they reported a series comprising of ≥ 10 patients. This minimum number was selected to reduce the risk of confounding from small clinical series that may be influenced by selection bias and the impact of the unit's low volume experience. The studies were examined and rated level I evidence: randomised controlled trials (RCTs); level II evidence: non-randomised controlled clinical trials or well-designed cohort studies; level III evidence: observational studies, as described by the US Preventive Services Task Force.

2.3. Data extraction and critical appraisal

Two reviewers independently appraised each article using a standard protocol. Data extracted include the methodology, quality criteria, characteristics of BCLM in patients undergoing hepatectomy, mortality rates, complication rate, survival outcome and prognostic factors associated with survival were extracted and tabulated from the relevant articles' texts, tables, and figures. Discrepancies were resolved by discussion and consensus. Following tabulation of the data, the results were synthesised.

3. Results

Literature search using the above described strategy through both MEDLINE and PubMed databases identified 219 articles. Through applying the limits to the search of year and language, 90 articles remained. The title and abstract of each article were carefully examined by two reviewers leading to an exclusion of 70 articles that include experimental studies, review articles, case reports, non-breast cancer studies, articles that did not fulfil the study's endpoints and articles on ablative and other interventional therapies. The remaining 20 articles were examined and 9 articles were excluded due to lack of fulfilment of the minimum number of patients (6 articles), repeat publication (1 article), and the inability to obtain the articles (2 articles). Through reviewing the references of included manuscripts, a further 8 articles were included. This led to a total of 19 studies being included in this review. The studies were heterogeneous with regard to patient selection and baseline characteristics to allow a quantitative meta-analysis. A systematic review was therefore undertaken (Fig. 1).

3.1. Study characteristics

The 19 studies included comprised of 553 patients in total with a median of 21 (range, 10–85) patients per study. In three studies where the total number of breast cancer patients was reported, 69 of 19,541 patients underwent hepatectomy, corresponding to a rate of 0.3%.^{6–8} When each study was examined, the number of patients undergoing hepatectomy over the study period was 1.8 (range, 0.7–7.7) patient per annum at each institution. From eight studies reporting the rates of patients being explored and who underwent hepatectomy, 383 patients underwent a laparotomy of which 311 patients

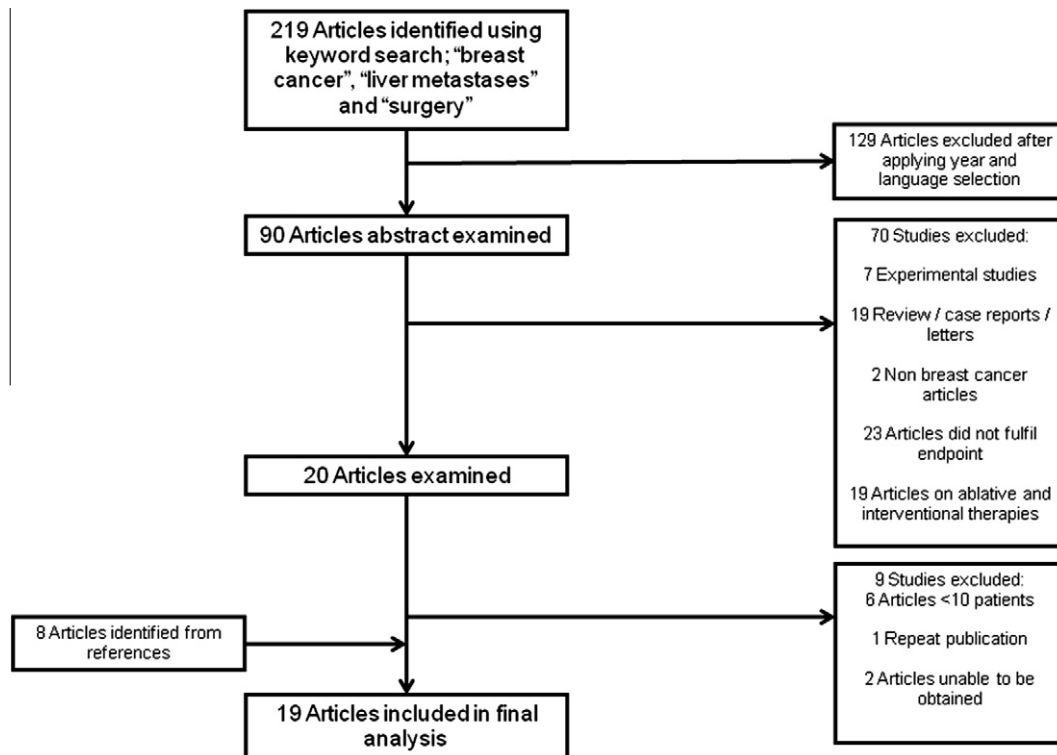


Fig. 1 – Flow diagram describing the selection of studies included in this review.

(81%) underwent hepatectomy. Peritoneal carcinomatosis was the most common reason of un-resectability (Table 1).

3.2. Histopathological clinical and procedural characteristics

The histopathological and clinical characteristics were not well reported in the studies reviewed. From eight studies, the histological subtype of BCLM was ductal carcinoma in 90% (range, 78–100%) of patients and this was the most common histological subtype.^{6–13} Eight percent (range, 0–14%) had lobular carcinoma and 2% (range, 0–11%) had other subtypes.^{6–12} Estrogen and progesterone receptor positivity in either primary or metastatic tumour occurred in 58% (range, 18–75%),^{8–12,14–16} and 35% (range, 13–75%)^{9–12,14,15} of patients, respectively. Only four studies reported HER2 positivity rates for which is likely to be due to the time period where the patients were recruited for the study cohort. HER2 positivity occurred in 28% (range, 21–29%) of patients.^{6,9,11,12} The median time from the primary tumour to development of liver metastases was 40 (range, 23–77) months^{6–11,14–17} (Table 2).

Hepatectomy was undertaken in patients with mostly solitary or with limited number of BCLM with a median of 2 (range, 1–4) as reported in 10 studies.^{7–9,11,13–16,18,19} The median size of the largest liver metastases was 30 (range, 25–57) mm as reported in seven studies.^{7–9,11,13,14,18} In 11 studies, resectional surgery required a major hepatectomy (resection of greater than 3 segments) in 50% (range, 0–64%) of patients.^{6–11,13–16,19} Dissection of the porta hepatis to sample or resect porto-caval lymph nodes was performed in a median of 11% (range, 0–100%) of patients as reported in six

studies.^{6,8,11,13,14,19} Concomitant extrahepatic disease that was controlled with systemic therapy or resected at the time of hepatectomy was reported in 13 studies in a median of 6% (range, 0–33%) of patients.^{6–11,13–19} A complete resection with histologically negative margins was possible in a median of 83% (range, 66–100%) of patients as reported in 10 studies^{6,8–11,13,14,16,17,19} (see Table 3).

3.3. Safety and clinical efficacy of hepatectomy for breast cancer liver metastases

The postoperative mortality rate was 0% (range, 0–6%). The postoperative complication (any complication) rate was 21% (range, 0–44%) as reported in 15 studies.^{6,8–11,14–23} The post hepatectomy median overall survival was 40 (range, 15–74) months as reported in 18 studies.^{6–23} The corresponding median 5-year survival rate was 40% (range, 21–80%) as reported in 16 studies.^{6–15,17–21,24} In two studies, the median overall survival from the primary tumour was 151 months⁶ and 211 months¹¹ with a 10-year survival rate of 76%¹¹ (Table 4).

3.4. Clinicopathologic factors impacting survival

Studies reporting prognostic factors associated with survival were tabulated to examine clinicopathologic factors that may guide the selection of patients for hepatectomy for BCLM. Age, stage of the primary tumour, involvement of lymph nodes, grade of the primary tumour, time to development of liver metastases, having prior metastatic recurrences, extent of hepatectomy, number of liver lesions, maximum size of the largest lesion, hepatectomy surgical

Table 1 – Demographic characteristics of hepatectomy studies for breast cancer liver metastases (NR refers to not reported).

| First author | Country of origin | Institution city | Year published | Study period | Level of evidence | Total breast cancer patients(n) | Patients undergoing surgery for liver metastases | | | Resections per year (n) |
|------------------------|-------------------|------------------|----------------|--------------|-------------------|---------------------------------|--|--------------|------------------|-------------------------|
| | | | | | | | Explored (n) | Resected (n) | Unresectable (n) | |
| Rubino ⁶ | Italy | Milan | 2010 | 1997–2005 | III | 2500 | 22 | 18 | 4 | 2.0 |
| Hoffmann ¹¹ | Germany | Heidelberg | 2010 | 1999–2008 | III | NR | 50 | 41 | 9 | 4.1 |
| O'Rouke ²¹ | UK | Basingstoke | 2008 | 1986–2006 | III | NR | NR | 11 | NR | 0.7 |
| Lubrano ¹⁵ | France | Rouen | 2008 | 1989–2004 | III | NR | 20 | 16 | 4 | 1.0 |
| Caralt ¹⁰ | Spain | Barcelona | 2008 | 1988–2006 | III | NR | NR | 12 | NR | 0.7 |
| Thelen ¹⁹ | Germany | Berlin | 2008 | 1988–2006 | III | NR | NR | 39 | NR | 2.2 |
| Kollmar ¹⁷ | Germany | Saar | 2008 | 2000–2007 | III | NR | NR | 27 | NR | 3.4 |
| Reddy ²² | USA | Durham NC | 2007 | 1995–2005 | III | NR | NR | 20 | NR | 1.8 |
| Lendoire ²⁴ | Argentina | Multicentre | 2007 | 1989–2006 | III | NR | NR | 19 | NR | 1.1 |
| Martinez ¹² | USA | Santa Monica CA | 2006 | 1995–2004 | III | NR | NR | 20 | NR | 2.0 |
| Adam ⁹ | France | Villejuif | 2006 | 1984–2004 | III | NR | 108 | 85 | 23 | 7.7 |
| Cordera ²⁰ | USA | Rochester MN | 2005 | 1988–1998 | III | NR | NR | 10 | NR | 0.9 |
| Weitz ²³ | USA | New York | 2005 | 1981–2002 | III | NR | NR | 29 | NR | 1.3 |
| Sakamoto ⁷ | Japan | Tokyo | 2005 | 1985–2003 | III | 11000 | NR | 34 | NR | 1.8 |
| Ercolani ¹⁸ | Italy | Bologna | 2005 | 1990–2003 | III | NR | NR | 21 | NR | 1.5 |
| Vlastos ¹³ | USA | Houston | 2004 | 1991–2002 | III | NR | 33 | 31 | 2 | 2.6 |
| Elias ¹⁴ | France | Villejuif | 2003 | 1986–2001 | III | NR | 65 | 54 | 11 | 3.4 |
| Selzner ⁸ | USA | Durham NC | 2000 | 1987–1999 | III | 6041 | 33 | 17 | 16 | 1.3 |
| Pocard ¹⁶ | France | Cedex | 2000 | 1988–1997 | III | NR | 52 | 49 | 1 | 4.9 |
| Total | – | – | – | – | – | – | – | 553 | – | – |
| Range | – | – | – | – | – | – | – | 10–85 | – | 0.7–7.7 |
| Median | – | – | – | – | – | – | – | 21 | – | 1.8 |

Table 2 – Histopathological and interval to liver metastases (NR refers to not reported).

| First author | Histological type | | | ER positive (%) | PR positive (%) | HER2 positive (%) | Median time to liver metastases (months) |
|------------------------|-------------------|-------------|-----------|-----------------|-----------------|-------------------|--|
| | Ductal (%) | Lobular (%) | Others(%) | | | | |
| Rubino ⁶ | 78 | 11 | 11 | NR | NR | 29 | 35 |
| Hoffmann ¹¹ | 96 | 2 | 2 | 21 | 13 | 21 | 41 |
| O'Rourke ²¹ | NR | NR | NR | NR | NR | NR | NR |
| Lubrano ¹⁵ | NR | NR | NR | 75 | | NR | 54 |
| Caralt ¹⁰ | 92 | 8 | | 42 | | NR | 55 |
| Thelen ¹⁹ | NR | NR | NR | NR | NR | NR | NR |
| Kollmar ¹⁷ | NR | NR | NR | NR | NR | NR | 77 |
| Reddy ²² | NR | NR | NR | NR | NR | NR | NR |
| Lendoire ²⁴ | NR | NR | NR | NR | NR | NR | NR |
| Martinez ¹² | 92 | 8 | 0 | 60 | 33 | 27 | NR |
| Adam ⁹ | 86 | 14 | 0 | 52 | 25 | 28 | 34 |
| Cordera ²⁰ | NR | NR | NR | NR | NR | NR | NR |
| Weitz ²³ | NR | NR | NR | NR | NR | NR | NR |
| Sakamoto ⁷ | 88 | 3 | 9 | NR | NR | NR | 23 |
| Ercolani ¹⁸ | NR | NR | NR | NR | NR | NR | NR |
| Vlastos ¹³ | 81 | NR | NR | 58 | 35 | NR | NR |
| Elias ¹⁴ | NR | NR | NR | 59 | | NR | 39 |
| Selzner ⁸ | 100 | 0 | 0 | 18 | NR | NR | 29 |
| Pocard ¹⁶ | NR | NR | NR | 68 | NR | NR | 60 |
| Range | 78–100 | 0–14 | 0–11 | 18–75 | 13–75 | 21–29 | 23–77 |
| Median | 90 | 8 | 2 | 58 | 35 | 28 | 40 |

margin, extrahepatic disease, hormonal expression status and HER2 status were included for examination.

From Table 5, the synthesised results suggest that stage of the primary tumour (8 of 8 studies; 100%), involvement of lymph nodes at the primary setting (6 of 7 studies; 86%), extent of hepatectomy (5 of 6 studies; 83%), number of liver metastases (7 of 8 studies; 88%) and size of the liver metastasis (5 of 6 studies; 83%) were not associated with survival. A positive hepatectomy surgical margin (3 of 4

studies; 75%) was shown to be associated with a poorer overall survival.

4. Discussion

The prognosis of patients with metastatic breast cancer is poor and the majority of patients will ultimately succumb to the disease. Treatment with systemic chemotherapy and incorporating the use of hormonal and targeted therapies

Table 3 – Surgical procedural characteristics (NR refers to not reported).

| First author | Median number of lesions (n) | Median size of largest lesion (mm) | Major hepatectomy (>3 segments) (%) | Porto-Caval lymphadenectomy (%) | Concomitant extrahepatic disease (%) | R0 margin (%) |
|------------------------|------------------------------|------------------------------------|-------------------------------------|---------------------------------|--------------------------------------|---------------|
| Rubino ⁶ | NR | NR | 28 | 22 | 0 | 100 |
| Hoffmann ¹¹ | 2 | 30 | 53 | 0 | 29 | 78 |
| O'Rourke ²¹ | NR | NR | NR | NR | NR | NR |
| Lubrano ¹⁵ | 1 | NR | 56 | NR | 0 | NR |
| Caralt ¹⁰ | NR | NR | 50 | NR | 8 | 92 |
| Thelen ¹⁹ | 2 | NR | 51 | 36 | 33 | 72 |
| Kollmar ¹⁷ | NR | NR | NR | NR | 0 | 85 |
| Reddy ²² | NR | NR | NR | NR | NR | NR |
| Lendoire ²⁴ | NR | NR | NR | NR | NR | NR |
| Martinez ¹² | NR | NR | NR | NR | NR | NR |
| Adam ⁹ | 2 | 28 | 64 | NR | 6 | 66 |
| Cordera ²⁰ | NR | NR | NR | NR | NR | NR |
| Weitz ²³ | NR | NR | NR | NR | NR | NR |
| Sakamoto ⁷ | 2 | 40 | 44 | NR | 26 | NR |
| Ercolani ¹⁸ | 1 | 57 | NR | NR | 0 | NR |
| Vlastos ¹³ | 2 | 29 | 13 | 0 | 0 | 81 |
| Elias ¹⁴ | 4 | 36 | 54 | 100 | 33 | 81 |
| Selzner ⁸ | 1 | 25 | 0 | 0 | 6 | 100 |
| Pocard ¹⁶ | 2 | NR | 37 | NR | 0 | 98 |
| Range | 1–4 | 25–57 | 0–64 | 0–100 | 0–33 | 66–100 |
| Median | 2 | 30 | 50 | 11 | 6 | 83 |

Table 4 – Safety and clinical efficacy of surgery for breast cancer liver metastases (NR refers to not reported).

| First author | Postoperative mortality (%) | Postoperative complication (%) | Median overall survival after hepatectomy (months) | 5-Year survival after hepatectomy (%) | Median overall survival from primary (months) | 10-Year survival from primary (%) |
|------------------------|-----------------------------|--------------------------------|--|---------------------------------------|---|-----------------------------------|
| Rubino ⁶ | 0 | 11 | 74 | 80 | 151 | NR |
| Hoffmann ¹¹ | 0 | 44 | 58 | 48 | 211 | 76 |
| O'Rourke ²¹ | 1 | 21 | 38 | 40 | NR | NR |
| Lubrano ¹⁵ | 0 | 38 | 42 | 33 | NR | NR |
| Caralt ¹⁰ | 0 | 25 | 36 | 33 | NR | NR |
| Thelen ¹⁹ | 0 | 13 | 38 | 42 | NR | NR |
| Kollmar ¹⁷ | 0 | 0 | 52 | 50 | NR | NR |
| Reddy ²² | 4 | 39 | 67 | NR | NR | NR |
| Lendoire ²⁴ | 2 | NR | NR | 53 | NR | NR |
| Martinez ¹² | 0 | NR | 32 | 33 | NR | NR |
| Adam ⁹ | 0 | 22 | 46 | 41 | NR | NR |
| Cordera ²⁰ | 2 | 7 | 39 | 40 | NR | NR |
| Weitz ²³ | 0 | 33 | 15 | NR | NR | NR |
| Sakamoto ⁷ | 0 | NR | 36 | 21 | NR | NR |
| Ercolani ¹⁸ | 0 | 21 | 40 | 25 | NR | NR |
| Vlastos ¹³ | 0 | NR | 62 | 61 | NR | NR |
| Elias ¹⁴ | 0 | 13 | 34 | 34 | NR | NR |
| Selzner ⁸ | 6 | 6 | 27 | 22 | NR | NR |
| Pocard ¹⁶ | 0 | 12 | 42 | NR | NR | NR |
| Range | 0–6 | 0–44 | 15–74 | 21–80 | – | – |
| Median | 0 | 21 | 40 | 40 | – | – |

are major progress made in the systemic management of metastatic breast cancer. This has led to improved 5-year survival of about 10% in the 1970s to 40% in the late 1990s.²⁵ In metastatic colorectal cancer, as with metastatic breast cancer, there has been significant progress made through the use of new era improved systemic therapy. This has led to a paradigm shift towards incorporating surgery in highly selected patients to provide a durable cure or survival prolongation.²⁶ Surgery has been approached mainly with a palliative intent in metastatic breast cancer for patients with fungating tumours, brain metastases, vertebral metastases with cord compression or impending pathologic fractures and lung metastases. In breast cancer, an individualised approach towards accurate disease re-staging, re-documentation of hormone sensitivity and HER2 positivity of the metastatic disease, selecting patients with chemo-responsive disease with limited metastatic disease and most importantly an understanding of the individual's tumour biological behaviour before selecting for surgery may hold the promise of long-term survival without compromising the quality of life. Prior reviews have broadly explored the role of metastasectomy in metastatic breast cancer.^{27,28} Howlader et al. more recently suggested that the outcomes of resection of liver metastases from breast cancer were comparable to that for colorectal cancer to suggest that it should become incorporated into the management guidelines.²⁹ In this review, we critically examined the safety and clinical efficacy of hepatectomy for breast cancer liver metastases (BCLM).

The literature covered in this topic centres around retrospective institutional case series. All studies were single-arm evaluating resection without a comparator group. The data suggest that hepatectomy for BCLM can be undertaken safely in the majority of selected patients as shown by a median postoperative mortality rate of 0%. This surgical option

was mostly provided in specialised centres performing hepatectomy for various primary and secondary liver tumours. Complications occurred at an acceptable rate of 21% and major complications were likely lesser. This safety profile is especially important in this group of patients with metastatic breast cancer where the goals in management are to prolong survival with an emphasis on restricting treatment-related toxicity by estimating the duration of survival and expected survival gains from treatment to select optimal therapies.

The efficacy data synthesised through review of the published studies where the median post hepatectomy survival of 40 months and 5-year survival of 40% suggests that surgery for BCLM may be an effective therapeutic strategy. It may compliment and serve as a chemotherapy-sparing intervention in patients with isolated and limited liver metastases. However, it must be emphasised that majority of the studies included in this review had included only patients with limited liver metastases, minimal residual extrahepatic that has completely responded to chemotherapy or with minimal resectable extrahepatic disease. In addition, the accurate sequence of perioperative chemotherapy is lacking. In colorectal liver metastases, the EORTC Intergroup randomised trial 40983 comparing perioperative chemotherapy involving six cycles of fluorouracil, leucovorin, and oxaliplatin (FOLFOX-4) before and six cycles after surgery or to surgery alone demonstrated a 9.2% progression-free survival benefit 3 years (chemotherapy 42.4% versus surgery alone 33.2%; $p = 0.025$) in the perioperative chemotherapy plus surgery group.³⁰ This management strategy may serve as a platform to orchestrate hepatectomy for BCLM given the chemo-responsiveness of this disease.

The histopathological data extracted in the reviewed series are limited due to lack of reporting. However, some authors have demonstrated that hormone refractory BCLM

Table 5 – Prognostic clinicopathologic factors of patients undergoing hepatectomy for breast cancer associated with poorer overall survival by univariate analysis.

| | Association with poorer overall survival | |
|--|--|--|
| | Significant (Positive association) | Non-significant (No association) |
| Younger age | Lubrano, ¹⁵ Martinez ¹² 2 studies | Hoffmann, ¹¹ Thelen, ¹⁹ Adam, ⁹ Vlastos, ¹³ Elias ¹⁴ 5 studies |
| Advanced primary tumour | | Hoffmann, ¹¹ Lubrano, ¹⁵ Thelen, ¹⁹ Adam, ⁹ Sakamoto, ⁷ Vlastos, ¹³ Elias, ¹⁴ Pocard, ¹⁶ 8 studies |
| Node positive primary | Pocard ¹⁶ 1 studies | Thelen, ¹⁹ Martinez, ¹² Adam, ⁹ Sakamoto, ⁷ Elias, ¹⁴ Selzner, ⁸ 6 studies |
| Poorly differentiated | | Lubrano, ¹⁵ Thelen, ¹⁹ Adam, ⁹ 3 studies |
| <1 year to liver metastases <1 year | Hoffmann, ¹¹ Selzner, ⁸ 2 studies | Lubrano ¹⁵ (<24/>24 months), Caralt ¹⁰ (<24/>24 months), Adam, ⁹ Vlastos, ¹³ Elias, ¹⁴ Pocard ¹⁶ (<24/>24 months) 6 studies |
| Previous metastases | Thelen ¹⁹ 1 study | Hoffmann, ¹¹ Selzner ⁸ 2 studies |
| Major hepatectomy Major | Lubrano ¹⁵ 1 study | Hoffmann, ¹¹ Thelen, ¹⁹ Vlastos, ¹³ Selzner, ⁸ Pocard ¹⁶ 5 studies |
| Multiple liver metastases | Lubrano ¹⁵ 1 study | Thelen, ¹⁹ Martinez, ¹² Adam, ⁹ Sakamoto, ⁷ Vlastos, ¹³ Elias, ¹⁴ Pocard ¹⁶ 7 studies |
| Larger tumour size | Hoffmann ¹¹ 1 study | Thelen, ¹⁹ Adam, ⁹ Vlastos, ¹³ Elias, ¹⁴ Selzner ⁸ 5 studies |
| Positive resection margin | Hoffmann, ¹¹ Thelen, ¹⁹ Adam ⁹ 3 studies | Elias ¹⁴ 1 study |
| Extrahepatic disease | Adam ⁹ 1 study | Hoffmann, ¹¹ Sakamoto, ⁷ Selzner ⁸ 3 studies |
| Hormone sensitive disease | Lubrano ¹⁵ 1 study | |
| Hormone refractory disease | Hoffmann, ¹¹ Martinez, ¹² Elias ¹⁴ 3 studies | Thelen, ¹⁹ Adam, ⁹ Sakamoto, ⁷ Vlastos ¹³ 4 studies |
| HER2 positive disease | Martinez ¹² 1 study | Thelen, ¹⁹ Adam ⁹ 2 studies |

is a negative predictor of overall survival.^{11,12,14} One study conversely indicated that hormone sensitive disease was a negative predictor of overall survival.¹⁵ More recently, an unpublished abstract presented at the 64th Annual Cancer Symposium describing the experience of the MD Anderson Cancer Centre reported a study of 68 patients undergoing hepatectomy for BCLM examined various clinicopathologic factors using a multivariate regression model and identified patients with oestrogen receptor positive disease and response to chemotherapy as independent factors associated with prolonged survival.³¹

Consistent data reported from the studies did not identify any impact of the following clinicopathologic variables on survival; primary tumour stage, involvement of lymph nodes at the primary setting, extent of hepatectomy, number of liver metastases and size of the liver metastases. A factor that appeared to influence survival was the hepatectomy surgical margin. Hoffman et al.¹¹ and Thelen et al.¹⁹ demonstrated significant survival difference in patients undergoing an R0 compared to R1/R2 hepatectomy. Adam et al.⁹ reported a median survival of 43 months, 46 months and 16 months in patients

undergoing a R0, R1 and R2 hepatectomy, respectively. Given that the initial two studies reported survival benefits of R0 versus R1/R2 and the third study showing similar survival of R0/1, it appears difficult to determine the adequacy of margin in hepatectomy for BCLM and this requires further investigation. Elias et al. showed in his experience that patients with R0 and R1/2 had a median survival of 40 months and 31 months respectively and this was not statistically different. However, the influence of surgical margin in his series might be confounded by the use of intra-arterial chemotherapy.¹⁴ Abiding with oncologic surgical principles, if a resection is performed with intent for cure, striving for an R0/R1 margin would likely achieve the best result. This is similar to colorectal liver metastases where it is recognised that an R0 and R1 margin achieves equivalent overall survival as a result of currently available effective chemotherapy.³²

Further, in the treatment of BCLM, there are emerging studies of local hepatic ablative therapies that have shown promising survival results. Meloni et al. reported 52 patients undergoing ultrasound guided radiofrequency ablation of BCLM where local tumour progression occurred in 25% with

a median survival and 5-year survival rate of 30 months and 27%, respectively.³³ Mack et al. described a technique using magnetic resonance image guided laser ablation using laser-induced interstitial thermotherapy applied in a large study of 232 patients where median survival was 52 months and 5-year survival was 41%.³⁴ These novel techniques are best applied in patients with small tumours (<4 cm). It is minimally invasive and avoids a laparotomy. However, it is highly operator dependent, the tumour location if near large vessels would be susceptible to a heat-sink phenomenon and is not widely available in interventional radiology units. The results however merit further research to determine if percutaneous or open ablation may be an equivalent substitute to resectional surgery.

At present, the bulk of workload of hepatic surgeons is in surgery for colorectal metastases. This is clearly reflected from this review that demonstrates only 1.8 case per annum of liver surgery was performed for BCLM. There is currently no consensus with regard to whether surgery and metastasectomy in pursuit of survival prolongation should be the approach in metastatic breast cancer. In general, the consensus would be that once a patient has a systemic breast cancer, metastasectomy has no role in survival prolongation. This was once the dogma in the management of colorectal cancer. However, in view of overwhelming non-randomised evidence of hepatectomy combined with effective systemic chemotherapy, this therapeutic option for colorectal liver metastases is now the standard of care. The improvements in survival that have resulted from effective systemic therapy for breast cancer warrant the conduct of a randomised controlled trial comparing chemotherapy alone to chemotherapy plus resection or ablation of breast cancer liver metastases. This will allow a definitive evaluation of the efficacy of surgery in combination with chemotherapy adjusting for selection bias that is inevitably present in observational series.

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Conflict of interest statement

None declared.

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