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Review

# Systematic review of early and long-term outcome of liver resection for metastatic breast cancer: Is there a survival benefit?



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#### ABSTRACT

*Background:* Isolated liver metastases occur rarely in patients with metastatic breast cancer. The success of liver resection (LR) for other metastatic disease has led centres to explore the option of LR for patients with isolated breast cancer liver metastases (BCLM). A number of small series have been published in the literature, however the evidence is conflicting. This study aimed to systematically review the literature to determine the perioperative outcome and survival of patients undergoing LR for BCLM.

*Methods:* An electronic search of Medline and Embase databases was performed to identify all published series. Patient demographics, management, peri-operative outcome and overall survival (OS) were obtained.

*Results*: A total of 1705 articles were identified of which 531 included patients with non-colorectal and non-neuroendocrine metastases. 43 articles including 1686 patients, met all the inclusion and exclusion criteria. R0 resection was achieved in 83% (683/825). Morbidity and 30-day mortality rates were 20% (174/852) and 0.7% (6/918), respectively. The median OS was 36 months (12–58 months). The median 1-, 3-and 5-year OS were 90%, 56% and 37%, respectively.

*Conclusions:* LR for BCLM can be carried out with acceptable peri-operative risks in selected patients with survival outcomes that appear to be superior to chemotherapy alone.

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#### 1. Introduction

Breast cancer is the most common cancer affecting females, with a life time risk of 12% [1]. If diagnosed early, the prognosis remains excellent. However, approximately 25–40% will develop metastatic disease [2,3]. Metastatic breast cancer is generally regarded as a systemic disease and has historically been treated with a palliative intent. However, over the course of time, the mortality rate from metastatic breast cancer is decreasing at 1–2% every year [4] which could be associated with the development of accurate diagnostic tools, identifying metastatic diseases at an earlier stage which are more responsive to treatment and the improvement of adjuvant systemic therapies. Recent figures have

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shown that 70–92% of patients with metastatic breast cancer have an ECOG score of one or less meaning that the aim of treatment is no longer about palliating symptoms but rather about prolonging life [5–7].

In patients with isolated metastatic disease, it remains debatable whether surgical resection alters patient survival. Isolated breast cancer liver metastases (BCLM) are reported in 2–12% of all patients with metastatic breast cancer [8–10]. If untreated it is associated with a survival limited to a few months [11,12]. Treatment with systemic chemotherapy leads to a prolongation of survival to 8–27 months and a 5-yr survival of 8–12% [10,13–16]. The outcome of surgical resection of BCLM is not well defined.

Improvements in patient evaluation, surgical technique and adjuvant treatments have enabled liver resection (LR) to be performed with low postoperative morbidity (22%) and mortality (2-4%) [17,18]. LR is regarded as a standard treatment for a number of cancers, including metastatic colorectal cancer. The biology of metastatic colorectal cancer differs in that the liver is the first site of

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drainage of the splanchnic circulation. In contrast, liver metastases from breast cancer would have travelled through the systemic circulation to reach the liver. It is likely that the breast cancer is disseminated by the time liver metastases are diagnosed. It is therefore questionable whether LR of BCLM influences patient survival.

The current literature only reports single centered retrospective studies. The number of patients in each series is small, and the majority have included patients operated on during the infancy of LR. Earlier systematic reviews have demonstrated that LR is a suitable treatment for a specific group of patients. However, these reviews include a small number of patients and describe a narrow range of disease and treatment details [19,20]. The aim of this study is to systematically review the literature to determine the perioperative morbidity and mortality and survival of patients undergoing LR for metastatic breast cancer.

#### 2. Methods

This systematic review was conducted according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [21].

#### 2.1. Literature search strategy

A systematic literature search was conducted using: Medline and Embase since inception of the databases until July 2015. No restrictions were applied with regard to language or publication date. The search was carried out to identify all manuscripts describing patients undergoing LR of non-colorectal and nonneuroendocrine (NCRNNE) metastases using the following keywords and Medical Subject Headings: 'liver or hepatic resection', 'hepatectomy', 'liver neoplasms [Surgery]' combined with 'liver neoplasms [Secondary]' whilst excluding 'colorectal', 'hepatocellular carcinoma', 'neuroendocrine carcinoma', 'cholangiocarcinoma', 'biliary tract neoplasms' and 'liver neoplasms [Radiotherapy]'. Titles were then electronically searched, and abstracts were obtained for all manuscripts that included patients undergoing LR for BCLM. Articles were included if they were original research containing data on patient survival following resection, excluding single case reports, systematic reviews, letters to editor and editorials. An assessment of risk of bias was not carried out due to the fact that the current literature regarding this topic has only shown retrospective, non-randomized articles.

#### 2.2. Data extraction

A reviewer (TY) appraised each article using a standard proforma which was then cross-checked by a second reviewer (AB). Discrepancies between the two reviewers were resolved by discussion and consensus. The data extracted from the articles' texts, tables and figures, included number of patients, age, patient selection criteria, characteristics of the breast cancer and its treatment, characteristics of the BCLM and treatment, presence of extrahepatic metastases, postoperative hospital stay, postoperative morbidity, follow-up, prognostic factors and the primary outcome being the overall survival. The data was extracted manually and electronically tabulated into Microsoft Excel spread sheet for analysis.

#### 3. Results

An initial search identified 1150 and 781 citations from Medline and Embase, respectively (Fig. 1). After exclusion of duplicates, the remaining citations were screened by reviewing the title and abstract to identify relevant articles. Of the 1705 potentially relevant citations, 1174 were excluded due to content not being relevant (n = 1085; colorectal or neuroendocrine metastases, ablative treatment methods, radiological imaging), patient survival not stated (n = 76), manuscripts could not be obtained (n = 3) or the article was not original research (n = 10: letters, editorials and commentaries). A total of 531 articles remained that included patients with metastases from adrenal (n = 9), breast (n = 44), gastric (n = 80), gastrointestinal stromal (n = 34), gynecological and germ cell (n = 41), lung (n = 7), melanoma (n = 43), esophagus (n = 3), pancreas (n = 50), renal (n = 32), sarcoma (n = 25) and other (n = 163). All these articles were searched electronically and a further 8 manuscripts were identified that described outcome of patients undergoing LR for BCLM. A total of 52 articles were obtained in print and read in detail. Nineteen articles were excluded due to being single case reports (n = 5), reviews (n = 11) and studies with duplicate data (n = 3). A further 10 articles were identified from reviewing the reference list. Forty-three articles met the study criteria and formed the basis of this systematic review

The 43 studies contained data on 1686 patients (Table 1). The studies were published between 1988 and 2014. All were retrospective studies; 1 was a case control study [22], and 88% (38/43) were single center reviews. The median number of patients in each of the studies was 25 (range, 3–454). Only 6 studies reported results for more than 50 patients [22–27]. The median age at diagnosis of BCLM was 51 years (range, 43–63) and all were female.

Operative details were provided by 15 studies, including 452 patients. Fifty-eight percent (264/452) of patients underwent mastectomy while the remainder, 42% (188/452), had breast conserving surgery (lumpectomy, quadrantectomy or wide local excision). Chemotherapy was administered prior to breast cancer surgery in 23% (38/168) of the patients and following breast cancer surgery in 57% (144/254) of the patients.

#### 3.1. Primary breast cancer histopathology

Twenty-nine studies describing 902 patients reported data on the breast cancer primary, stage and pathology (Table 2).

The TNM staging system was used by the majority of studies (17/ 29; 59%). Eighty-two percent of primary tumors were staged as T1 or T2 (445/541). There was no lymph node involvement (N0) in approximately half the patients (314/557; 56%). The M status was infrequently reported, being described in only 4 studies (n = 121) [24,28–30]. Seven studies gave the overall stage (n = 229); 72% were either stage I or stage II (165/229), 15% were stage III (35/229) and 13% were stage IV (29/229) [31–37].

The majority of tumors were invasive ductal carcinoma (525/611; 85.9%) and 12.8% (78/611) were lobular carcinomas. There were 5 patients (0.8%) with 'mixed' tumors and 3 (0.5%) patients were described as 'other' and excluded from the analysis [24,34,38,39].

Hormone receptor status was reported in 20 studies, involving 632 patients. Sixty-seven percent were estrogen receptor positive (231/346) and 40% were progesterone receptor positive (98/244). Six studies reported the presence of hormone receptors however they did not specify whether they were estrogen or progesterone (n = 285). Data on HER-2 receptor status was provided in 9 studies (n = 268) all of which were published after 2008. Thirty-seven percent (100/268) were positive for HER-2.

#### 3.2. Characteristics of BCLM

The details of the BCLM was described in 35/43 studies (81%), involving 1084 patients (Table 3).

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