



Original Research

Breast cancer liver metastases in a UK tertiary centre: Outcomes following referral to tumour board meeting^{☆,☆☆}Hiba Abbas¹, Simon Erridge¹, Mikael H. Sodergren, Michail Papoulas, Aamir Nawaz, Krishna Menon, Nigel D. Heaton, Andreas A. Prachalias, Parthi Srinivasan^{*}

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HIGHLIGHTS

- Patients who underwent locoregional treatment for BCLM had improved overall survival.
- Extrahepatic disease and R0 resection were identified as prognostic factors for overall survival.
- Presence of bony metastases was not a prognostic factor of overall survival.

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ABSTRACT

Introduction: To assess the outcomes from multidisciplinary board meetings (MDM) for patients with breast cancer liver metastases (BCLM) and identify prognostic factors for survival.

Materials and methods: A retrospective review of MDM records for patients referred with BCLM to a tertiary centre between 2005 and 2016. Patient demographics, clinicopathological factors and intervention type were analysed to find predictive factors for overall survival.

Results: 61 patients with BCLM were referred to the MDM. Treatment pathways included surgical resection (n = 23), radiofrequency ablation (RFA, n = 11), or chemotherapy (n = 27).

Surgical resection patients had an improved median overall survival compared to chemotherapy (49 v 20mo; p < 0.001). RFA showed comparable survival benefit (37 v 20mo; p = 0.011). Resection and RFA showed no significant difference in survival over one another (49 v 37mo; p = 0.854). Survival analysis identified that resection (p = 0.002) and RFA (p = 0.001) were associated with improved overall survival compared to chemotherapy.

Multivariate analysis identified extrahepatic disease (HR = 14.21; p = 0.044) and R0 resection (HR = 0.068; p = 0.023) as prognostic factors.

Conclusions: Surgical resection of BCLM may improve the overall survival in selected patient groups. This study identifies a cohort of patients, without extrahepatic disease and responsive to chemotherapy, who may particularly benefit from surgery.

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1. Introduction

Breast cancer is the most prevalent female cancer. The most recent epidemiological study conducted by the World Health Organisation on cancer identified that there were 1.67 million new diagnoses of breast cancer in 2012 [1]. The global incidence of breast cancer has risen substantially over the past 30 years and continues to rise due to increased pervasiveness of risk factors [1–3]. The survival of patients with breast cancer has improved over a similar time period. This has been attributed to the development of better systemic therapies and earlier diagnosis [4–6].

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The prevalence of distant metastases in invasive breast cancer can range from 29.0% to 53.2% [2]. The 5-year overall survival (OS) for localised breast cancer is 98.6%, which is prolonged, compared to 24.3% with distant metastases [7].

The liver is the 3rd most common site for breast metastases [8,9]. Approximately 50% of patients with metastatic breast cancer will eventually develop breast cancer liver metastases (BCLM) [10]. Patients with solitary BCLM have a median survival of approximately 25 months with chemotherapy [11,12]. The 2nd international consensus guidelines for advanced breast cancer (ABC2) outlined that systemic therapy, with chemotherapy and hormone therapy, is the current first line treatment modality in patients with BCLM [13]. However, there is a lack of knowledge as to the best treatment modalities in BCLM due to a paucity of randomised data for the use of loco-regional treatments. It is therefore currently recommended that both surgery and radio-frequency ablation (RFA) of liver deposits are carried out in a highly selective patient cohort. The most recent systematic review of resection and ablation identified that these treatments may, however, have the potential to improve survival producing 5-year OS rates between 21–61% and 27–41% respectfully [14].

Resection and ablation are both used with curative intent in the treatment of both colorectal liver metastases (CLM) and neuroendocrine liver metastases. Guidelines for both diseases indicate that hepatic resection is best indicated when it is possible to obtain a clear-margin resection with acceptable residual functioning volume, and controllable extrahepatic disease [15,16]. These provide favourable OS at 5-years compared to medical treatment [17,18]. In the most recent systematic review for BCLM, however, no prognostic factors for survival were identified [14]. Consequently there is a paucity of guidelines available to advise treatment in this cohort. Howlander et al. produced the only identified published guidelines in 2011 [19]. In the absence of randomised data on treatment for BCLM, a report on outcomes and identification of prognostic factors for OS in patients with BCLM would be valuable.

The primary aim of this study is to compare the survival outcomes for patients with BCLM discussed at multidisciplinary board meetings (MDMs). Additionally, this study hoped to identify prognostic factors for OS in patients with BCLM.

2. Materials and methods

A retrospective review was conducted for patients referred for treatment of BCLM at King's College Hospital, a tertiary centre for liver disease, between January 2005 and August 2016. The review utilised MDM and clinical records for all consecutive patients referred in this time period. Confirmation of BCLM was made via radiological criteria and clinical evaluation with/without percutaneous core liver biopsy. The study cohort included patients who underwent resection, radiofrequency ablation (RFA) or chemotherapy as their definitive treatment for BCLM. Patients with concurrent extrahepatic metastases were also included.

Patient demographics, clinicopathological characteristics, intervention type and survival data were collected. The estrogen receptor (ER), progesterone receptor (PR) and HER2 status were assessed for both primary tumour and BCLM. Staging was based upon the most up-to-date guidelines from the American Joint Committee on Cancer [20]. Synchronous presentation was defined as a time interval between the diagnosis of the primary breast cancer and development of BCLM within 6 months. The disease free interval was calculated as the difference in time between treatment for primary cancer and diagnosis of BCLM. Response to chemotherapy was calculated according to RECIST criteria [21]. Disease free survival (DFS) and OS were calculated from the date of commencement of chemotherapy regimen or surgery, as

applicable. DFS was calculated by presence of recurrence by the latest follow-up recorded.

2.1. Treatment algorithm

Case-by-case based discussion at the MDM was carried out to reach a consensus with regards to treatment modality. All patients were discussed in a MDM with surgeons and oncologists present. Prior to discussion at the MDM it was established whether patients demonstrated systemic dissemination via staging. If patients had systemic disease they were treated with first line chemotherapy and subsequently evaluated in the MDM to identify if systemic control had been obtained. A treatment algorithm, outlined in Fig. 1, was used to aid management decision. Patients with unresectable disease were offered chemotherapy. If these patients had a good or partial response they were restaged for discussion at a future MDM. Those who had resectable metastases underwent positron emission tomography-computed tomography (PET-CT) to determine the presence of extrahepatic disease. For those with isolated BCLM, they underwent hepatectomy or RFA. Those patients with BCLM and a single bony metastasis were treated using the same algorithm as those with isolated BCLM on a case-by-case consideration. Otherwise, those with extrahepatic disease had chemotherapy.

Liver Resections were performed either via laparoscopic or open techniques. Major resections were defined as those consisting of 3 or more liver segments. Data regarding postoperative morbidity and mortality, R0 resection, and repeat liver resections were collected. Postoperative morbidity was defined as complications within 90 days of surgery according to the Clavien–Dindo classification [22].

2.2. Follow up

Follow up schedule was dependent on MDM outcome. Those who underwent surgery were followed up within one month post-operatively following MDM discussion with regards to histopathological findings and the resection margins of the tumour. Those who had RFA had a follow up interval CT scan at 6 weeks post-RFA with MDM discussion of the scan the following week and clinic review at 8 weeks. Those who were referred to oncology for systemic chemotherapy were discussed in the MDM after completion of their intended treatment course and assessment of their response to treatment.

2.3. Data analysis

Continuous variables were analysed using one-way ANOVA and Kruskal-Wallis tests according to whether the data was parametric. The type of distribution was confirmed by a Shapiro-Wilk test. Analysis of categorical variables was carried out using either χ^2 test or Fischer's exact test. Statistical significance was set a $p < 0.05$.

Survival data were estimated using the Kaplan-Meier method and were compared using a stratified log-rank test. Univariate analysis was used to identify prognostic factors for OS. Prognostic factors with a p -value < 0.05 were included in a cox regression model. A cox regression model of univariate factors of $p < 0.1$ and $p < 0.2$ was constructed to further investigate importance of prognostic factors. In multivariate analysis, significance was determined by $p < 0.05$. All statistical analysis was carried out using SPSS (v.24.0.0.0, IBM, Armonk, NY, USA).

3. Results

A total of 80 consecutive patients were treated for breast cancer liver metastases (BCLM) at KCH between 2005 and 2016. KCH is a

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