

Surgical treatment of the primary tumour improves the overall survival in patients with metastatic breast cancer: A systematic review and meta-analysis

HANNAH HEADON, UMAR WAZIR, ABDUL KASEM and KEFAH MOKBEL

The London Breast Institute, Princess Grace Hospital, London W1U 5NY, UK

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Abstract. Traditionally, stage IV metastatic breast cancer has been treated with systemic therapy and/or radiotherapy in order to decrease cancer-associated symptoms, maintain quality of life and control disease burden. Previous research suggests that surgical treatment of the primary tumour may prolong survival, as well achieve local control of disease. Using the PubMed and Ovid SP databases, a literature review and meta-analysis was performed in order to assess whether surgical resection of the primary tumour in metastatic breast cancer prolongs survival. In this meta-analysis, a pooled hazard ratio of 0.63 (95% confidence interval, 0.58-0.7; $P < 0.0001$) was revealed, equating to a 37% reduction in risk of mortality in patients that underwent surgical resection of the primary tumour. Therefore, it was concluded that surgery of the primary tumour in stage IV breast cancer appears to offer a survival benefit in metastatic patients.

Introduction

A small percentage of patients presenting with breast cancer are found to have metastatic disease at the point of presentation. Breast cancer, with distant metastases beyond the regional lymph basin, remains a therapeutic challenge. The mainstays of therapy in such advanced disease are systemic therapies, including chemotherapy or endocrine therapy, or palliative loco-regional strategies, including targeted radiotherapy or surgery to metastases (1). Current recommendations for treatment of such advanced stage IV disease include no curative resection, as evidence of a survival benefit for primary resection in such cases is lacking (2).

However, recent previous studies suggest that primary tumour resection may be an independent factor in improving

survival and in addition, control of local symptoms (3,4). It has been suggested that resection of the primary tumour in stage IV disease aids survival by reducing the tumour burden, specifically the number of circulating tumour cells (5). Additionally, recent evidence have postulated a model in which metastases can 'self-seed' and circulate back to the primary tumour, accelerating growth and angiogenesis through cytokine action (6). Furthermore, the role of the primary tumour in advanced disease is a central theme of currently debated disease models centred around the postulated role of cancer stem cells (7).

However, a consensus regarding a curative role for primary resection in stage IV disease remains to be determined, as the relevant evidence is far from unanimous. It is suggested that the beneficial effect observed in other previous studies may be the result of a selection bias.

In order to better examine this issue, the present study performed a systematic review of the literature and a meta-analysis in order to calculate the survival benefit of primary resections in stage IV breast cancer.

Materials and methods

Data sources and searches. A comprehensive search of the PubMed (<http://www.ncbi.nlm.nih.gov/pubmed>) and Ovid SP (<http://ovidsp.ovid.com/sp-3.18.0b/ovidweb.cgi>) databases was performed to identify relevant published literature prior to February 25th 2015. The search keywords used were as follows: 'Stage IV breast cancer' and 'surgical excision' or 'surgery' or 'local treatment'.

The authors as per pre-specified inclusion and exclusion criteria assessed the articles identified.

Inclusion and exclusion criteria. Prospective clinical trials and retrospective case series regarding female adult patients with reported outcomes as a function of surgical resection of primary breast cancer in the presence of histologically confirmed distant metastases were included. Conservative and extended resections were included, with no stipulations regarding systemic therapies and the use of radiation or surgery in the regional lymph basin.

The exclusion criteria were as follows: i) Studies reporting no hazard ratios (HRs) for overall survival of adult female patients, according to multivariate analysis; ii) studies that

Correspondence to: Professor Kefah Mokbel, The London Breast Institute, Princess Grace Hospital, 45 Nottingham Place, London W1U 5NY, UK
E-mail: kefahmokbel@hotmail.com

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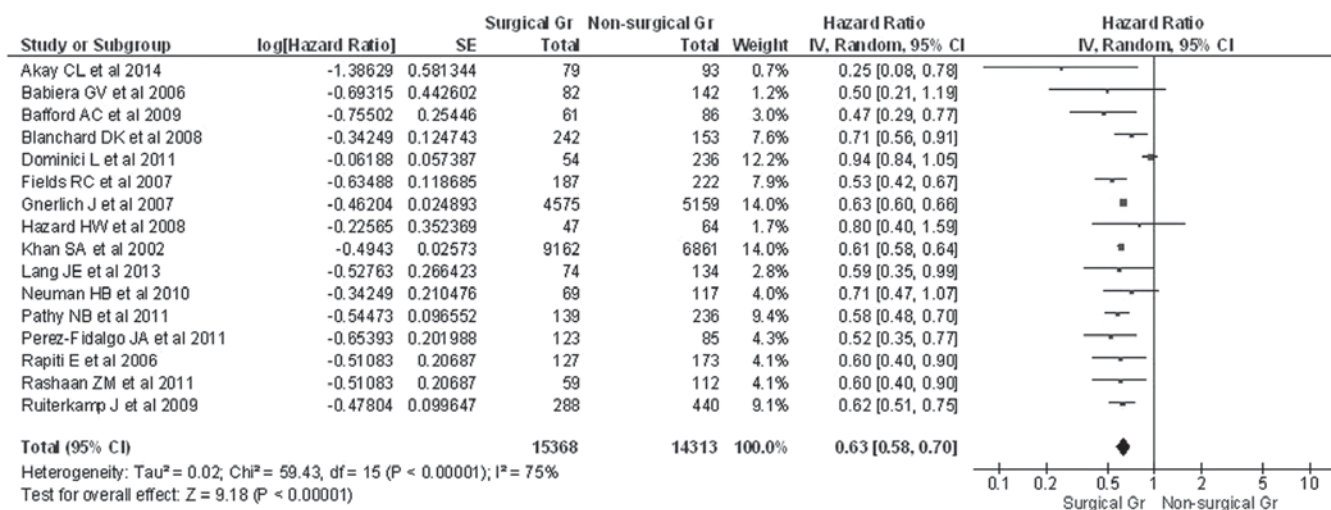


Figure 1. Forest plot of hazard ratios and pooled analysis for overall mortality for surgery, vs. no surgery in patients with stage IV breast cancer.

failed to report 95% confidence intervals (CIs) for the HRs; iii) unavailability of full text for data extraction; iv) reviews, case reports, letters or commentaries.

Data extraction and management. Data was extracted by the authors independently using characteristics of included studies, the baseline characteristics of included patients and the aforementioned outcomes. The recorded data included author, publication date, study design, participants, interventions, median age, oestrogen receptor (ER) status, human epidermal growth factor receptor 2 status and metastatic sites.

Measures of treatment effect and statistical analysis. HRs and CIs for overall survival as a function of surgery of primary breast cancer with or without other treatment modalities were retrieved for each study. An HR<1 meant a reduced risk of mortality for surgically treated patients compared with those who did not undergo primary tumour resection.

A meta-analysis of HRs was performed with both fixed effect and random effect models considered. Statistical heterogeneity among the included studies was assessed using Cochran's Q test, and a χ^2 test and I² statistic was used to quantify the inconsistency: A value of 0-100% indicated increasing heterogeneity. The assumption of homogeneity was considered invalid for P<0.1. Summary estimates were reported from the random-effects models.

Potential publication biases were evaluated with Begg's funnel plots for overall survival and subsequently with both Begg's and Egger's tests. Duval and Tweedie's trim and fill method was also performed.

Results of the meta-analyses were reported as a classical forest plot. Statistical analyses were performed using Review Manager 5.1 and Comprehensive Meta-Analysis version 3.0.

Results

Literature search results and the characteristics of the included studies. A total of 1,628 studies were retrieved, of which 19 initially met the inclusion criteria. Of these studies,

two were excluded at the end of the selection phase due to a lack of HRs for overall survival (OS) in the multivariate analysis. One additional study was excluded as it failed to report a 95% CI for HR, thus precluding calculation of the standard error for meta-analysis. Therefore, 16 studies met the full inclusion criteria for this meta-analysis (Table I) (2-4,8-20). All previous studies were retrospective case studies.

Meta-analysis for OS. The present study first tested the overall null hypothesis, which stated that all treatment effects equalled zero. This is equivalent to testing whether all HRs in all studies are equal to 1, indicating no effect from surgery. Both non-directional and directional tests rejected the null hypothesis.

The HRs for OS and standard errors for the estimated HRs were reported or extrapolated for all included studies. Significant heterogeneity was observed by calculating the χ^2 test for heterogeneity (P<0.0001) and the I² test demonstrated an index of 75%, indicating considerable inconsistency between the selected studies. Therefore, the present study assumed a random effects model that takes into account variability within and between studies. The pooled HR for OS was 0.63 with a 95% CI of 0.58-0.70 (Table I), confirming the suggestion that surgery is beneficial in terms of reducing the risk of mortality by 37%. These results all illustrated in the forest plot in Fig. 1.

The funnel plot for risk of bias in OS (Fig. 2) revealed that all studies, with the exception of Dominici *et al* (10), fall within the 95% CI, and they are relatively symmetrically distributed. Therefore, it would be reasonable to surmise that there are significant systematic differences between the individual studies.

Evidence of publication bias was not revealed in the present analysis, despite the use of multiple tests for this purpose (Egger's test, P=0.40785; Begg test, P=0.50 Mazumdar's rank correlation test, P=0.50).

According to Duval and Tweedie's 'trim and fill' method under the random-effect model (point estimate=0.64674; 95% CI=0.58774-0.71167), the imputed point estimate for OS remained unchanged.

Table I. Characteristics of the included previous retrospective case studies.

| Author, year | No. participants/No. surgically treated/No. not surgically treated | Follow-up time (months) | Age (years) | HR (95% CI) P-value | Use of systemic therapy/radiotherapy (%) | Factors associated with increased overall survival | (Refs.) |
|------------------------------------|--|-------------------------|------------------|--|--|--|---------|
| Akay <i>et al.</i> , 2014 | 172/79/93 | 33 | 51 (mean) | 0.9 (0.2-1.6) P=0.0001 | 45 (57%) | Local control significantly associated with surgery | (3) |
| Babiera <i>et al.</i> , 2006 | 306/224/82 | 32.1 (median) | 52 (22-88) | 0.5 (0.21-1.19) P=0.12 | 98%/NR | Number of metastatic sites Her2neu status | (4) |
| Bafford <i>et al.</i> , 2009 | 147/61/86 | NR | 49.2 (28.5-79.7) | 0.47 P=0.003 | 87 (CT) 57 (HT)/38 | Positive ER and Her2neu status | (8) |
| Blanchard <i>et al.</i> , 2008 | 395/242/153 | NR | 63.30 | 0.71 (0.556-0.906) P=0.006 | NR | ER and PR positive status. Reduced number of mets. Surgery with negative margins (HR=0.5) | (9) |
| Dominici <i>et al.</i> , 2011 | 290/54/236 | NR | 53.4 (mean) | 0.94 (0.84-1.05) P=0.27 | 39 (74%)/ 7 (13%) | ER+, fewer met sites and use of ET associated with longer survival | (10) |
| Fields <i>et al.</i> , 2007 | 406/187/222 | 142 (123-157) | 55.9 (mean) | 0.53 (0.42-0.67) P<0.0001 | NR/NR | Presence of bny mets vs visceral mets, lower age | (11) |
| Gnerlich <i>et al.</i> , 2007 | 9,734/4,575/5,159 | NR | 62 | 0.63 (0.60-0.66) P<0.001 | NR/34 | NR | (12) |
| Hazard <i>et al.</i> , 2008 | 11/47/64 | 26.9 (2.5-138) | 52.7 (mean) | 0.798 (0.40-1.60) P=0.520 | 100/67 | Median survival times noted | (13) |
| Khan <i>et al.</i> , 2002 | 1,602/39,162/6,861 | NR | 62.3 (mean) | 0.61 (0.58-0.61) negative surgical margins 0.751 (0.71-0.793) positive surgical margins P<0.0001 | 77.5/NR | CT, HT negative surgical margins, reduced number of met sites and soft tissue vs visceral mets indicated a higher rate of overall survival | (14) |
| Neuman <i>et al.</i> , 2010 | 186/69/117 | 52 | 53 | 0.71 (0.47-1.06) P=0.1 | NR/NR | ER+, PR+ and HER2+ associated with longer survival | (16) |
| Pathy <i>et al.</i> , 2011 | 375/139/236 | NR | 49 | 0.58 (0.48-0.69) P=NR | CT 75 (54%) HT 92 (66.2%)/ 93 (66.9%) | Age under 65 benefited most as surgery as did negative surgical margins | (17) |
| Pérez-Fidalgo <i>et al.</i> , 2011 | 208/123/85 | 29.86 | 55.9 (mean) | 0.52 (0.35-0.77) P<0.001 | CT 103 (83.8%) HT 19 (15.4%)/57 (46.3%) | Benefits seen mainly in those with visceral disease | (18) |
| Rapiti <i>et al.</i> , 2006 | 300/127/173 | NR | 61.8 | 0.6 (0.4-1.0) P=0.049 overall negative surgical margins 0.5 (0.3-0.7) P=0.0003 positive surgical margins 0.8 (0.5-1.1) | 53 (CT) 43 (HT)/21 | Effect particularly evident for women with only bony metastases | (19) |

Table I. Continued.

| Author, year | No. participants/No. surgically treated/No. not surgically treated | Follow-up time (months) | Age (years) | HR (95% CI) P-value | Use of systemic therapy/ radiotherapy (%) | Factors associated with increased overall survival (Refs.) |
|--------------------------------|--|-------------------------|-------------|--|--|--|
| Ruiterkamp <i>et al</i> , 2010 | 728/288/440 | NR | 60.2 (mean) | 0.62 (0.51-0.76) P<0.0001 | 89/34 | Age, number of metastatic sites, use of systemic therapy (2) |
| Rashaan <i>et al</i> , 2012 | 171/59/112 | NR | NR | 0.9 (0.6-1.4) P=0.5 | NR/NR | Age <50 found to be associated with a better outcome as was a small tumour and no comorbidity (20) |
| Shien <i>et al</i> , 2009 | 344/160/184 | 33 (29.2-38.0) | 54 | 0.89 P-value not reported as insignificant) | 100/NR | Age <50 (23) |

NR, not reported; CI, confidence intervals; HR, hazard ratio; ER, oestrogen receptor; HER2, human epidermal growth factor receptor 2; CT, chemotherapy; HT, hormone therapy; PR, progesterone receptor.

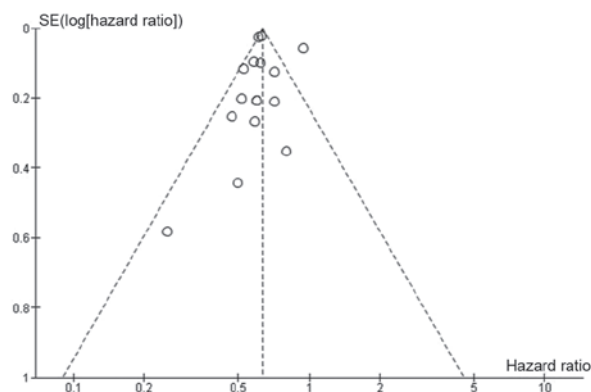


Figure 2. Funnel plot for overall survival meta-analysis. All previous studies, with the exception of that by Dominici *et al* (10), were within the 95% confidence intervals and were relatively symmetrically placed.

Discussion

The present meta-analysis confirmed the hypothesis that resection of the primary tumour in a patient with concomitant metastatic disease is beneficial in terms of survival, with a 37% reduction in mortality. These results reiterated the benefits of surgical resection of the primary tumour in metastatic disease, not just for advanced breast cancer, but also potentially for other advanced cancer types.

A number of hypotheses can be postulated regarding the mechanisms underlying the beneficial effects on prognosis of primary resection in metastatic breast cancer. Aside from the self-evident role of reducing the overall tumour burden, removal of the primary tumour has been shown to reduce the number of circulating tumour cells, which has been associated with improved disease outcomes (5).

Furthermore, recent previous studies describe a disease model termed 'tumour self-seeding', in which the primary tumour may release cells into the circulation to seed metastases, which in turn seed the primary tumour, leading to more virulent disease (6).

Additionally, some of the suggested effects of primary resections may be explicable under the currently topical cancer stem cell model, in which metastatic disease is postulated as a systemic disorder orchestrated by a more finite number of stem cells within the primary tumour, which recruit further cells by maintaining an oncogenic microenvironment (7,21). Furthermore, primary resection of tumours may assist in restoring an immunocompetent status by reactivating autoimmunity, therefore increasing the efficacy of any concomitant medication despite the presence of metastatic disease (22). Whilst this model remains highly contentious, the findings of the present study are highly suggestive of an active role of the primary tumour in metastatic disease, which suggests a role for surgery in this context in addition to palliation and local symptom control.

A number of the previous studies included here highlighted additional positive prognostic factors in terms of OS in the course of univariate analysis. The most common were: A reduced number of metastatic sites ('oligometastatic state'); positive ER status; a younger age; a smaller primary tumour (2,4,8-11,16,17,20,23). Additionally, Pathy *et al* (19)

observed that patients with positive margins received no benefit from resection in terms of OS (17). Rapiti *et al* (19) reported similar findings in the course of their study (19). This may have important implications regarding the surgical treatment that would be beneficial in this patient group. Furthermore, it raises the question whether a mastectomy would be a more appropriate intervention compared with tumour resection. Finally, the timing of the surgery in relation to adjuvant and neo-adjuvant therapies remains an area of uncertainty. These questions fall out of the remit of this meta-analysis and are worthy issues for exploration in course of future prospective studies.

A major limitation of this meta-analysis is that the paucity of prospective data in the available literature. Furthermore, despite adjusting for heterogeneity through use of random-effect modeling, a high level of inconsistency remains. Another limitation that must be acknowledged was the lack specificity regarding the non-surgical treatment administered (i.e., whether the patients underwent chemotherapy, radiotherapy, endocrine therapy or a combination). Finally, patient populations that underwent surgery were predominantly younger, therefore precluding comparison with other patient groups.

Prospective data would be required to confirm or refute the present findings. One ongoing trial may answer some of these questions. It is randomised cohort trial comparing immediate resection of the primary tumour, followed by systemic therapy and systemic therapy, followed by delayed surgical resection (24). It is prudent to revise this meta-analysis when the results of this and other similar trials become available.

Whilst acknowledging the limitations of this study, the present findings are highly suggestive of a significant benefit for resection of the primary tumour in advanced metastatic breast cancer, and would support a discussion regarding the inclusion of primary resection in the treatment options offered to the patient.

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