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ORIGINAL ARTICLE – BREAST ONCOLOGY

Meta-Analysis to Determine if Surgical Resection of the Primary Tumour in the Setting of Stage IV Breast Cancer Impacts on Survival

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ABSTRACT

Introduction. The role of primary tumor excision in patients with stage IV breast cancer is unclear. Therefore, a meta-analysis of relevant studies was performed to determine whether surgical excision of the primary tumor enhances oncological outcome in the setting of stage IV breast cancer.

Methods. A comprehensive search for relevant published trials that evaluated outcomes following excision of the primary tumor in stage IV breast cancer was performed using MEDLINE and available data were cross-referenced. Data were extracted following review of appropriate studies by authors. The primary outcome was overall survival following surgical removal of the primary tumor.

Results. Data from ten studies included 28,693 patients with stage IV disease of whom 52.8 % underwent excision of the primary carcinoma. Surgical excision of the primary tumor in the setting of stage IV breast cancer was associated with a superior survival at 3 years (40 % (surgery) versus 22 % (no surgery) (odds ratio 2.32, 95 % confidence interval 2.08–2.6, $p < 0.01$). Subgroup analyses for selection of patients for surgery or not, favored smaller primary tumors, less competing medical comorbidities and lower metastatic burden ($p < 0.01$). There was no statistical difference between the two groups regarding location of metastatic disease, grade of tumor, or receptor status.

Conclusions. Patients with stage IV disease undergoing surgical excision of the primary tumor achieve a superior survival rate then their nonsurgical counterparts. In the absence of robust evidence, this meta-analysis provides evidence base for primary resection in the setting of stage IV breast cancer for appropriately selected patients.

Breast cancer is the most common cancer that affects women in the developed world.[1] However, only a small proportion (5–10 %) has stage IV disease at presentation.[2] In addition, a number of patients initially treated with curative intent for stage I, II, or III breast cancer unfortunately progress to develop stage IV disease. Currently the role of the primary cancer and its impact on distant metastatic disease and patient survival is controversial. In the setting of stage IV disease, symptom palliation is the only indication for local therapy of the primary tumor. However, with advances in adjuvant therapies and a better understanding of tumour biology, survival of stage IV patients appears to be improving.[3,4] Furthermore, the profile of metastatic breast cancer has changed with the integration of more sensitive imaging modalities. Patients with a single metastatic deposit deemed "stage IV" on modern positron emission tomography/computed tomography (PET/CT) imaging may represent a very different cohort than those staged 10 years ago with multiple lung metastases on chest X-ray. Therefore, with more advanced and sensitive metastatic detection methods patients with "low burden" stage IV disease can be identified. Equally, the designation of these patients who may only have micrometastatic disease defined as stage IV, also may be presenting us with a skewed view of improved survival, which may be the result of earlier disease detection.[5]

Currently, the prevailing dogma for the treatment of metastatic breast cancer is that survival is determined by metastatic disease burden and that local therapy does not affect survival. However, removing the primary tumor has been shown to improve survival in other settings, such as metastatic melanoma,[6] renal cell carcinoma,[7] colorectal cancer,[8] and gastric cancer.[9] Despite this, extrapolating

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results from cancers with different disease profiles, biological behaviors, and sensitivities to other treatments must be viewed with caution.

It is possible that removal of the primary tumor may have an immunomodulatory effect, decrease overall tumour burden, remove a "seed source" of new metastases or decrease the likelihood of potentially resistant cell lines developing.[10,11] It also is possible that enhanced survival in breast cancer patients treated with surgery may be explained by selection bias.[12] It may be that those patients that have been offered surgery have been younger, healthier, had a lower burden of disease, or metastases in more favorable locations or a more favorable tumor profile than those where surgery was not considered.

These controversies compelled us to perform a meta-analysis to determine whether excision of the primary tumor in patients with stage IV breast cancer had any impact on survival. In addition, a subgroup analysis was performed to determine how patients were selected for surgery from identified studies.

METHODS

Identification of Studies

A search was performed using MEDLINE and EMBASE using the following in the searching algorithm: Stage IV OR metastatic AND Breast Cancer AND Primary Surgery OR Surgery. We set English language as a restriction. The latest search was done on April 30, 2012. Two authors (EH and MK) independently examined the title and abstract citations. The full texts of potentially suitable studies were obtained. The reference list of retrieved papers was screened for further suitable studies.

Eligibility Criteria

Studies of patients with stage IV breast cancer comparing primary surgery with conventional systemic treatment were included. Studies were included if appropriate survival data were available for patients with stage IV breast cancer undergoing surgery or not and if definitive evidence (pathological or radiological) of stage IV disease was included for all patients. In addition, it was imperative that all patients were staged according to the TNM or AJCC Cancer Staging Manual. Studies were excluded if the survival data were incomplete or if the patients were not staged appropriately.

Data Extraction and Outcomes

The following information was recorded for each eligible study: authors' names, journal, year of publication, and study design items (sourcing of patients, source of data—patient files, databases etc.). To analyze each study, we recorded the number of patients in each arm and where available: comorbidities, size of tumor, nodal status, grade of tumor, histology, sites of metastases, number of metastatic sites, receptor status, and type of surgery. The data with regard to systemic therapies were incomplete. The primary outcome was 3-year survival.

Statistical Analysis

The odds ratio (OR) was estimated with its variance and 95 % confidence interval (CI). Heterogeneity between the ORs for the same outcome between different studies was assessed by use of the χ^2-based Q statistic.[13] General variance methods were used to combine data across studies with fixed and random effects models. The fixed effects analysis weighted the natural logarithm of each study's OR by the inverse of its variance plus an estimate for the between-study variance in the presence of between-study heterogeneity. In the absence of this, fixed and random effects coincide because the between-study variance is zero. Analyses were conducted using Statsdirect version 2.5.6 (StatsDirect Limited, Cheshire, UK) and SPSS® version 12.0 (SPSS, Inc., Chicago, IL). All statistical tests were two-tailed.

RESULTS

Ten studies were deemed eligible for meta-analyses and 37 were excluded due to incomplete survival data, failure to provide appropriate evidence of correct staging, or insufficient duration of follow-up (see consort flow, Fig. 1). No randomized trials comparing surgery and systemic treatment alone were available. Nine studies were retrospective cohort studies, and one was a case control study (Table 1). Seven studies covered the period 1988–2005; three of the smaller studies had results dating back to the 1970s.[14–23] Seven were multicenter studies.

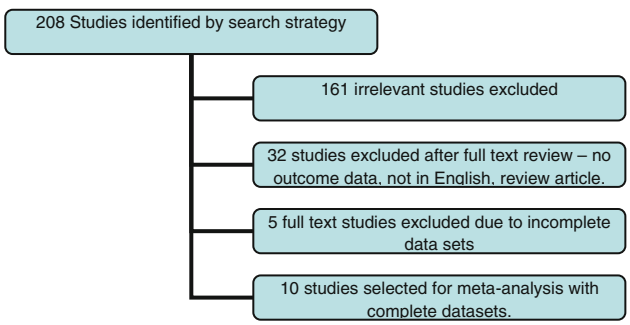

FIG. 1 Consort flow of studies selected for meta-analysis comparing surgery versus no surgery for primary breast cancer in the setting of stage IV disease

A total of 28,693 patients were included in the 10 studies: 15,162 underwent surgery, and 13,531 were treated with systemic treatment alone. All studies included both premenopausal and postmenopausal patients. Patients were staged according to the TNM or AJCC Cancer Staging Manual. The majority of patients were classified as stage IV at initial presentation or within 30 days of presentation.[15–17,19–23] Three-year survival was increased in those undergoing surgery (OR 2.32, 95 % CI 2.08–2.6, $p < 0.01$) and more importantly 22 % of patients who underwent systemic therapy alone were alive compared with 40 % of those who underwent surgical intervention (Fig. 2). Patients undergoing surgery were younger in all studies except two.[14–18,20–22] Information on comorbidities was available for 1,137 patients, which represents only 4 % of the studied population. Those undergoing surgery tended to have fewer comorbidities ($p < 0.001$) than those who were treated with systemic therapy alone [16,20] (Fig. 3); however, given the small numbers involved it is difficult to make any meaningful conclusions overall.

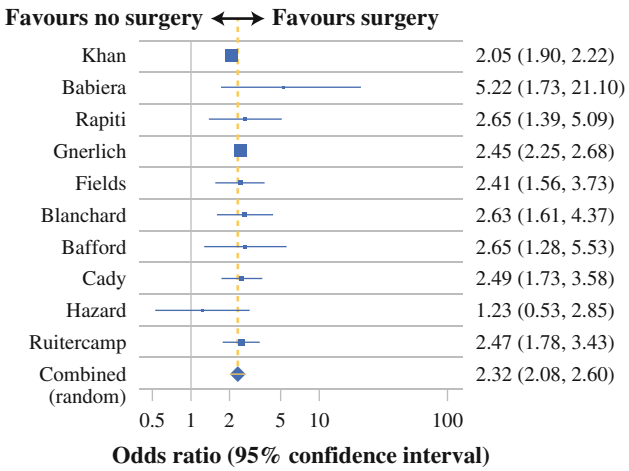

FIG. 2 Forrest box-plot of survival meta-analysis of studies comparing surgical excision of the primary with no surgery for stage IV breast cancer (OR 2.32, 95 % CI 2.08–2.6, $p < 0.01$)

Type of Surgery

Data for the type of surgery were available for 14,488 patients; 61 % underwent a mastectomy and 39 % were treated with a breast-conserving procedure. A study that compared the two procedures found no difference in outcome between BCS and mastectomy.[20] With regard to the axilla ($n = 486$), 93 % had axillary lymph node dissection and 7 % had sentinel node biopsy. However, two studies found no improvement in overall survival in patients undergoing axillary surgery.[19,20] Another study demonstrated reduced risk of death with axillary surgery in the setting of negative margins at the primary site, but this did not achieve statistical significance.[21]

Margin status ($n = 5{,}791$) was positive in 43 % and negative in 57 %. Two studies demonstrated that patients who underwent surgery with negative margins had the longest survival time, followed by those with positive margins; patients who did not undergo surgery had the shortest overall survival.[19,21] Only two studies documented the indications for surgery: one recorded that 53 % underwent operation for palliation of symptoms, 29 % to "establish diagnosis" with 14 % for "definitive treatment" presumably indicating that metastatic disease was only discovered following surgery.[16] Another study indicated that the majority (50 %) of surgeries were to "treat definitively" (approximately a quarter of these with curative intent), 35 % to establish diagnosis, 9 % for palliation, and 6 % for other reasons.[14]

Tumor Characteristics

Information on tumor size was available for 24,894 patients. Patients who underwent extirpation of the primary tumor tended to have smaller tumors than those who did not have any operative intervention ($p < 0.001$; Table 2):

TABLE 1 Studies selected for meta-analysis

Author	Study period	Stage	Outcome	Follow-up surgery	Follow-up - no surgery	Hazard ratio
Babiera	1997–2002	IV	Overall survival	n/a	n/a	0.5
Bafford	1998–2005	IV	Median survival	3.52 yrs	2.36 yrs	0.47
Blanchard	1973–1991	IV	Median survival	27.1 mo	16.8 mo	0.71
Cady	1970–2002	IV	2- and 5-year survival	24 mo	24 mo	n/a
Fields	1996–2005	IV	Median survival	31.9 mo	15.4 mo	0.53
Gnerlich	1988–2003	IV	Median survival	36 mo	21 mo	0.63
Hazard	1990–1993	IV	3-year survival/median survival	26.3 mo	29.2 mo	0.798
Khan	1990–1993	IV	3-year survival/mean survival	26.9–31.9 mo	19.3 mo	0.61
Rapiti	1977–1996	IV	5-year survival	n/a	n/a	0.6
Ruiterkamp	1993–2004	IV	5-year survival/median survival	31 mo	14 mo	0.62

mo months, *yrs* years, *n/a* not available

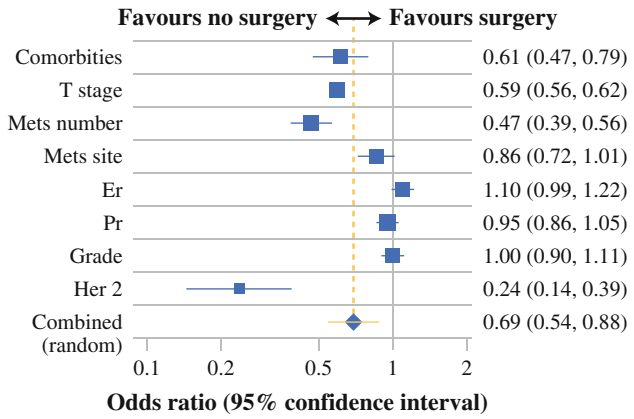

FIG. 3 Forrest-box plot of combined profile of medical comorbidities and tumor characteristics in patients with stage IV breast cancer undergoing surgical excision of the primary or not (OR 0.69 (0.54, 0.88), $p < 0.001$)

63 % of patients in the surgical group had a tumor that was T2 or smaller compared with 49 % in the nonsurgical group. The grade of tumor ($N = 6{,}029$) was similar in both groups: 60 % of patients in both groups had high-grade tumors, 35 % had moderate grade tumors, and 4 % had low-grade tumors (Table 2).

Estrogen receptor status data were available for 7,216 patients: 71 % of the surgical group was estrogen receptor-positive compared with 73 % of the nonsurgical group (Table 2). Progesterone receptor data ($n = 6{,}557$) was similar for both groups (58 % surgical, 57 % nonsurgical; Table 2). Due to the timing of some of the studies, HER-2 receptor status data were limited ($n = 402$; Table 2).

Metastases

Patients in the surgical group had fewer metastases than those treated with conventional systemic treatments ($n = 1{,}888$). In the surgical group, 63 % had metastases in only one location compared with 44 % in the nonsurgical group ($p < 0.001$; Table 3). With regard to metastases ($n = 2{,}395$), bone (nonvisceral) metastases were slightly more common in the surgical group (42 vs. 39 %) and visceral metastases were less common (58 vs. 61 %), but this did not reach statistical significance (Table 3). One study demonstrated a survival advantage in the surgical group when they had bone metastases only.[21] Another showed increased survival in both the surgical and non-surgical groups who had only bone metastases.[16] In contrast, Blanchard et al. [22] reported no increased survival in those patients with bony metastases only who underwent surgery.

TABLE 2 Available data on tumor characteristics of stage IV breast cancer patients undergoing/not undergoing surgical excision of the primary

Tumor characteristics	Surgery (n =)/ %	No surgery (n =)/ %
T0/Tx/T1/T2	(8,743) 63 %	(5,350) 49 %
T3/T4	(5,314) 37 %	(5,487) 51 %
Low grade	(161) 4.4 %	(121) 4.9 %
Moderate grade	(1,262) 35.6 %	(878) 35.1 %
High grade	(2,119) 60 %	(1,489) 60 %
ER+	(2,756) 71 %	(2,402) 73 %
ER−	(1,147) 29 %	(911) 27 %
PR+	(2,121) 58 %	(1,641) 57 %
PR−	(1,542) 42 %	(1,253) 43 %
Her-2+	(69) 44 %	(63) 26 %
Her-2−	(87) 56 %	(183) 74 %

Systemic Therapy

Data on systemic therapy were limited. In general, where information was available, systemic therapy consisted of anthracycline-based chemotherapy or antihormonal therapy with tamoxifen with aromatase inhibitors, or both. Four studies reported that the majority of patients had some form of systemic therapy.[14,16,18,22] Ruiterkamp et al.[20] reported that the surgical group was more likely to have systemic therapy than the nonsurgical group (89 vs. 79 %). Interestingly, Cady et al.[23] found that surgical patients who had preoperative chemotherapy had better outcomes than those who had postoperative chemotherapy.

DISCUSSION

The standard treatment for patients with stage IV breast cancer is systemic therapy, suggesting that specific therapy for the primary tumor is not beneficial. However, this meta-analysis suggests that appropriately selected patients may derive a survival benefit from resection of the primary tumor. Collated data from 28,693 patients from 10 trials demonstrate that patients undergoing surgery on the primary tumor have improved 3-year survival times (40 %) compared with those treated with systemic therapy alone (22 %). The reasons for this are multifactorial; however, it

TABLE 3 Metastatic number and location of patients with stage IV breast cancer undergoing/not undergoing surgical excision of their primary tumor

Metastatic number	Surgery (n =)/ %	No surgery (n =)/ %
1 Site	(529) 63 %	(466) 44 %
>1 Site	(309) 37 %	(584) 56 %
Metastatic site		
Nonvisceral	(437) 42 %	(525) 39 %
Visceral	(607) 58 %	(826) 61 %

is likely that selection bias plays a significant role. Currently, there are five randomized, controlled trials in progress in the United States, India, Austria, Netherlands, and Turkey that will address and hopefully clarify the role of primary tumor excision in the setting of stage IV breast cancer. It therefore is critical that the oncology community support accrual for these randomized trials. Until, these trials are completed, this meta-analysis demonstrates a robust association between excision of the primary and prolonged survival in appropriately selected patients. However, the results of this study must be interpreted with extreme caution and each patient should be counseled on the risks and benefits of such treatment including the limitation of the available data.

Interestingly, as a proxy for primary surgery, radiation studies have demonstrated improved overall survival in those receiving local treatment.[24–26] This would be supported by the findings of a number of studies in this meta-analysis, which looked at margin status and its effect on outcome. Khan and Rapiti both found that not only did surgical patients live longer than nonsurgical patients but that those with negative margins did better than those with positive margins.[19,21] This supports the argument that it is not only patient selection that contributes to this better survival but that patients do better with a more complete oncological resection. Furthermore, the finding of Khan that patients undergoing total mastectomy did better than those having a partial mastectomy also would indicate that surgery itself is significant, as presumably those undergoing more radical surgery had more extensive chest wall disease and therefore would not have been "more favorable" to begin with.

The mechanism by which surgery might limit systemic disease is still unclear. It has been shown that extirpation of the primary tumor may remove tumor-induced immunosuppression, self-seeding of primary tumor cells to distant sites, and may remove a source of potentially chemoresistant cell lines or may simply be a debulking exercise, with the primary tumor simply being considered another metastatic site.[10,11,27–30] On evaluating chest wall disease and its influence on outcome, Arriagada et al.[28] found that the development of distant metastases was related to local failure as a time-dependent covariate. This was echoed by Hazard and colleagues, who reported that uncontrolled chest wall disease was associated with decreased overall survival, independent of surgical intervention. This would support the theory of reduced seeding or reduced potentially resistant cell lines. It has been established that the number of metastatic sites negatively influences survival, and it also could be argued that the primary tumor constitutes a further metastatic site. This is supported by studies that indicate improved survival in patients with limited metastatic breast cancer when a single metastatic site is treated aggressively.[31]

However, concerns have been raised that surgery to the primary tumor can actually adversely affect survival.[32–34] In animal models, it has been demonstrated that removal of the primary tumor can stimulate metastatic growth.[35–37] It is hypothesized that this is mediated by the interruption of tumor cell dormancy or induction of angiogenesis in metastases.[38] In humans, surgery and general anesthesia in general have been shown to decrease the immune response.[39] Retsky et al.[40] demonstrated that primary surgery accelerated relapse in premenopausal node-positive women. So, it is possible that primary surgery actually has a deleterious effect on outcome, but this is masked by the favorable profile of the patients who undergo it. Surgery as a preventative strategy, however, is probably becoming increasingly important with increased longevity. Hazard et al.[18] did find that 36 % of women not initially offered surgery did require some form of locoregional therapy, either surgical or radiotherapeutic, to control chest wall disease. Only 17 % of the nonsurgical group was maintained with asymptomatic, intact tumors in the breast throughout their course.

There are some limitations to this meta-analysis and its conclusions. The data presented are limited to retrospective studies and results are confounded by the fact that surgical patients have a more favorable profile before operative intervention. Therefore, the apparent better outcome may be attributable to selection bias of surgical patients. In addition to the limitation of selection bias, these results are limited by the fact that patients may have undergone excision of metastatic sites, which may not have been recorded in a retrospective study. Equally, stage migration is a limiting factor for interpreting retrospective studies as this phenomenon may not be captured. Furthermore, it is unclear from certain studies whether patients received chemotherapy in a neoadjuvant setting rather than an adjuvant setting. However, this should not alter the survival data because published meta-analysis have failed to demonstrate any survival benefit with neoadjuvant versus adjuvant chemotherapy.[41] Her-2 data also are limited in many of the studies and therefore it is difficult to achieve any meaningful conclusions regarding the role of primary excision in the setting of Her-2-positive stage IV disease. Further studies are required to determine the optimal timing, most favorable tumor biology, and indications for surgery to the primary tumor.

Breast cancer outcomes are steadily improving, and the paradigm shift of viewing stage IV disease as a chronic illness to be managed, rather than a terminal event, means that the role of surgery will be constantly evolving. Finally, whereas surgery is a limited treatment modality, the potential for more advanced targeted adjuvant chemotherapies are limitless and therefore constant reevaluation of current standards of care are necessary to ensure that we

provide the optimum care for breast cancer patients of all stages.

Conflict of interest None of the authors have a conflict of interest to declare.

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