Focus On

Management of the intact breast primary in the setting of metastatic disease

H. Bermas, S. A. Khan

Department of Surgery and Lynn Sage Comprehensive Breast Center, Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL, USA.

Abstract Women who present with new breast cancer and synchronous metastases have traditionally been treated with systemic agents, with no specific therapy for the primary tumor unless local symptoms require palliation. However, a number of retrospective analyses of survival outcomes in these patients show that surgery for the primary tumor is associated with prolongation of survival. These studies suggest the possibility that local therapy for the primary tumor provides value beyond palliation of symptoms and points to the need for prospective data to guide treatment plans for women with de novo metastatic breast cancer. The coherence of the available data is improved by the findings that surgical resection of the primary tumor is of value only when free surgical resection margins are achieved, and that maintenance of local control at the primary site is associated with a survival advantage. Nevertheless, many questions remain, including the optimal timing of surgery for the primary tumor, whether the potential benefit applies only to women with favorable metastatic sites (e.g. bone-only metastases), and whether local radiotherapy should follow surgical treatment of the primary tumor if this is elected. There is also a lack of data addressing the value of axillary surgery in the metastatic setting. These substantial knowledge gaps limit our ability to deploy optimal use of therapeutic modalities for a patient population that reaches large numbers world-wide, and among whom survival duration is increasing due to more effective systemic therapy.

Introduction

About 5% of all breast cancer patients present with metastatic disease and an intact primary tumor in the breast. For these patients, overall survival is dictated by systemic disease burden rather than progression of the primary disease. Consequently, systemic therapy is the primary treatment modality and resection of the primary tumor is usually not recommended. Classically, surgical resection of an intact primary is recommended only to avoid future complications of uncontrolled local disease (ULD) or to palliate chest wall recurrences once they have occurred.

Metastatic breast cancer patients in the 21st century differ from historical Stage IV breast cancer patients. Improvements in multimodality systemic therapy (chemotherapy, hormonal therapy and targeted monoclonal antibody therapy) are being applied aggressively in the metastatic setting. The use of new and increasingly sensitive imaging modalities (positron emission tomography) has resulted in the identification of a group of women with minimal metastatic disease burden who are categorized as Stage IV, thus increasing the number of patients in this category [1]. There is emerging data that novel surgical approaches such as metastasectomy (lung, liver) [2–5] and resection of the intact primary may also be beneficial [6–13].

Although the concept of elective (rather than palliative) resection of the intact primary in the setting of metastatic disease is new to breast cancer, there is historical precedent in other malignancies. For example, in metastatic renal cell carcinoma, two

Correspondence to: Seema A. Khan, MD, Professor of Surgery, Bluhm Family Professor of Cancer Research, 303 E Superior, Lurie 4-103, Chicago, IL 60611, USA. E-mail: skhan@nmh.org; Tel: (312) 503-2112; Fax: (312) 503-2555

prospective, randomized trials (SWOG (Southwestern Oncology Group) and EORTC (European Organization for Research & Treatment of Cancer)) compared radical nephrectomy to non-operative management of the primary tumor in patients treated with systemic therapy (interferon alfa-2b). Both trials demonstrated a statistically significant survival advantage for patients treated with surgery (11.1 vs. 8.1 months, $P = 0.05$; 17 vs. 7 months, $P = 0.03$, respectively) [14,15]. Longer survival rates have also been shown in studies of gastric cancer [16–19], ovarian cancer [20], and colorectal carcinoma [21–23].

As a result of advances in treatment and a more aggressive approach, patients with metastatic disease are living longer. Andre et al. evaluated the effect of temporal trends on survival in patients with metastatic breast cancer and found that patients diagnosed in an earlier time period (1987–1993) had a 27% 3-year survival, whereas those diagnosed in a later period (1994–2000) had a 44% 3-year survival [24]. Additionally, some patients with limited Stage IV disease can be treated with curative intent. Several trials have shown that a minority of patients with distant metastases treated with multimodality therapy can achieve long-term survival of 20 years or more [25,26].

Prompted by the data from trials of metastatic renal cell carcinoma, we questioned the current paradigm that surgical resection of an intact primary in the setting of metastatic disease has only palliative value. Our original study [6] demonstrated a survival advantage for surgically treated patients and it has been followed by seven retrospective studies that have addressed the same hypothesis. As of March 2008, a total of 35 986 women have been studied. Key aspects of all the studies are provided in Table 1. The results are strikingly similar with six out of the eight studies demonstrating a survival advantage for surgically treated patients with an adjusted hazard ratio (HR) of death between 0.43–0.63. If it is true that patients with metastatic disease derive therapeutic benefit from surgical resection of the intact primary, it opens up the possibility that local control of the primary tumor has quantitatively similar value in women with overt metastatic disease as those with early stage breast cancer.

Retrospective data regarding primary tumor resection in Stage IV breast cancer

There are four multi-institutional studies which have utilized data from the National Cancer Data Base (NCDB) of the American College of Surgeons, the Geneva Tumor Registry, and the Surveillance Epidemiology and End-Results Reporting (SEER)

Table 1. Key features of retrospective studies.

Study	Multi-institutional	Time period	N	Patients treated surgically (%)	T 1–2 Tumors (%)[1]	Free margins (%)[2]	Axillary surgery (%)[2]	3-year survival of surgical group (%)	Adjusted hazard ratio (95% CI)
Khan, 2002	Yes	1990–1993	16 024	57	45.7	37	56	35	0.6 (0.58–0.65)
Gnerlich, 2007	Yes	1998–2003	9734	47	41.2		–	37	0.63 (0.60–0.66)
Rapiti, 2006	Yes	1977–1996	300	42	31	48	24	41[3]	0.6 (0.58–0.65)
Vlastos, 2007	Yes		8761	55					0.58 (0.55–0.62)
Babiera, 2006	No	1997–2002	224	37	38.4	62	63	83[3]	0.50 (0.21–1.19)
Blanchard, 2008	No	1973–1991	427	61	60.3			40[3]	0.61 (0.49–0.76)
Fields, 2007	No	1996–2002	409	46	44 (includes T0, Tis, Tx)	49	77	46[3]	0.53 (0.42–0.67)
Barkley, 2007	No	1998–2005	107	44				65[3]	0.43 (NA)

NA: not applicable.
[1] Percentage of total patients presenting with Stage IV disease.
[2] Percentage of surgical patients.
[3] Estimated from published survival curves.

database of the National Cancer Institute. Each of these databases has distinct strengths and weaknesses, which are pertinent for drawing conclusions from the data. In addition, four single institution studies have been conducted (MD Anderson, Baylor University, Washington University, Brigham and Women's Hospital). Single institution studies may suffer from institutional referral bias, but allow more detailed analyses regarding chest wall status, rate of positive margins, and use of axillary surgery.

All trials looked at the effect of resection of the primary tumor on survival. The percent of patients undergoing surgical resection ranged from 42% [8] to 61% [27] and fewer than half of those patients underwent some form of axillary surgery. Of the patients who had surgery, 54–69% underwent total mastectomy and the remainder were treated by partial mastectomy. The majority of patients received either chemotherapy or endocrine therapy, or both (range, 92–100%).

Patients in the surgical groups, when compared to the non-surgical groups, tended to be younger (58 vs. 62, average), have smaller tumors, and fewer metastatic sites. Surgical patients were more likely to have T1 or T2 tumors, whereas T4 patients were more likely to be treated non-operatively. The utilization of surgical resection was influenced by race in some [7,27], but not all studies [9,10]. Surgical patients were more likely to have oligometastases confined to bone/soft tissue compared to non-surgical patients who were more likely to have multiple metastatic sites which were visceral.

Given the younger age of the surgical group in several series, it is of interest that the presence and magnitude of co-morbid conditions (none, mild, moderate, and severe) did not did not influence selection for surgery or account for the survival advantage seen in the surgical group in one study [9].

Maximizing local control

If surgical resection of the intact primary is important for survival in Stage IV patients, then the next logical question is whether maximal local control (primary tumor resection with tumor-free margins, with axillary dissection, followed by radiation therapy) would add incremental benefit. In contrast to the importance of negative margins in early stage breast cancer, clear margins are not considered essential in metastatic patients. Only four out of the eight studies recorded the percentage of free margins, which was achieved in just less than 50% of patients. In the NCDB study, the adjusted HR of death for patients with negative margins was 0.61 (95% CI = 0.58–0.65) and for patients with positive margins was 0.75 (95% CI = 0.71–0.79). Rapiti *et al.* also found a benefit for negative margins [8]. Five-year breast cancer specific survival was 27% for patients with negative margins, 16% for positive margins, 12% for unknown margin status, and 12% for no surgery ($P = 0.0002$). In the studies where surgical margin was evaluated relative to survival, the prolonged survival in the surgical group was largely or entirely explained by the free resection margins, with minimal or no survival difference seen when surgery was performed with involved margins of resection.

The use of loco-regional radiotherapy has not been adequately evaluated, but there is a suggestion that it confers a benefit [8,13]. Few patients with metastatic disease are treated with loco-regional radiation therapy, and when used, it appears to be more common following surgical tumor resection. In both the Geneva study and the SEER study, patients in the surgical group were more often treated with radiation (21% vs. 5%, $P < 0.0001$, and 41% vs. 34%, respectively), but it did not improve overall survival (HR = 1.0 vs. 1.6, 95% CI = 1.0–2.5, respectively). In a separate analysis of SEER data, Vlastos *et al.* did find a reduction in breast cancer specific mortality for patients treated with radiotherapy (HR = 0.93, 95% CI = 0.88–0.98; $P = 0.0049$).

There are insufficient data regarding axillary surgery in these studies to reach any conclusions, as axillary surgery for patients with Stage IV is not usually performed, even when the primary tumor is resected. Only the NCDB, Geneva, Washington University, and MD Anderson studies provided information about axillary dissection. The percentage of patients who underwent axillary surgery ranged from 35% (NCDB) to 77% (Washington University) and the surgical groups tended to have less nodal disease than non-surgical groups. Two of these studies showed a trend towards improved survival in patients who had axillary surgery, although this did not reach statistical significance. However, if local control were beneficial for women with metastatic disease, the resection of clinically apparent axillary disease would seem reasonable.

The modest additional benefit of radiation therapy to resection with negative margins adds strength to the hypothesis that maximizing local control leads to the best outcomes. These data are consistent with the results of the Oxford Overview, which demonstrate that for every four patients who are spared a local recurrence, one cancer death is avoided [28].

Factors influencing survival

All four multi-institutional studies demonstrated a survival advantage for surgically treated patients. The 3-year survival rates were 35% vs. 17% in the NCDB, 37% vs. 20% in the SEER, and 41% vs. 18% from the Geneva study (estimated value from

published survival curves). Survival duration in surgically treated patients ranged from 7.6–15 months longer than non-surgically treated patients. From analyses that have attempted to define the subset which derives the greatest benefit from surgery, there is a suggestion that women with osseous metastases and hormone receptor positive disease benefit more. However, whether this represents the natural history of hormone responsive disease, or the effect of intervention, is open to question.

In the single institutional studies, three of the four studies [9,12,27] demonstrated a survival advantage with adjusted HR ranging from 0.425–0.61. In a fourth study (from MD Anderson Cancer Center) metastatic progression free survival for surgically treated patients was prolonged (HR = 0.54, 95% CI = 0.38–0.77), but overall survival was not [10]. This study is of interest because it differed from the other studies in several important ways. The surgical group included patients who had aggressive local therapy (including resection and radiotherapy) for isolated metastatic lesions, as well as patients who received primary tumor resection after systemic therapy failed to control local disease (non-responders). The survival curves were significantly better than any of the other studies (with a 3-year survival of 83%) but the follow-up was shorter (32.1 months). This combination of factors may have meant that there were too few events during the study period to demonstrate a survival benefit.

Selection of patients more likely to benefit from primary tumor resection

Variables that consistently and significantly correlated with survival (in addition to the use of surgery) included the site of metastasis (bone vs. visceral) and the number of organ systems involved. Single organ non-visceral metastatic disease was generally associated with better survival than multiple organ involvement and visceral metastases. The association with the number of metastatic sites is probably a reflection of disease burden, a known predictor of survival. Similarly, the longer survival of patients with bone-only metastasis is well established. Despite the differences in the variables included in multivariate models (mainly disease related in the NCDB and Geneva analyses, and mainly demographic in the SEER analyses), the HR of death remained similar across studies. The benefit of surgical resection was independent of these parameters, and persisted when metastatic site and number of organ systems involved were controlled for, along with other significant variables such as the use of systemic therapy. However, despite statistical adjustments for confounding variables, the possibility of selection bias cannot be ruled out (i.e. women with single site, indolent disease are offered surgery more frequently than those with multi-organ and visceral disease).

Timing of surgery

The timing of surgery relative to the diagnosis of metastatic disease is not well described; it is likely that many of the studies included patients who were diagnosed with metastatic disease during a post-operative metastatic survey prompted by advanced pathologic stage. These patients would presumably have a lower disease burden than patients who present with symptomatic metastatic disease and therefore might be expected to live longer. Rapiti et al. attempted to evaluate this effect by eliminating 12 patients who were diagnosed with metastatic disease 1 to 2 months after surgery. Only 4% of patients fell into this category and surgically treated patients still demonstrated a survival benefit. In contrast, a subset analysis in a recently reported study suggests that the benefit of surgical resection may be mainly applicable to women who undergo resection of the primary tumor prior to the diagnosis of metastatic disease. However, it is notable that this analysis was performed on 25 vs. 36 women [12].

Hazard et al. have also examined the issue of timing of primary tumor resection prior to or following diagnosis of metastases, and did not detect a difference in the apparent benefit of surgery when metastases were diagnosed pre-operatively or a post-operative metastatic survey prompted by a finding of multiple positive nodes [29]. In a reanalysis of the MD Anderson data, Rao et al. looked at the timing of surgery relative to survival. The optimal timing appears to be the 3–9 months following diagnosis [30], but in reality, this favorable interval is most likely a surrogate for response to systemic therapy, since women who were operated on more than 3 months following diagnosis were likely to be those who responded to systemic therapy.

Uncontrolled local disease

A separate, but related topic exists with chest wall control. ULD can lead to fungating chest wall tumors which significantly impairs quality of life. Fear of ULD probably accounts for the surprisingly widespread use of surgical resection of the primary tumor in metastatic breast cancer patients, despite a lack of Level I evidence to support the practice [31]. If surgical resection improves survival in women with distant metastases, it is likely to do so through improved local control. It is of interest, therefore, to relate chest wall control to survival in this group of patients.

The largest series of chest wall outcomes is from a retrospective review of the experience at North-western Memorial Hospital, where chest wall control was related to use of surgery and to survival in patients who presented with metastatic breast cancer and an intact primary tumor [29]. A controlled chest wall was more often maintained in patients treated surgically (82% vs. 34%; $P = 0.002$). Surgical resection was associated with longer time to first progression (HR = 0.5, 95% CI = 0.298–0.838), but there was no statistically significant difference in terms of overall survival. However, women who maintained a controlled chest wall (either via local or systemic therapy) survived significantly longer than those who developed symptomatic chest wall disease (HR = 0.415, 95% CI = 0.260–0.662; $P = 0.0002$).

In the analogous situation of women who develop ipsilateral breast tumor recurrence (IBTR) following breast-conserving therapy, resection seems to protect against both ULD and death. Dalberg *et al.* [32] found that patients with IBTR who were treated non-operatively had the highest rate of ULD compared to patients who were treated with salvage mastectomy (32% and 10%; $P = 0.004$). Patients who achieved local control lived longer than patients who developed ULD (5-year survival, 78% vs. 21%), suggesting that the maintenance of chest wall control results in better survival.

Arguments for a randomized, controlled trial

The existing data, although remarkably consistent in suggesting the association of a survival advantage with the use of surgical resection of the primary tumor, do not eliminate the alternative explanation of bias for this association: that is, women who are being offered surgery are a favorable group who would survive longer with or without resection of the primary tumor. It seems unlikely that this can be definitively settled without a prospective, randomized trial testing the use of local therapy for the intact primary in women with Stage IV disease.

Such a trial is presently under consideration, and the likely design will entail the recruitment of women with Stage IV disease who will undergo primary systemic therapy following standard recommendations. Women who do not progress at distant sites during induction therapy would then be randomized to: (a) receive early local therapy for the primary tumor according to guidelines for the therapy of non-metastatic disease, or (b) have resection of the primary disease only if and when it is needed for palliation. The objective of such a trial would be to establish whether early local therapy of the intact primary disease in women with Stage IV breast cancer, who respond to initial systemic therapy, will result in prolonged survival, compared to women who receive local therapy for palliation only if the local disease progresses while on systemic therapy. In addition to providing level I evidence to guide the management of women with de-novo Stage IV disease, such a trial would provide an opportunity to gain biological insights into the metastatic process through correlative science studies on samples of peripheral blood, primary, and metastatic tumor.

Biological hypotheses

Within the last decade, theories about cancer stem cells (CSCs), cancer-induced immunosuppression, tumor dormancy, and stem cell 'niches' have been proposed which may help to explain cancer progression and metastasis. If there is a survival benefit for local control in metastatic disease, then determining the factors that contribute to a cancer's ability to metastasize and the role of the primary tumor is essential.

In the 1990s, CSCs were identified in studies of leukemia [33]. They have since been identified in a variety of tumors, including breast tumors [34] and appear to have the ability to migrate to remote sites, initiate growth, and remodel the microenvironment to support growth of metastatic foci [35,36]. Patients found to have circulating tumor cells (CTCs) in peripheral blood have been shown to have poorer overall survival, which may be due to the fact that a subset of CTCs may be CSC capable of establishing a metastatic colony [37]. It is unknown where these CSCs originate from, but if the intact primary serves as a reservoir of CSCs which are shed into circulation and are more efficient at initiating new metastatic lesions than cells that are shed from metastatic sites [10], then removal of the intact primary would carry unique benefits, distinct from the systemic treatment of distant lesions.

Cancer stem cells are known to exist in a 'niche', which is a 'physiologically defined supportive microenvironment' [34]. There is an increasing body of evidence suggesting that there is molecular communication between the primary tumor and the pre-metastatic niche (a site remote from the tumor which is being prepared for tumor migration and implantation [38]). Secretion of growth factors, proliferation factors, and stimulatory signals originating from the primary tumor may play a role in preparing a site for future metastasis. If the intact primary were involved in 'crosstalk' with a metastatic site, then removing the intact primary would deprive the site of essential signals thereby blocking future metastases and/or progression of existing metastases. Measuring levels of biomarkers and cytokines in the blood before and after resection

could provide information to implicate or absolve the primary tumor. Evaluating metastatic tissue samples before and after surgery could shed light on whether these deposits are stimulated stabilized or regressed by removal of the primary tumor.

It is well established in animal models that cancer causes immunosuppression. Malignancy-induced immune system defects have been demonstrated in cytokine production, recognition of foreign antigens, and T and B cell function. A correlation between the number of micrometastases (defined as circulating epithelial cells in the bone marrow) and the degree of immunosuppression has been demonstrated [39]. Furthermore, using a mouse model, Danna *et al.* were able to demonstrate that removal of an intact primary mammary tumor in the setting of metastatic disease could restore the immunocompetence of the host [40]. Restoring immunocompetence may improve the host's ability to fight cancer. If specific primary tumor-related defects can be identified in blood samples, then interventions can be designed to target those areas.

The Gompertzian theory of breast cancer growth is based on the supposition that tumors exhibit a continuous growth pattern which is rapid when there are few cells and decelerates as the tumor mass increases [41]. Recent studies have favored the 'tumor dormancy' hypothesis, which describes quiescent micrometastases that do not grow until activated by specific host factors. An increase in circulating growth factors and a decrease in angiogenic inhibitors after surgery have been shown to play a role in tumor growth and progression [42,43]. If surgical extirpation of the intact primary leads to a 'blossoming' effect, then metastatic patients treated surgically would be expected to have accelerated disease progression and death. None of the studies found a survival disadvantage for surgical patients. Retsky *et al.* proposed an alternative explanation, which is that surgery increases angiogenesis making the host more susceptible to therapeutic interventions [44] such as chemotherapy or endocrine therapy. Studying the tissue samples from metastatic sites before and after removal of the intact primary might identify cellular changes resulting from surgical extirpation.

Conclusions

Improvements in cancer treatment have extended the life expectancy of patients with Stage IV disease beyond historic controls. The importance of prospective, unbiased data regarding issues of locoregional treatment in the setting of metastatic breast cancer is highlighted by the recent recognition of the importance of local control to survival in women with non-metastatic breast cancer. Furthermore, the likelihood of ULD will increase as overall survival continues to improve with multi-modality therapy. If there is indeed a survival benefit from surgical resection of the intact primary in the presence of overt metastases, this has major implications for our understanding of cancer biology and the process of metastasis.

Acknowledgement

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