Does Removal of the Primary Tumor in Metastatic Breast Cancer Improve Survival?

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Abstract

Although relative survival for breast cancer has improved in recent years, patients who present with metastatic disease have a less than 30% 5-year survival. Thus, improvements in treatment for these patients have the potential to have a significant impact on outcomes. Historically, removal of the primary breast tumor has been offered to these patients only for palliation. However, there have been recent reports that removal of the primary tumor may improve survival. Here, we review the theories and data at the center of the debate, the landmark studies that historically guided treatment, the retrospective data that revisited the role of removal of the primary tumor, as well as the latest advances in basic science and the accruing clinical studies to provide for future directions in this field. Although the definitive role of removal of the primary tumor in metastatic breast cancer is not settled, it is critical to understand the complexities of this debate in order to make further gains in breast cancer survivorship.

Introduction

OVER THE PAST SEVERAL YEARS, there has been a significant improvement in survival for patients with breast cancer, with relative 5-year survival for localized breast cancer near 90%.¹ The greatest gains in survivorship were achieved after the 1990s with widespread use of mammography.¹ Simultaneously, however, the incidence of breast cancer has been increasing over the past few years, with increased interest in how to make further gains on improving survival.¹

Although relative survival for breast cancer is high, patients with metastatic disease have a much worse prognosis, with a 5-year survival less than 30%.^{2,3} Of all women with breast cancer, 3%–6% present with metastatic disease, and 20%–30% of early-stage breast cancer patients will eventually develop disseminated disease.^{2,3} Therefore, improvements in the treatment of patients with metastatic disease have the potential to have a great impact on breast cancer survivorship.

Basis of Reservation on Removal of the Primary Tumor in Metastatic Breast Cancer

Historically, the role of removal of the primary tumor, mastectomy vs. lumpectomy, in patients with metastatic disease has been relegated to palliation alone because it may

contribute substantially to palliation but not to survival of the patient. Because patients with metastatic disease are immune compromised, the surgical stress of the operation has been thought to promote metastatic proliferation.⁴ In addition, because the primary lesion is thought to inhibit angiogenesis in metastatic lesions, resection of the primary tumor has been thought to remove that inhibition and thus promote the progression of metastatic lesions.⁵ However, these theories are based on animal studies of metastatic cancer utilizing models that have not been critically evaluated. Because of the importance of these theories in the management of patients with metastatic breast cancer, it is important to briefly review the data on which these theories are based.

Folkman demonstrated that the primary tumor actively secretes angiostatin, which suppresses the angiogenic activity of metastatic cancer, and that resection of the primary tumor also removes that suppression and thus induces metastatic proliferation.⁵ However, these experiments did not use breast cancer cells or clinically relevant endpoints, such as overall survival. Because of the growth of the field of angiogenesis and the increased importance of targeting this pathway in cancer treatment, these findings have been thought to determine survival in removal of primary tumor in metastatic breast cancer, even though the link to overall survival has not been established with any animal or human studies.

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Fisher demonstrated that animals with metastatic disease are immunologically compromised and that surgical stress releases growth factors, which in turn stimulates metastatic proliferation.⁶ The experiments from which he drew his conclusions did not focus on breast cancer specifically; nor were clinically relevant endpoints, such as overall survival, utilized. Without animal or human data in breast cancer, extrapolation of these findings to breast cancer is in question. However, because of the growth of the field of immune responsiveness in cancer and the importance of targeting this pathway in cancer treatment, these findings have been thought to determine survival in removal of the primary tumor in metastatic breast cancer, even though no animal or clinical prospective data have established the link.

Over the past few decades, interest in this topic has increased, with recent reports that surgical injury enhances the expression of genes to promote breast cancer metastasis to the lung⁷ and that removal of the primary tumor in breast cancer increases cancer cell presence in sentinel lymph nodes.⁸ However, these studies never evaluated translational clinical endpoints, such as disease-free or overall survival; nor did they discuss the clinical reports that contradicted the results of their animal experiments.

In fact, because of the finding in metastatic renal cell carcinoma that radical nephrectomy improves survival^{9,10} and of the effect of improved local control with radiotherapy on improving overall survival,^{11,12} there has been an increased interest in evaluating the role of removal of the primary tumor in metastatic breast cancer, with a proliferation of multiple retrospective studies addressing this question (Table 1).

Data from Retrospective Studies Argue for the Removal of the Primary Tumor

In 2002, a retrospective review of 16,203 patients with stage IV disease at initial presentation in the National Cancer Data

Base, where 57.2% underwent partial or complete mastectomy between 1990 and 1993, reported that complete mastectomy improved 3-year survival from 26% to 35% compared to partial mastectomy, a superior prognosis with a hazard ratio of 0.61 (95% confidence interval [CI] 0.581–0.646).¹³ Their multivariate analysis demonstrated the number of metastatic sites, site of metastasis, and extent of primary tumor resection as significant independent covariates, thus calling into question the historical solely palliative role of mastectomy in stage IV breast cancer.¹³

In 2003, a retrospective review of all patients with metastatic breast cancer treated with removal of the primary tumor from 1993 to 1999 (20 patients) in a regional breast cancer unit in the United Kingdom reported a median survival of 23 months.¹⁴ This report was in agreement with a review of 45 stage IV breast cancer patients with 53% 44-month survival after resection who were treated at a single institution in Texas from 1985 to 1996.¹⁵ These two smaller studies, although with limitations, were significant in that they also did not demonstrate a precipitous increase in mortality associated with mastectomy, as would have been otherwise predicted by extrapolation from the historical animal data discussed earlier.

In 2006, two retrospective reviews reported that mastectomy improves survival in metastatic breast cancer. The first paper reviewed 224 such patients, 82 treated with mastectomy vs. 142 who did not undergo surgery at a single institution in Texas from 1997 to 2002.¹⁶ This study reported a trend toward improved overall survival ($p=0.12$) and significantly improved disease-free survival ($p=0.007$).¹⁶ The second paper reviewed 300 such patients, 127 treated with mastectomy vs. 173 who did not undergo surgery in the Geneva Cancer Registry between 1977 and 1996.¹⁷ This study reported a 40% reduced risk of death ($p=0.49$), especially in patients who had only bone metastasis.¹⁷ This finding underscores the importance of considering metastatic site when

TABLE 1. RETROSPECTIVE STUDIES ON THE OUTCOME OF THE REMOVAL OF THE PRIMARY TUMOR IN METASTATIC BREAST CANCER

<i>Studies^a</i>	<i>Number of patients</i>	<i>Outcome</i>
Khan, Stewart, Morrow ¹³	16,203 (57.2% had surgery)	3-year survival improved from 26% to 35%
Carmichael et al. ¹⁴	20 had surgery	Median survival 23 months
Blumenschein et al. ¹⁵	45 had surgery	44 months survival was 53%
Babiera et al. ¹⁶	224 (82 had surgery)	Improved disease-free survival, trend toward improved overall survival
Rapiti ¹⁷	300 (127 had surgery)	40% reduced risk of death
Gnerlich et al. ¹⁸	9,734 (47% had surgery)	Median survival improved from 21 months to 36 months
Fields et al. ¹⁹	409 (187 had surgery)	Median survival improved from 15.4 months to 31.9 months
Blanchard et al. ²⁰	224 (82 had surgery)	Improved progression-free survival if only one site of metastasis, complete resection, and Caucasian race
Rao et al. ²¹	295 (142 had surgery)	Median survival improved from 16.8 months to 27.1 months
Cady et al. ⁴	622 (38% had surgery)	No correlation between surgery and survival, cited selection bias
Bafford et al. ²²	147 (61 had surgery)	Improved survival confounded by stage migration
Leung et al. ²³	204 (52 had surgery)	Survival benefit associated with chemotherapy, not surgery
Neuman et al. ²⁴	186 (69 had surgery)	Improved survival in estrogen-receptor-positive patients only
Le Scodan et al. ²⁵	581 (320 had locoregional XRT, 78% XRT only, 13% surgery only, 9% both)	3-year survival improved from 26.7% to 43.4%
Petrelli, Barni ²⁶	Meta-analysis of studies	Improved survival independent of confounding factors, directly proportional to exposure to systemic and radiotherapy, inversely correlated with estrogen-receptor status

^aSuperscript numbers in this column refer to entries in the References section of this article.

XRT, radiation therapy.

evaluating the role of therapies, such as primary tumor removal, in patients with stage IV breast cancer. Similar to the 2002 study,¹³ the study also reported that incomplete primary tumor resection provides no benefit.¹⁷

In 2007, two more publications reported data in support of the role of mastectomy in stage IV breast cancer. The first study reviewed 9,734 such patients in the Surveillance, Epidemiology, and End Results (SEER) program database, 47% of whom underwent surgery between 1988 and 2003, and reported that overall survival increased from 21 months to 36 months ($p < 0.001$), even after controlling for confounding variables and propensity scores.¹⁸ The second study reviewed 409 such patients, 187 surgically treated between 1996 and 2005 at a single institution in Missouri, and reported that there was improved overall survival (31.9 months compared to 15.4 months, $p < 0.0001$), even after controlling for confounding factors.¹⁹

In 2008, two more studies provided further support for the role of mastectomy in metastatic breast cancer,^{20,21} whereas a third study reported conflicting results and called into question the validity of all the other prior studies.⁴ The first study reviewed 82 such patients treated with surgery compared to 142 who did not at a single institution in Texas from 1997 to 2002 and reported that patients who had only one site of metastasis, complete resection, and Caucasian race, had improved progression-free survival.²¹ Furthermore, the study reported that non-Caucasian patients were more likely to undergo palliative rather than curative-intent surgical therapy and that there was improved progression-free survival with synchronous resection of their distant disease.²¹ The second study reviewed 142 such patients treated with surgery compared to 153 who did not from 1973 to 1991 in the central lab database at another institution in Texas and reported that overall survival was 27.1 months vs. 16.8 months ($p < 0.0001$), even after multivariate analysis.²⁰ The third study reviewed 622 such patients in the tumor registries of the Massachusetts General Hospital and Brigham and Women's Hospital; 62% had no surgery and 38% had complete resection between 1970 and 2002.⁴ This study reported no correlation between surgical therapy and survival benefit and attributed the reported benefits in other studies to case-selection bias.⁴

The theory that selection bias and other confounding factors may explain the results of many of these prior retrospective studies supporting the role of mastectomy was raised again in several subsequent studies. A 2009 single-institution review in Massachusetts of 147 such patients—61 who underwent surgery and 86 who did not between 1998 and 2005—reported improved survival in the surgical group, which was confounded by stage migration.²² In addition, a 2009 single-institution review of 52 such patients who underwent surgery compared to 152 who did not between 1990 and 2000 in Virginia reported no survival benefit from surgery, only from chemotherapy.²³ In fact, a 2010 review of 186 such patients—69 who underwent surgery and 117 who did not between 2000 and 2004 at a single institution in New York—reported that surgery was associated with improved survival only in patients who were receptor positive ($p = 0.004$).²⁴ However, a 2009 review of 581 such patients, 320 of whom received locoregional radiotherapy (78% radiotherapy and 13% surgery and 9% both) vs. 261 who did not between 1980 and 2004 at a single institution in France, found that local therapy improved survival (43.4% vs. 26.7%

3-year survival [$p = 0.00002$]), even after multivariate analysis.²⁵ These authors went on to suggest that perhaps radiotherapy is a reasonable alternative to surgical therapy in these patients.²⁵

Without prospective clinical data currently available, a 2012 meta-analysis of the retrospective data was performed.²⁶ The meta-analysis of the retrospective studies reported that resection improved survival with a hazard ratio (HR) of 0.69 ($p < 0.00001$), independent of confounding factors, proportional to the rate of patient exposure to systemic and radiotherapy, while inversely correlated with estrogen-receptor status, emphasizing the importance of multimodality therapy.²⁶ The strength of this study was that it evaluated all the retrospective data available from multiple studies in an attempt to address the criticisms discussed earlier.

With a lack of prospective randomized data and the importance of animal studies underlying the various theories of the role of mastectomy in metastatic breast cancer, a 2013 animal study utilizing a validated orthotopic murine metastatic breast cancer model to investigate the assumptions supporting the current paradigm was reported.²⁷ The animal study examined the effects of primary tumor resection on metastatic progression, overall tumor burden, and overall survival by orthotopically implanting 4T1-luc2 murine mammary gland adenocarcinoma cells into syngeneic Balb/c mice under direct vision into the mammary gland. When they were found to have developed metastatic disease by bioluminescence, the animals were randomized while controlling for overall tumor burden to surgical stress vs. primary resection vs. observation. The authors reported that, although surgical stress transiently increased metastatic proliferation and primary resection increased the proliferation of metastatic lesions, it was overall tumor burden that determined survival and thus removal of the primary tumor that significantly reduced overall tumor burden compared to observation alone improved survival.²⁷ The benefits of this study are that it evaluated the role of removal of the primary tumor in the context of the underlying theories against removal without such variables as chemotherapy and radiation, while utilizing a validated orthotopic model with translatable endpoints, such as overall tumor burden and overall survival.²⁷ The study provided a system to evaluate the effects of primary tumor resection *per se* on metastatic proliferation, overall tumor burden, and survival. Furthermore, the study also provided potential avenues for adjuvant systemic therapies, a critical element of management of patients with stage IV breast cancer. In addition, other advances in the basic sciences provide support for the role of primary tumor resection in metastatic breast cancer.

Over the past several years, there has been a greater understanding of the epithelial-to-mesenchymal transition in the metastatic process, with important implications for cancer stem cells and circulating tumor cells.²⁸ It has been shown that factors released at the primary tumor–stromal level facilitate distant metastatic proliferation,²⁹ which demonstrates the importance of tumor microenvironment in breast cancer progression. Tumors are not a mere homogenous accumulation of cancer cells, and recent studies indicate that the progression from primary tumor to metastasis is a much more dynamic and multidirectional process than once thought.²⁸ In fact, it has been validated in multiple experimental models

that metastatic lesions self-seed other sites as well as the primary breast tumor itself, which may link local control with controlling distant recurrence.³⁰ Furthermore, the role of antitumor immunity has also been implicated in this discussion because it has already been shown that tumor-burden reduction can restore immunity, even in the presence of metastatic disease through the role of myeloid-derived suppressor cells.^{27,31} The latest report by Rashid et al. in a validated immunologically intact murine system places its results in the context of the well-reported mechanisms that had once been thought to argue against mastectomy in metastatic breast cancer and once again emphasizes the importance of overall tumor burden in determining survival.²⁷

Future Direction: Ongoing Clinical Trials

Despite these retrospective studies and animal studies, the role of mastectomy in metastatic breast cancer remains in question. Currently, multiple prospective clinical trials are accruing patients around the world to evaluate the role of mastectomy and lumpectomy in patients who present with stage IV breast cancer.

The NCT00941759 trial, sponsored by Memorial Sloan-Kettering Cancer Center, is a prospective cohort study to evaluate response to first-line therapy, frequency of surgical referral, proportion of patients undergoing primary tumor resection, molecular characteristics of the primary tumor, circulating tumor cells, and metastatic tumor samples. This study has the potential to provide further insights into appropriate patient selection, considering such factors as tumor characteristics and metastatic site.

NCT01015625, a randomized prospective trial sponsored by the Austrian Breast and Colorectal Cancer Study Group to evaluate median survival and time to distant and local progression, focuses more on clinical factors that have been thought to selection of patients with favorable tumor biology.

NCT00193778, sponsored by Tata Memorial Hospital (India), is a randomized prospective trial evaluating overall and disease-free survival, as well as changes in serum levels of vascular endothelial growth factor, basic fibroblast growth factor, angiostatin, and endostatin, which has direct application to the classic effects discussed earlier.

NCT01242800, sponsored by the Eastern Cooperative Oncology Group, is a randomized phase III trial evaluating overall survival, uncontrolled chest wall disease, health-related quality of life, circulating tumor cell burden, and molecular markers of primary tumor and metastatic lesion interaction. NCT00557986, sponsored by the Federation of Breast Diseases Societies (Turkey), is a prospective randomized trial evaluating all causes of mortality, quality of life, and morbidities. These two studies also address the important question of breast cancer survivors' quality of life, which directly addresses the traditional role of primary tumor resection in stage IV breast cancer as solely palliation.

NCT01392586, sponsored by Jeroen Bosch Ziekenhuis (The Netherlands), is a prospective randomized trial evaluating overall survival, quality of life, number of unplanned local therapies, differences in systemic therapy, resection margin, and number of axillary lymph node treatments. This study investigates further the differences in systemic therapy, a critical factor in the management of stage IV breast cancer, as

well as addresses the issue of the degree to which local and regional control may benefit these patients.

Conclusion

Further improvement in the overall survival of breast cancer relies upon making greater advances in the treatment of patients with metastatic disease. Historically, the role of removal of the primary tumor in these patients has been limited to palliation alone. However, the theories underlying this approach have been based on animal studies, without translational clinical endpoints to determine to what degree they affect survival. In fact, multiple retrospective studies, as well as recent animal studies, call these theories into question. As several clinical trials across the world accrue patients, there is promise to discover which patients with metastatic breast cancer may benefit from removal of the primary tumor to improve survival.

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