

Local Therapy for the Primary Breast Tumor in Women With Metastatic Disease

Claudia B. Perez, DO, and Seema A. Khan, MD

Dr. Perez is a Breast Surgery Fellow in the Department of Surgery and Dr. Khan is Professor of Surgery at the Feinberg School of Medicine of Northwestern University in Chicago, Illinois.

Address correspondence to:
Seema A. Khan, MD
Professor of Surgery
Feinberg School of Medicine
of Northwestern University
303 East Superior Street, Lurie 4-111
Chicago, IL 60611
E-mail: skhan@nmh.org
Phone: 312-503-2112
Fax: 312-503-2555

Abstract: The management of de novo stage IV breast cancer focuses on systemic therapy for distant sites. The underlying assumption is that such therapy will control the primary tumor sufficiently well for the remainder of the patient's life, and that specific therapy for the primary tumor is not beneficial. This concept is being re-evaluated because of the lengthening survival of stage IV patients, the tendency towards decreasing metastatic disease burden at diagnosis, and accumulating data suggesting that local therapy for the primary site may be beneficial. Retrospective data on more than 30,000 women from North America and Europe have now been published, showing a robust association between surgery or radiotherapy for the primary tumor and prolonged survival. Many questions remain, most importantly, whether this observed association reflects a selection of women with good prognosis for primary site therapy; others relate to the fraction of women in published studies who were diagnosed with metastatic disease postoperatively, whether specific subsets would derive greater benefit, and the appropriate timing and extent of local therapy. These issues can be definitively addressed only in a randomized trial. Two trials are open in India and Turkey; a third is being planned in the United States and is expected to open in 2011. Given the importance of these questions for the approximately 10,000 women who are diagnosed with stage IV breast cancer in the United States—and the many more worldwide—it is hoped that the US trial will receive strong support from breast cancer physicians and from our patients.

Introduction

The importance of effective local therapy as a means of optimizing survival in women with stages 0–III breast cancer is well established.¹ However, approximately 5% of women with primary breast cancer in the United States present with de novo stage IV disease, (ie, with an intact primary tumor).² The traditional approach to this problem has been to treat with systemic therapy, with local therapy being reserved for women who require palliation at the primary

Keywords

Breast cancer, primary breast tumor, metastatic disease

site. There is presently no consensus regarding optimal local therapy for these women, and treatment may vary from mastectomy (ostensibly for the purpose of preventing uncontrolled primary disease during the remainder of the patient's life) to obtaining a tissue diagnosis with needle biopsy. If the primary tumor is resected, follow-up radiation is rarely used in the setting of distant metastases. According to the classic paradigm, once metastases have occurred, local therapy provides no survival advantage and should not be pursued. However, recent data suggest that an alternative needs to be considered; namely, that the primary tumor is a source of continued seeding of distant sites and, therefore, elimination of this source of metastasizing cells may be of benefit by reducing the development of new lesions. Pertinent data include a randomized trial in patients with metastatic renal cell carcinoma that examined the benefit of adding nephrectomy to standard-of-care systemic therapy (interleukin). Results from this trial show an improvement in median overall survival for the nephrectomy group, from 8 months without nephrectomy to 11 months for patients in the nephrectomy arm.³ Thus, a viable possibility exists that resection of the primary tumor has a favorable effect on survival in patients with a variety of metastatic solid tumors.

In the area of breast cancer, the past decade has witnessed significant advances in systemic therapy and in sensitive imaging techniques that reveal lower burdens of metastatic disease than previously possible, along with an accumulation of retrospective data suggesting that women with distant metastases undergoing surgical resection of the primary tumor experience improved survival. In this review, we will focus on the last of these 3 developments, recognizing that improved systemic therapy has prolonged the lives of women with stage IV breast cancer,⁴ and that metastases can now be identified when the disease burden is minimal.⁵ The opportunity for an uncontrolled primary tumor to cause significant quality of life problems has therefore increased in proportion to the increasing survival of women who are being treated with effective systemic therapy, often in the setting of minimal metastatic disease.

Biologic Aspects of the Primary Site and Metastasis Interaction

Data from studies going back several decades raise concerns that resection of the primary tumor in the setting of metastatic disease will enhance the growth of distant lesions.^{6,7} The pioneering work of Folkman and colleagues⁸ has identified protein factors synthesized by primary tumors that restrict tumor growth at metastatic sites, so that distant lesions grow once the primary lesion is resected.⁹ This phenomenon remains to be demonstrated in humans, whereas recent data suggest that the primary tumor may have a unique role in the propagation of

metastases by acting as a reservoir for tumor stem cells. An increasing body of evidence suggests that there is molecular communication between the primary tumor and the premetastatic niche.¹⁰ Secretion of growth factors (such as transforming growth factor type β), proliferation factors, and stimulatory signals originating from the primary tumor may play a role in priming the niche for implantation and growth of the metastatic lesion. Provocative recent data suggest a specific role for mesenchymal stem cells that are released from the bone marrow and populate primary tumor sites more efficiently than metastatic sites.¹¹ These mesenchymal stem cells then endow primary tumor cells with enhanced metastatic capacity, providing a possible explanation for a beneficial role for resection of the primary tumor even in the setting of established distant disease.

Another potential mechanism for interaction between the primary tumor and metastatic lesions is through tumor-induced immunosuppression, defects in cytokine production, recognition of foreign antigens, and T-cell and B-cell function. In a study comparing the peripheral blood samples of breast cancer patients and healthy controls, CD4-positive and CD8-positive T-cell subsets capable of producing type 1 and 2 cytokines were reduced in breast cancer patients.¹² There was a correlation between the number of micrometastases (defined as circulating epithelial cells in the bone marrow) and the degree of immunosuppression. Using a mouse model, Danna and colleagues 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.¹³ Mice with bulky tumors had T-cell and B-cell deficiencies compared to healthy mice. In mice that underwent resection, antigen-specific antibody responses and T-cell responses to foreign antigens recovered compared to mice that did not undergo surgery.

Thus, there are several potential biologic explanations for the benefit of primary tumor resection. These, along with the clinical data reviewed below, provide strong rationale for a randomized clinical trial of local therapy in stage IV patients, testing the hypothesis that primary site therapy is beneficial in the setting of metastatic disease.

Review of Retrospective Studies

Eleven retrospective studies have examined the impact of surgical resection of the primary tumor in the presence of overt metastatic disease,¹⁴⁻²³ and one has addressed the use of primary radiotherapy.²⁴ These studies were performed in a variety of settings: a large database of hospital registries in the United States (the National Cancer Database of the American College of Surgeons),¹⁴ the Surveillance Epidemiology and End-Results (SEER) database of the National Cancer Institute,¹⁷ 2 population-based

Table 1. Retrospective Studies Evaluating Surgical Resection of the Primary Tumor in Patients With Metastatic Disease

Study	Number of Patients	Time Period	Treated Surgically (%)	3-Year Survival in Surgery Group (%) [‡]	3-Year Survival Difference Between Groups (%)	Adjusted Hazard Ratio (95% CI)
Khan 2002* ¹⁴	16,024	1990–1993	57	35	18	0.6 (0.58–0.65)
Babiera 2006 ¹⁶	224	1997–2002	37	95	15	0.50 (0.21–1.19)
Rapiti 2006* ¹⁵	300	1977–1996	42	41	19	0.6 (0.58–0.654)
Blanchard 2008 ¹⁹	427	1973–1991	61	40	20	0.61 (0.49–0.76)
Fields 2007 ¹⁸	409	1996–2002	46	46	18	0.53 (0.42–0.67)
Gnerlich 2007* ¹⁷	9,734	1998–2003	47	37	18	0.63 (0.60–0.66)
Cady 2008* ²⁰	622	1970–2002	38	42	17	Not reported
Bafford 2009* ²³	147	1998–2005	41	62	26	0.47
Le Scodan 2009 ²⁴	581	1984–2004	55 [†]	43 [§]	16	0.70 (0.58–0.85)
Leung 2010 ²¹	157	1990–2000	33	38	13	Not reported
Ruiterkamp 2009* ²²	728	1993–2004	40	40	15	0.62 (0.51–0.76)

*Multi-institutional study. †Locoregional radiotherapy for primary site. ‡Three-year survival of surgical group estimated from survival curves (%).

§Benefit seen in patients receiving locoregional therapy, consisting of radiotherapy alone in 78%.

CI=confidence interval.

European tumor registries,^{15,22} 7 large comprehensive cancer centers in the United States,^{16,18–21,23} and 1 French regional cancer center.²⁴ These studies show that surgical resection or (as in France) radiotherapy of the primary tumor is being performed in 30–55% of women with de novo stage IV disease and is associated with a remarkably consistent survival advantage for women who undergo therapy for the primary tumor in the setting of metastatic disease compared to those who do not. The observed reduction in the hazard of death ranges from 40–50% (Table 1). However, these studies also show that surgical therapy for the primary tumor is more likely in women who are younger, and who have smaller tumors, fewer metastatic sites, or bone or soft tissue (rather than visceral) metastases. Some of these biases are highlighted in Table 2. Additionally, although difficult to measure, the surgical groups in the reported analyses very likely have better access to care because they tend to be younger, of European ancestry, and married, all characteristics that are associated with medical insurance. This last point is important with reference to other therapeutic modalities, since access to care also determines optimal systemic therapy, so that the use of surgery may simply be a surrogate for better treatment overall. Thus, the observed association between primary site surgery and improved survival cannot yet be causally attributed to the resection of the primary tumor, even after statistical adjustment for known biases (remember-

ing that unknown biases cannot be adjusted for) because in most studies, the women in the surgical groups had more favorable characteristics overall than the women in the nonsurgical groups. Additionally, it is not possible from these retrospective studies to assess the value of local therapy components other than resection of the primary tumor (ie, axillary dissection and primary site radiotherapy).

Impact of Surgical Therapy on Overall Survival

In almost all of the multi-institutional studies in the literature, the use of surgical therapy for the primary tumor has been associated with improved survival (see Ly and coworkers²⁵ for a review). In the National Cancer Data Base (NCDB) analysis, the 3-year survival was 35 months in patients surgically resected with free margins and 17 months in the nonsurgical group.¹⁴ In the analysis of SEER data, surgically treated patients lived 11–15 months longer than those patients treated nonsurgically.¹⁷ Similarly, the Geneva Tumor Registry data¹⁵ and a recent publication from the southern Netherlands²² show hazard ratios of 0.60 (95% confidence interval [CI], 0.58–0.654) and 0.62 (95% CI, 0.51–0.76), respectively.

In single institution reviews, the survival differences are only somewhat less consistent. The less positive studies deserve comment. In the MD Anderson Cancer Center experience, a significant prolongation of overall survival was not seen (the median survival had not been reached),

Table 2. Characteristics of Study Populations Evaluating Surgical Resection of the Primary Tumor in Patients With Metastatic Disease

Study	Population	Fraction With Visceral Metastases (%)		Fraction With Single Organ System Involved (%)		Hormone-Receptor-Positive Tumors (%)	
		Surgical Group	Nonsurgical Group	Surgical Group	Nonsurgical Group	Surgical Group	Nonsurgical Group
Khan 2002 ^{*14}	NCDB	Fractions not reported, but significant hazard ratios reported for all 3 parameters in a multivariate model that included the effect of surgery					
Babiera 2006 ¹⁶	MDACC	54 (66) [‡]	74 (52) [‡]	67 (82) [‡]	99 (70) [‡]	42 (51)	95 (70)
Blanchard 2008 ¹⁹	Baylor	85 (39) [‡]	97 (67) [‡]	195 (81) [‡]	75 (49) [‡]	116 (51) [‡]	49 (37) [‡]
Fields 2007 ¹⁸	Washington University	Fractions and hazard ratios for these parameters not reported					
Gnerlich 2007 ^{*17}	SEER	Not reported				2,196 (48) [‡]	1,779 (35) [‡]
Cady 2008 ^{*20}	Boston	Case-control matching based on organ site involvement and hormone receptor status					
Le Scodan 2009 ²⁴	St. Cloud, France	121 (38) [‡]	92 (35) [‡]	225 (70) [‡]	117 (45) [‡]	156 (49)	104 (40)
Leung 2009 ²¹	Virginia	35 (67)	64 (61)	–	–	–	–
Ruiterkamp 2009 ²²	Southern Netherlands	153 (53) [‡]	265 (60) [‡]	213 (74)	249 (57)	–	–
Bafford 2009 ^{*23}	Boston	Not reported		9 (10)	20 (33)	55 (64)	35 (57)

*Multi-institutional study. †Primary radiotherapy. ‡Significant differences.

MDACC=MD Anderson Cancer Center; NCDB=National Cancer Data Base; SEER=Surveillance Epidemiology and End-Results.

but the progression-free interval was significantly improved for the surgical group.¹⁶ In another analysis of 157 patients, there was no survival advantage after adjustment for the use of chemotherapy; 54% of patients received chemotherapy and 51% received endocrine therapy,²¹ but the number of women receiving both forms of treatment or not receiving any systemic therapy was not provided. Median survival was 25 months for the patients treated with chemotherapy and only 8 months for those not treated with chemotherapy, of whom one-third had visceral metastases. This relatively rural population may have contained an unusually large fraction of women whose disease was too advanced for therapy, explaining the poor survival in women who did not receive chemotherapy. Finally, a study interpreted by the authors as showing that the association between surgical therapy and improved survival is a result of selection bias deserves discussion. The investigators identified stage IV cases from 2 large hospital tumor registries; they matched women who underwent primary-site surgery with those who did not, and they analyzed survival relative to the use of surgery for the primary site.²⁰ They compared matched to unmatched analyses and found essentially similar and significant positive relationships between surgery and survival for

all subsets except for the 100 women with visceral-only disease, in whom the matched analysis yielded a *P* value of 0.09, favoring the surgical group. Thus, this study too supports the possibility of improved outcomes with the use of surgical resection.

Extent of Surgical Intervention

The possible surgical interventions for the primary tumor consist of breast-conserving tumor excision or mastectomy (ideally with free resection margins), with or without axillary dissection. Margin data have not been available in all series published so far. When analyzed, the results are mixed. In the original analysis of NCDB data, survival was longer in women with tumor-free surgical margins than in women with resection margins that were involved with the tumor.¹⁴ Tumor-free margins are more likely in women undergoing total mastectomy compared with partial mastectomy, which may explain the somewhat improved outcomes associated with total mastectomy in this study. The benefit of surgery was confined to the negative margin group in data from the Geneva Tumor Registry.¹⁵ However, in the analysis from the Netherlands, margin data were not available, but there was no significant difference in overall survival between

those with breast-conserving surgery versus mastectomy.²² Interestingly, in the matched case-control study by Cady and associates,²⁰ women were assigned to the nonsurgical group if “there was clearly no attempt to remove all disease (clinically palpable axillary nodes unresected but biopsied) or if there was only an excision that resulted in extensive positive margins with no re-excision performed.” Thus, it appears that margins were largely free in the surgical group, and margin status was not included in the analysis. In the relatively large analysis from Washington University (409 women; 187 had surgical resection and 92 had free resection margins), there is no mention of the effect of margin status on the survival analysis. Other single-institution studies were smaller, and it is not clear if margin status was analyzed.

The percentage of patients who had axillary surgery ranges from 24–77%.^{15,18} In the NCDB study,¹⁴ extent of nodal disease was not significantly related to survival, but women undergoing total mastectomy were more likely to have nodal dissection, and it is possible that this factor may have contributed to the survival advantage observed in the total mastectomy group. In the Geneva study, axillary dissection was performed in 24% of patients, and there was a trend toward a larger benefit for women who had both negative surgical margins and axillary dissection (hazard ratio [HR], 0.2; 95% CI, 0.02–1.9).¹⁵ Of note, 50% of surgical patients had N1 disease, whereas N3 patients were most often treated nonsurgically (3% vs 14%; $P=.0005$). In the analysis from the Netherlands, there was a trend towards a benefit in patients undergoing axillary dissection compared to those without, but this was limited to the first year after treatment, without an effect on overall survival.²² It appears logical that if local tumor ablation is beneficial, regional nodal disease should also be addressed, but the available data do not allow any conclusions regarding the possible benefit of axillary surgery in women with distant metastases.

Identification of Metastatic Disease After Definitive Local Therapy

Several of the published analyses show that primary tumors tend to be smaller (T1 and T2) in the surgical group.^{14,15,19,26} This finding is of interest because series from individual institutions have shown that approximately one-half to one-third of patients who are reported as having stage IV disease are in fact diagnosed with metastases following surgical treatment, as a result of metastatic surveys performed because of a high pathologic nodal burden.^{23,26-28} Thus, there may be a large fraction of patients included in the existing literature who underwent surgical resection with asymptomatic metastases that were detected on postoperative imaging. These patients most likely had a lower disease burden than those diagnosed

with symptomatic disease preoperatively, and they would be expected to have improved survival. Three groups of investigators have attempted to examine this issue in single-institution (therefore small) data sets, with conflicting results. When patients undergoing surgery prior to chemotherapy were compared to women who received chemotherapy first, Cady and associates²⁰ found no difference in survival outcomes. Using a slightly different approach, Rao and colleagues attempted to define the optimal timing for surgery relative to diagnosis, and found that women operated on 3–9 months from diagnosis had better survival than when surgery was performed within 3 months of diagnosis, implying that when surgical treatment follows the delivery of some amount of systemic therapy, outcomes are better.²⁸ Another aspect of the timing question has to do with whether metastases are diagnosed preoperatively or postoperatively, because those with postoperative identification of stage IV disease presumably have a smaller tumor burden. Again, the results are conflicting and based on scant data; one study did not identify a significant difference in survival when metastases were diagnosed preoperatively or postoperatively,²⁷ but another analysis found that the benefit of surgery was confined to women who underwent surgical resection for presumed nonmetastatic disease.²³

Locoregional Radiotherapy

Data on the use of postoperative radiotherapy in the setting of stage IV disease is variable and very limited. In the time interval analyzed (1990–1994), the NCDB did not distinguish locoregional radiotherapy from radiotherapy to distant sites.¹⁴ The Geneva study¹⁵ and the SEER study¹⁷ found that patients in the surgical groups were more often treated with radiation (21% vs 5%; $P<.0001$, and 41% vs 34%, respectively), whereas another single-institution study found that only 0.3% of patients were treated with locoregional radiotherapy.²⁹ In a more recent study examining SEER data and published in abstract form,³⁰ radiotherapy was given equally (approximately 40%) in the mastectomy and breast-conservation patients alike, and it was associated with a significantly longer median survival in the breast conservation group (24 months in patients without radiotherapy and 31 months in those who received it; P log-rank test less than .0001). In the mastectomy group, the corresponding values were 32 versus 31 months (P log-rank test equal to .330). In multivariate analysis, surgery and radiotherapy were associated with a statistically significant reduction in the hazard of death, with a ratio of 0.93 (95% CI, 0.88–0.98; $P=.0049$) for radiotherapy versus no radiotherapy,³⁰ suggesting that adjuvant local radiation therapy may also improve patient survival. This small effect of radiotherapy is difficult to assess, but it is clear that any prospective evaluation of the

value of local therapy for the primary site needs to include radiotherapy as a local treatment modality.

Systemic Therapy

Systemic therapy is the established primary therapy for stage IV breast cancer, and therefore most patients in the reviewed literature received chemotherapy, endocrine therapy, or both. This was true for both the surgical and nonsurgical groups. The published literature contains no details on the systemic therapy used, and therefore a more in-depth analysis is not possible. It is unclear if the use of surgical therapy for the primary tumor was associated with overall more aggressive systemic therapy. A recent retrospective study examined the survival of 186 de novo stage IV patients (almost half of whom had been diagnosed with metastases postoperatively) relative to the use of primary site surgery and the biologic subtype of the cancer.²⁶ An improvement in survival was seen only in women with hormone receptor–positive or human epidermal growth factor receptor 2 (HER2)-positive disease, with the triple negative group deriving no benefit from surgery for the primary tumor. These data highlight the importance of effective systemic therapy in the management of stage IV breast cancer, and they suggest that surgical resection of the primary tumor is unlikely to add benefit in the presence of disease that is nonresponsive to systemic therapy.

Data on Chest Wall Outcomes

The frequent use of surgical resection in women presenting with stage IV disease is somewhat surprising. The main justification for surgical intervention in this setting is to avoid uncontrolled local disease or to palliate chest wall recurrences once they have occurred, but data on chest wall outcomes in women with metastatic disease are sparse. It is reasonable to assume that no (or incomplete) resection of local disease is a risk factor for the occurrence of uncontrolled chest wall disease in stage IV patients, as it is in the nonmetastatic setting. A recent retrospective analysis included 111 women presenting with stage IV breast cancer; chest wall outcomes were examined relative to the use of early (within 6 months) surgical resection of the primary tumor. The early use of surgery reduced the odds of symptomatic chest wall disease by 86% (adjusted OR, 0.14; 95% CI, 0.039–0.491), and a controlled chest wall reduced the hazard of death by 60% (HR, 0.4; 95% CI, 0.260–0.662). Data from pooled Danish trials of breast conserving therapy support this finding; women with synchronous local and distant recurrence following breast conserving therapy of an initial breast carcinoma experienced better local control and overall survival if the in-breast recurrence was resected.³¹ Failure to resect the primary site recurrence was the strongest determinant of

uncontrolled chest wall disease (adjusted HR, 12.7; 95% CI, 4–41). Thus, the quality of life impact of primary site therapy for all patients with distant disease must be balanced against the risk of uncontrolled chest wall disease in a proportion of patients.

The Role of Local Therapy in Metastatic Breast Cancer

Despite the consistency of the growing literature evaluating the surgical treatment of the intact breast tumor in patients with metastatic disease, the question remains as to whether the women who are being offered surgery are a group that would survive longer because of a combination of favorable features related to tumor biology and access to care rather than surgical resection of the breast tumor. This question cannot be definitively settled without the protection from bias afforded by the randomization of patients to the combination of systemic and primary site local therapy compared with systemic therapy alone, and the consistency of therapeutic interventions that can be achieved in a prospective study. Randomized trials are under way in India and in Turkey. The study by Badwe and colleagues in India utilizes 6 cycles of preoperative anthracycline-based therapy followed by randomization to local therapy for the primary site or no local therapy, with a planned accrual of 350 women.³² The trial being conducted in Turkey (NCT00557986) does not include preoperative systemic therapy; randomization to locoregional surgery plus radiotherapy versus systemic therapy occurs following diagnosis of metastatic disease. The accrual goal is 270 women.³³

ECOG Trial E2108

A phase III trial is in the final planning stages under the aegis of the Eastern Cooperative Oncology Group (ECOG).³⁴ With an accrual goal of 880 women (16 per month), it will evaluate whether local therapy of intact primary disease in women with stage IV breast cancer will result in prolonged survival compared to women who receive local therapy only if and when necessary for palliation of local symptoms. All patients will be followed for survival and for primary site control and health-related quality of life for 5 years. All patients will receive induction systemic therapy (cytotoxic, endocrine, or biologic) appropriate to their age, metastatic organ sites, and tumor biologic profile. The specific regimen will be chosen by the treating physician, with adherence to general guidelines regarding optimal first-line therapy in the metastatic setting. Those who have either stable or responsive disease at the end of approximately 4 months of therapy will be randomized to local therapy (surgery plus radiotherapy) that mirrors the standards applied in the nonmetastatic setting (Figure 1). The primary objective will be to compare overall survival in patients receiving early, elective

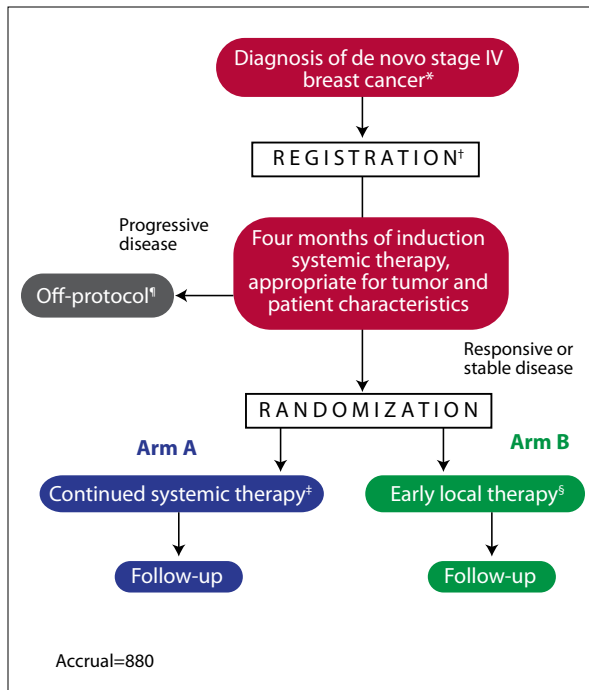


Figure 1. Schema of the E2108³⁴ study: Early Surgery or Standard Palliative Therapy in Treating Patients With Stage IV Breast Cancer.

*Women with intact primary tumors and metastatic disease at any site are eligible (anticipated survival >6 months).

†Patients may register at any time within 4 months of initiation of systemic therapy and may be randomized after 4 months of therapy if stable or responsive disease is documented.

‡Local therapy only if needed for palliation of symptoms from primary site progression; it may include surgery or radiotherapy, as needed.

§Defined as surgery and radiotherapy for the primary tumor following standards used for nonmetastatic disease.

¶Will be followed for survival.

local therapy to the primary site to those who receive continued systemic therapy, although local treatment can be used for palliation of local symptoms if these develop. Other objectives will include documenting the frequency of, and the time to, uncontrolled chest wall disease and the effect of local therapy and uncontrolled chest wall disease on health-related quality of life in the 2 arms.

Eligibility Women with intact primary breast tumors and metastatic disease at any site will be eligible, unless their projected survival is estimated to be 6 months or less, either because of the burden of disease or comorbidities. Women with recurrent breast cancer and those with a synchronous contralateral primary tumor will be excluded. Because induction systemic therapy is not strictly defined,

patients may be registered at any time following diagnosis within the first 4 months of systemic therapy, and those with stable or responding disease will be randomized following the 4-month evaluation.

Local Therapy for the Primary Site The choice of local therapy was vigorously debated in many settings during the development of this trial. Much consideration was given to the merits of testing of surgery alone, rather than the combination of surgery and radiotherapy. However, surgery alone is now definitively recognized to be *incomplete* local therapy in the majority of patients with biologically aggressive disease¹ (which by definition includes all patients with metastatic disease). Therefore if partial local therapy (ie, surgery) is helpful in the metastatic setting, any trial testing this hypothesis should logically test *complete* local therapy (surgery plus radiotherapy). A further consideration was the fact that positive results from a trial testing surgery alone would immediately be followed by the question of whether radiotherapy would add greater benefit, and negative results would leave open the question of whether the trial would have been positive if radiotherapy had been included. Therefore, the final consensus was that the local therapy component of this trial should include standard-of-care local therapy following the principles used in the nonmetastatic setting.

The design of E2108 allows the specific surgical treatment in the experimental arm (early local therapy) to be chosen by the patient and the physician according to the criteria that are generally accepted for breast conserving therapy (BCT) or total mastectomy. For patients who elect BCT, free surgical margins must be achieved with re-excision or mastectomy with no minimum margin width required. Axillary management in this trial parallels that used for nonmetastatic breast cancer. Axillary dissection is required unless a negative axilla is documented with sentinel node biopsy. The standard therapy group will receive continued systemic therapy, but if primary progression becomes symptomatic—requiring palliation of symptoms—the extent and sequence of local therapy is left to the discretion of the physician.

Radiation Therapy After BCT, all patients will receive definitive breast irradiation to include the whole breast. A boost to the primary tumor bed is optional, provided that the margins of excision are pathologically confirmed as negative. Nodal radiation can be added for node-positive patients at the discretion of the treating radiation oncologist. After mastectomy, postmastectomy radiation treatment (PMRT) will be given at the discretion of the treating surgeon and radiation oncologist. All patients with 4 or more pathologically positive axillary lymph nodes will be treated with PMRT; for those with 1–3 positive axillary

lymph nodes, a radiation oncology consultation will be recommended to determine whether PMRT is indicated.

Conclusion

The clinical course of metastatic breast cancer is changing. Overall, patients with stage IV disease are living longer; the combination of advances in systemic therapy and the diagnosis of lower volume metastatic disease presents a potential opportunity to improve outcomes through therapy for the primary tumor. At the moment, however, systemic agents remain the first line of therapy, and the use of local therapy for the primary site should be reserved for palliation and avoidance of uncontrolled local disease, recognizing that the interruptions of systemic therapy that may be required for delivery of local treatment carry a hazard for the patient with distant disease. In addition, the quality of life impact of surgery and radiation must be justified with unbiased data regarding the survival (or quality of life) value of improved local control. The timely accrual and completion of E2108 will be possible only with the support of the oncology community. Data from this trial will establish the value of primary site therapy in the setting of distant disease, will aid the understanding of the relationship of the primary tumor to disease at distant sites—with potential for guiding therapeutic concepts in nonmetastatic disease—and may spur similar trials for other organ sites.

References

- Clarke M, Collins R, Darby S, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet*. 2005;366:2087-2106.
- American Cancer Society. *Breast Cancer Facts & Figures 2009-2010*. Atlanta, GA: American Cancer Society, Inc. ww2.cancer.org/downloads/STT/F861009_final%209-08-09.pdf. Accessed January 18, 2011.
- Flanigan RC, Salmon SE, Blumenstein BA, et al. Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer. *N Engl J Med*. 2001;345:1655-1659.
- Andre F, Slimane K, Bachelot T, et al. Breast cancer with synchronous metastases: trends in survival during a 14-year period. *J Clin Oncol*. 2004;22:3302-3308.
- Schirmeister H, Kuhn T, Guhlmann A, et al. Fluorine-18 2-deoxy-2-fluoro-D-glucose PET in the preoperative staging of breast cancer: comparison with the standard staging procedures. *Eur J Nucl Med*. 2001;28:351-358.
- Gunduz N, Fisher B, Saffer EA. Effect of surgical removal on the growth and kinetics of residual tumor. *Cancer Res*. 1979;39:3861-3865.
- Fisher B, Gunduz N, Saffer EA. Influence of the interval between primary tumor removal and chemotherapy on kinetics and growth of metastases. *Cancer Res*. 1983;43:1488-1492.
- Folkman J. Proceedings: tumor angiogenesis factor. *Cancer Res*. 1974;34:2109-2113.
- O'Reilly MS, Holmgren L, Shing Y, et al. Angiostatin: a novel angiogenesis inhibitor that mediates the suppression of metastases by a Lewis lung carcinoma. *Cell*. 1994;79:315-328.
- Kaplan RN, Riba RD, Zacharoulis S, et al. VEGFR1-positive haematopoietic bone marrow progenitors initiate the pre-metastatic niche. *Nature*. 2005;438:820-827.
- Karnoub AE, Dash AB, Vo AP, et al. Mesenchymal stem cells within tumour stroma promote breast cancer metastasis. *Nature*. 2007;449:557-563.
- Campbell MJ, Scott J, Maecker HT, et al. Immune dysfunction and micrometastases in women with breast cancer. *Breast Cancer Res Treat*. 2005;91:163-171.
- Danna EA, Sinha P, Gilbert M, et al. Surgical removal of primary tumor reverses tumor-induced immunosuppression despite the presence of metastatic disease. *Cancer Res*. 2004;64:2205-2211.
- Khan SA, Stewart AK, Morrow M. Does aggressive local therapy improve survival in metastatic breast cancer? *Surgery*. 2002;132:620-626.
- Rapiti E, Verkooijen HM, Vlastos G, et al. Complete excision of primary breast tumor improves survival of patients with metastatic breast cancer at diagnosis. *J Clin Oncol*. 2006;24:2743-2749.
- Babiera GV, Rao R, Feng L, et al. Effect of primary tumor extirpation in breast cancer patients who present with stage IV disease and an intact primary tumor. *Ann Surg Oncol*. 2006;13:776-782.
- Gnerlich J, Jeffe DB, Deshpande AD, Beers C, Zander C, Margenthaler JA. Surgical removal of the primary tumor increases overall survival in patients with metastatic breast cancer: analysis of the 1988–2003 SEER data. *Ann Surg Oncol*. 2007;14:2187-2194.
- Fields RC, Jeffe DB, Trinkaus K, et al. Surgical resection of the primary tumor is associated with increased long-term survival in patients with stage IV breast cancer after controlling for site of metastasis. *Ann Surg Oncol*. 2007;14:3345-3351.
- Blanchard DK, Shetty PB, Hilsenbeck SG, et al. Association of surgery with improved survival in stage IV breast cancer patients. *Ann Surg*. 2008;247:732-738.
- Cady B, Nathan NR, Michaelson JS, et al. Matched pair analyses of stage IV breast cancer with or without resection of primary breast site. *Ann Surg Oncol*. 2008;15:3384-3395.
- Leung AM, Vu HN, Nguyen KA, Thacker LR, Bear HD. Effects of surgical excision on survival of patients with stage IV breast cancer. *J Surg Res*. 2010;161:83-88.
- Ruiterkamp J, Ernst MF, van de Poll-Franse LV, Bosscha K, Tjan-Heijnen VC, Voogd AC. Surgical resection of the primary tumour is associated with improved survival in patients with distant metastatic breast cancer at diagnosis. *Eur J Surg Oncol*. 2009;35:1146-1151.
- Bafford AC, Burstein HJ, Barkley CR, et al. Breast surgery in stage IV breast cancer: impact of staging and patient selection on overall survival. *Breast Cancer Res Treat*. 2009;115:7-12.
- Le Scodan R, Stevens D, Brain E, et al. Breast cancer with synchronous metastases: survival impact of exclusive locoregional radiotherapy. *J Clin Oncol*. 2009;27:1375-1381.
- Ly BH, Nguyen NP, Vinh-Hung V, Rapiti E, Vlastos G. Loco-regional treatment in metastatic breast cancer patients: is there a survival benefit? *Breast Cancer Res Treat*. 2010;119:537-545.
- Neuman HB, Morrogh M, Gonen M, et al. Stage IV breast cancer in the era of targeted therapy: does surgery of the primary tumor matter? *Cancer*. 2010;116:1226-1233.
- Hazard HW, Gorla SR, Scholtens D, Kiel K, Gradishar WJ, Khan SA. Surgical resection of the primary tumor, chest wall control, and survival in women with metastatic breast cancer. *Cancer*. 2008;113:2011-2019.
- Rao R, Feng L, Kuerer HM, et al. Timing of surgical intervention for the intact primary in stage IV breast cancer patients. *Ann Surg Oncol*. 2008;15:1696-1702.
- Blanchard DK, Bhatia P, Hilsenbeck SG, et al. Does surgical management of stage IV breast cancer affect outcome? *Breast Cancer Res Treat*. 2006;100:S118.
- Vlastos G, Rapiti E, Bouchardy C, et al. Optimal loco-regional treatment of the primary tumor in metastatic breast cancer patients is associated with a significant survival advantage. Abstract presented at: 30th San Antonio Breast Cancer Symposium. December 13–16, 2007; San Antonio, TX. Poster 5077.
- Dalberg K, Liedberg A, Johansson U, et al. Uncontrolled local disease after salvage treatment for ipsilateral breast tumour recurrence. *Eur J Surg Oncol*. 2003;29:143-154.
- ClinicalTrials.gov. Assessing impact of loco-regional treatment on survival in metastatic breast cancer at presentation. <http://clinicaltrials.gov/ct2/show/NCT00193778>. Accessed January 18, 2011. ClinicalTrials.gov Identifier: NCT00193778.
- Soran A, Ozbas S, Kelsey SF, et al. Randomized trial comparing locoregional resection of primary tumor with no surgery in stage IV breast cancer at the presentation (protocol MF07-01): a study of Turkish Federation of the National Societies for Breast Diseases. *Breast J*. 2009;15:399-403.
- ClinicalTrials.gov. Early surgery or standard palliative therapy in treating patients with stage IV breast cancer. clinicaltrials.gov/ct2/show/NCT01242800?term=ECOG+trial+E2108&rank=1. Accessed January 18, 2011. ClinicalTrials.gov Identifier: NCT01242800.