Treatment of Primary Breast Tumors in De Novo Metastatic Breast Cancer

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Abstract: *Background:* De novo metastatic breast cancer accounts for about 3% to 6% of the more than 200,000 new breast cancer cases annually in the United States. The treatment of the primary breast tumor in these cases is a widely debated topic. Some feel that surgical resection of the breast tumor is appropriate for selected patients, whereas others recommend surgical resection only to treat or prevent uncontrolled chest wall disease. *Methods:* We review the published data on treatment of the primary tumor in de novo metastatic breast cancer, including retrospective population-based and single-institution studies. We then report on the first 2 randomized controlled trials (RCTs) that evaluated the effect on survival of surgical resection of the primary breast tumor. *Results:* Results of the published retrospective analyses are varied, but in general they associate resection with improved outcome. Early results from the first RCTs point to no survival advantage with resection of the primary tumor in this population, but important limitations of the RCTs are noted. *Conclusions:* The early data from RCTs do not show survival benefit from surgical resection of the primary tumor in de novo metastatic breast cancer, but these studies have some important limitations and also suggest that certain subsets may benefit. The question therefore remains unanswered, which should provide greater impetus for the completion of ongoing RCTs.

Introduction

Approximately 210,000 individuals are diagnosed with breast cancer annually in the United States. Of these, approximately 3% to 6%—6000 to 12,000 patients—present with de novo metastatic disease.[1,2,3] The current treatment for metastatic breast cancer focuses on prolonging life and on improving or maintaining quality of life. Although rare, long-term survival—sometimes lasting more than 20 years—has been reported in 1% to 3% of metastatic breast cancer cases.[4,5]

Some studies suggest inherent survival differences between women with de novo stage IV and relapsed stage IV breast cancer. A retrospective study conducted at MD Anderson Cancer Center that evaluated 3500 women found a significantly longer median overall

survival (OS) among patients presenting with de novo stage IV disease than among those with relapsed disease (39.2 and 27.2 months, respectively; $P<.0001$).[6]

Historically, the role of surgery for the primary breast tumor in metastatic breast cancer has been to alleviate symptoms such as bleeding or ulceration. However, because it is possible that de novo metastatic breast cancer is a separate and more favorable entity than relapsed metastatic breast cancer, perhaps local therapy could play a different role.

Since 2002, several published retrospective studies have reported that surgical resection of the primary breast tumor is associated with improved OS.[7-13] It is clear that a number of factors affect the decision to resect the primary tumor in patients with metastatic breast cancer, including patient age, performance status, number and location of metastatic sites, hormone receptor status, and expression of human epidermal growth factor receptor 2 (HER2). Despite adjusting for many of those factors, biases—especially selection bias—cannot be completely eliminated given the retrospective nature of those studies.

The breast cancer community learned a sobering lesson about the limitations of nonrandomized data after observational studies in the 1980s and early 1990s suggested improved outcomes for patients with poor-prognosis early-stage breast cancer who underwent high-dose chemotherapy with autologous stem cell rescue vs conventional chemotherapy. Randomized controlled trials eventually were carried out that found no survival benefit from this approach, meaning that selection bias likely explained the improved outcomes seen in the nonrandomized trials. Furthermore, treatment-related morbidity was higher with this approach, and quality of life initially was poorer.[14]

In an attempt to address the inherent selection bias of the retrospective studies examining the role of early local therapy in patients with de novo metastatic breast cancer, 6 randomized clinical trials addressing this issue were initiated: one each in India, Turkey, Japan, the Netherlands, Austria, and the United States/Canada. Early results from 2 of these studies recently were reported.

To more completely understand the controversy surrounding the issue of treatment of the primary tumor in de novo metastatic breast cancer, we will first review the possible treatment approaches and the rationale supporting such approaches. We will then summarize the results of retrospective studies evaluating the effect of local therapy, and finally discuss the results of the 2 recently presented international randomized trials addressing this issue.

Approaches to Up-front Local Therapy

There are 2 possible ways to incorporate a combination of surgery and systemic therapy in de novo metastatic breast cancer. The first method employs surgery up front, followed by systemic treatment, such as conventional chemotherapy, hormonal therapy, and/or molecularly targeted therapy. This approach is similar to what commonly is used in the adjuvant setting. The second method involves first administering systemic treatment, in a fashion akin to the neoadjuvant setting. The remaining lesions then undergo resection, which typically is used in patients whose disease responds to systemic therapy.[15] This second approach, which maintains the primacy of systemic therapy, is felt to represent the best method for first identifying who has the potential to benefit from more aggressive treatment, as this group may survive long enough for locoregional therapies to matter.

An analysis from the BC Cancer Agency in Canada of patients with stage IV disease treated with locoregional therapy between 1996 and 2005 attempted to identify which patients with metastatic breast cancer would have the most favorable outcomes with locoregional therapy. In a study of 378 patients who received locoregional therapy, the best survival outcomes were in younger women and in those with good performance status, estrogen receptor (ER)–positive disease, clear surgical margins, distant disease limited to 1 site, bone-only involvement, or fewer than 5 metastatic lesions.[16] The authors concluded, therefore, that patients with those characteristics reasonably could be considered for locoregional therapy.

How Resection of the Primary Tumor Might Improve Outcome

The exact mechanism by which removal of the primary tumor might improve outcome in metastatic breast cancer is unclear, but several mechanisms have been proposed. One theory is that tumor-induced immunosuppression is lessened when the primary tumor is resected. In a 4T1 mouse mammary carcinoma, an established model for metastatic cancer, tumor-induced immunosuppression—specifically both T- and B-cell mediated immune function—can be restored with surgical removal of the primary tumor, even in the presence of disseminated metastatic disease.[17]

Another hypothesis is that cancer might be a disease of self-seeding, whereby tumor cells from distant metastases may return, via the circulation, to their original site of production at the source tumor. Self-seeding of the primary tumor has been validated in mathematical and animal models. Further, the idea that the primary tumor consists of both cells that have grown and invaded locally and cells that have broken off and traveled through the circulation before returning to the hospitable environment of the original tumor site could help explain the diverse nature of a tumor.[18]

Some also have hypothesized that the primary tumor is the source from which cells break off and seed distant sites. Thus, resection of the primary tumor removes the source of seeding, which otherwise could lead to distant metastasis. Findings from the Stockholm radiotherapy trial indicated that local recurrence was found to predict distant metastasis when analysis was performed examining local recurrence as a time-dependent covariate. This suggested that the decrease in distant metastasis was related to the prevention of local recurrence.[19]

Of note, others have argued that removal of the primary tumor actually may worsen outcome in patients with metastatic disease. Much of this argument is based on data published by Fisher and colleagues in 1989, which showed that removal of the primary tumor in the C3H mouse mammary model increased a serum growth factor, resulting in increased metastatic tumor growth. Furthermore, when this serum was transferred to tumor-bearing recipient mice, an increase in tumor size was noted.[20]

Selection Bias

Retrospective studies evaluating the effect of local therapy in patients with de novo metastatic breast cancer are inherently at risk for selection bias, because only those patients felt to have a good enough performance status to tolerate surgery and to live long enough to reap the potential benefits of such an approach are likely to be referred for surgery. Conversely, selection bias might cause patients with impending uncontrolled chest wall disease to be more likely to receive surgery. Although the authors of many of these studies have tried to control for selection bias, only a sufficiently large, prospective, randomized controlled trial can truly eliminate this type of bias.

In an attempt to describe some of these selection biases, a number of studies have evaluated whether the characteristics of the patients who underwent surgery differed from the characteristics of those who did not undergo surgery. The studies, however, have not been uniform in their findings, with some investigators reporting that patients undergoing surgery were younger[9,10,12,21,22] and had smaller primary breast tumors than those not undergoing surgery,[9,10,11,13,21] whereas others found that patients were older.[11] Additionally, a number of studies[9,12,13,23] noted that women were more likely to undergo resection if only 1 metastatic site was known or if the tumors were hormone receptor–positive[11] or HER2-negative,[13] and less likely when metastases were visceral.[9] These findings highlight the fact that selection biases are present in the retrospective studies, as the physician's impression of potential for prolonged survival might encourage surgical resection of the primary tumor.

We will next review the most instructive retrospective studies examining the effect of surgical resection in women with de novo metastatic disease and focus on the strengths and weaknesses of the various methodologies. The results of these and other relevant studies are summarized in Table 1.

Studies Showing a Positive Association Between Surgical Resection and Outcome

Population-Based Studies

Population-based cancer registries, which benefit from a large sample size, record all new cases of cancer in a defined population, with an emphasis on epidemiology and public health. Because rigorous characteristics are not used to select patients for inclusion in the study, the findings tend to be generalizable. A limitation of registry-based studies is that they tend to have incomplete data on treatment history and patient characteristics.

The largest population-based study that retrospectively evaluated the effects of local therapy on outcomes in metastatic breast cancer patients was published by Khan and colleagues[7] in 2002. This study, based on data reported to the National Cancer Data Base from 1990 to 1993, examined both the use of local therapy and its effect on survival in 16,023 women presenting with de novo metastatic disease. The authors compared 9162 women who underwent either partial or total mastectomy with 6861 women who either had no surgery or underwent only palliative or diagnostic procedures. More than half the patients in this series underwent surgical resection.

On multivariate testing, the factors that were each independently associated with patient outcomes were primary tumor resection, systemic therapy administration, number of metastatic sites, and type of metastatic disease. Women achieving negative margins with surgery had superior survival compared with those not undergoing resection (hazard ratio [HR], 0.61; 95% CI, 0.58-0.65, P=.01). In this study, median OS was higher with total mastectomy (31.9 months) than with partial mastectomy (26.9 months). Because surgical margins were negative more often in the total mastectomy group, margin status may have confounded the survival seen in this group. Additionally, women with only 1 site of metastasis as well as those with metastasis to soft tissue or bone were significantly more likely to undergo mastectomy, potentially resulting in selection bias.[7]

Retrospective population-based studies from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program data (n=9734),[10] the Eindhoven Cancer Registry in the Netherlands (n=728),[12] and the Geneva Cancer Registry (n=300)[9] also have all shown a positive association between resection of the primary tumor in de novo metastatic breast cancer and

Table. Summary of Studies

Study	Type of Study	No. of Patients	% Undergoing Surgery	HR	95% CI	Median Survival, mo, Surgery	Median Survival, mo, No Surgery	OS Benefit With Surgery? (*P* Value)
Khan,[7] 2002	Population	16,023	57	0.61[a]	0.58-0.65	26.9; 31.9[b]	19[b]	Yes
Rapiti,[9] 2006	Population	300	42	0.6[c]	0.4-1.0	NA	NA	Yes (.049)
Gnerlich,[10] 2007	Population	9734	47	0.63	0.6-0.66	36[d]	21	Yes (<.001)
Fields,[21] 2007	Single institution	409	46	0.53	0.42-0.67	31.9	15.4	Yes (<.0001)
Blanchard,[11] 2008	Population	395	61	0.71	0.56-0.91	27.1	16.8	Yes (<.0001)
Cady,[22] 2008	2 institutions	622	38	NA	NA	NA	NA	Yes
Hazard,[32] 2008	Single institution	111	42	0.798	0.4-1.52	26.3	29.2	No (.52)
Ruiterkamp,[12] 2009	Population	728	40	0.62	0.51-0.76	31	14	Yes (<.01)
Bafford,[23] 2009	3 institutions	147	41	0.47	NA	42.2	28.3	Yes (.003)
Neuman,[13] 2010	Single institution	186	37	0.71	0.47-1.06	40	33	Yes
Leung,[28] 2010	Single institution	157	33	NA	NA	25	13	No[e]
Dominici,[25] 2011[f]	Population	290	19	0.94	0.83-1.08	42	41	No (.38)
Lang,[24] 2013[g]	Single institution	208	36	0.58	0.35-0.98	56.1	37.2	Yes (.04)
Le Scodan,[33] 2009	Single institution	581	55.1	0.7	0.58-0.85	32[h]	21	Yes (.0002)[h]

HR, hazard ratio; mo, months; NA, not available; no., number; OS, overall survival.

[a] HR was surgery with negative margins compared with no surgery.

[b] Data reported as means; partial mastectomy 26.9 mo; total mastectomy 31.9 mo; no surgery 19 mo.

[c] HR is surgery with negative margins vs no surgery.

[d] Median survivals were for patients still alive at the end of the study period.

[e] Controlling for chemotherapy, *P*=.36.

[f] Case-matched.

[g] Same as Babiera 2006 data set.

[h] Locoregional therapy, 78% of which was exclusive radiotherapy.

outcome, even after controlling for patient- and tumor-specific factors associated with survival. In the SEER analysis, after controlling for confounders, women with metastatic breast cancer who underwent surgery for the primary breast tumor were 37% less likely to die during the 15-year study period than women who did not receive surgery, though notably this study lacked information about sites of metastases, use and type of systemic therapy, and surgical margin status.[10] Multivariate analysis from the Eindhoven Cancer Registry found that primary tumor resection, patient age, number of metastatic sites, and use of systemic therapy were all independently associated with prolonged survival. Unlike the data presented from the National Cancer Data Base,[7] the authors noted no difference in outcome between patients who underwent mastectomy and those who underwent lumpectomy.[12] Data from the Geneva Cancer Registry also highlighted the importance of resection with negative surgical margins, as the multiadjusted HR for death from breast cancer favored resection with negative margins over no resection (HR, 0.6; 95% CI, 0.4-1.0; *P*<.05), but no survival difference was noted between patients with positive surgical margins and those who did not undergo surgery. The benefit from surgery compared with no surgery was particularly apparent for women with bone-only metastases (HR, 0.2; 95% CI, 0.1-0.4; *P*=.001).[9]

Institution-Based Studies

The benefits of single-institution studies are that they often provide detailed surgical and patient data, and most provide more details about systemic therapy. Single-institution studies, however, tend to be relatively small and may be subject to particular geographic, ethnic, and socioeconomic factors that could influence outcomes. Nonetheless, until 2013 the remaining published data on whether surgery is beneficial in de novo metastatic disease were from retrospective single-institution studies, 6 of which showed that surgical resection of the primary tumor in de novo metastatic breast cancer was independently associated with improved outcome,[7,8,11,12,13,21,24] and several others that did not find the same association.[22,23,25] These studies served to provide background data on the topic, and to generate hypotheses for randomized controlled trials.

Several studies have evaluated how various treatment modalities, such as chemotherapy, hormonal therapy, radiation, and surgical resection, affect outcome in de novo metastatic disease. With the advent of targeted therapies, Neuman and colleagues[13] sought to clarify whether the benefits of surgical resection were specific to certain molecular subtypes of breast cancer. In a study of 186 patients with de novo stage IV breast cancer identified between 2000 and 2004 from Memorial Sloan Kettering Cancer Center's prospectively managed database, ER positivity, progesterone receptor (PR) positivity, and *HER2* amplification were all predictive of improved survival. Overall, a nonsignificant trend toward improved survival was observed with surgical resection of the primary breast tumor (HR, 0.71; 95% CI, 0.47-1.06; *P*=.1). In cases with ER- or PR-positive or *HER2*-amplified disease, however, surgery was associated with a significant improvement in survival (*P*=.004). This effect was not observed in those with triple-negative disease, suggesting that the benefit of surgery for the primary breast tumor is greatest in the presence of effective systemic targeted therapies.[13]

In 2013, Lang and colleagues published a follow-up of previously reported data[8] from MD Anderson Cancer Center that included 208 patients with metastatic breast cancer and intact primary breast tumors, about one-third of whom underwent resection of the primary tumor. The added benefit of this report was that specific details of systemic treatment and radiation therapy were known for all patients and assessed for effect on survival. After covariate adjustments, improved OS was observed only with surgery of the intact primary tumor, ER positivity, and having a single focus of metastatic disease.[24]

Another study identified 395 patients from a central laboratory database at the University of Texas Health Science Center. Cases included only women surviving longer than 90 days in an effort to eliminate any surgical selection bias from patients with life-threatening comorbidities or poor baseline performance status. Again, results indicated that surgical removal of the primary breast tumor was independently associated with improved outcome, even after controlling for tumor- and patient-related factors that are associated with outcomes (HR for death, 0.71; 95% CI, 0.56-0.91; *P*<.0001). The median survivals were 27.1 months and 16.8 months, respectively. In this study, margin status was not known in the majority of cases and survival was not affected by surgical resection in the subset with bone-only metastases.[11]

The group from the Netherlands carefully reviewed a 279-patient subset of their original 728-patient data set to assess the possibility that stage migration bias could explain the improved outcome associated with surgical resection.[12] In this subset, the median survival in patients treated with surgery was more than double what was seen in patients who did not receive surgery, and no differences were seen if disease was diagnosed preoperatively vs postoperatively, suggesting that there was no evidence of stage migration bias in their data.[26]

Meta-analysis of Retrospective Studies

A meta-analysis published in 2013 that included a number of the studies above, and totaled 28,693 patients with de novo metastatic breast cancer, concluded that 3-year OS was significantly higher with surgery than without surgery (40% vs 22%, *P*<.01).[27] Additionally, patients selected for surgery were more likely to have lower metastatic burden, smaller primary tumors, and fewer competing comorbidities, although data on these factors were available in only a minority of cases. Data on HER2 status was available in only 402 patients, highlighting the paucity of data for that subgroup in these studies.[27]

Studies Showing No Association Between Surgical Resection and Outcome

Many studies had suggested that surgical patient selection bias, which is inherent in retrospective data sets, and stage migration bias may account for at least part of the survival benefit seen with primary tumor resection in retrospective studies. Lack of data about surgical selection decision-making and lack of clear data on the patients' response to systemic therapy prior to primary tumor removal are other recurring critiques of the retrospective analyses.

Therefore, to evaluate for potential selection bias, Cady and colleagues[22] performed a retrospective matched-pair analysis using 622 patients with de novo metastatic breast cancer; patients who underwent primary tumor resection were matched to patients who were not resected. Cases were identified over a 32-year period from the Massachusetts General Hospital and the Brigham and Women's

Hospital tumor registries. Before performing case-matched analyses, survival data favored the surgically resected group in analyses of the total population and in subsets with either bone-only metastatic disease or visceral disease. After case matching, data demonstrated narrowed (bone-only metastatic cases), or in some cases eliminated (visceral metastatic cases) survival differences. The authors also observed that the greatest survival advantage occurred in patients who underwent systemic therapy prior to delayed resection. Further, on detailed analysis of long-term survivors, the authors observed incorrect staging. Some patients with stage III disease were noted as having stage IV disease, and higher proportions of ER-positive, oligometastatic, and bone-only metastatic cases occurred in the surgical group. These differences all could have falsely broadened the survival gap by selecting those patients for surgery who already may have had superior prognosis.[22]

Additionally, several studies that adjusted for tumor characteristics (eg, ER, PR, and HER2 status), number of metastatic sites, and systemic treatment found either no benefit from surgical resection of the primary breast cancer,[23,25] or no benefit from resection in those receiving chemotherapy.[28] In one of the studies, an improved median survival with resection was seen in patients when metastatic disease was diagnosed postoperatively, suggesting that stage migration bias may explain some of the survival benefit of resection. Of note, this finding is in contradistinction to that reported by the group from the Netherlands.[26]

The Role of Local Therapy

Based on data from these retrospective studies, a loud call for definitive prospective randomized trials was heard around the globe. Such studies are currently being conducted in India, Turkey, Japan, the Netherlands, Austria, Canada, and the United States. Early results from the trials from India (Badwe and colleagues)[29] and Turkey (Soran and colleagues)[30] were presented at the San Antonio Breast Cancer Symposium in December 2013. These trials have yet to be published, so the results should be viewed as preliminary.

In a trial conducted at Tata Memorial Hospital in Mumbai, India (NCT00193778),[29] 350 women with de novo metastatic breast cancer who had a documented objective response to first-line chemotherapy with 6 cycles of anthracycline (with or without a taxane) were randomly assigned to receive locoregional therapy (LRT) or not receive it (no LRT). Locoregional therapy included mastectomy or breast-conserving surgery, removal of axillary nodes, and postoperative radiotherapy in all patients. After randomization, all patients subsequently received endocrine therapy if tumors were hormone-sensitive. The primary endpoint of the trial was overall survival (OS). Stratification factors included site of metastases, number of metastases, and hormone receptor status. Data were presented after 77% of the participants had died and no difference in OS was noted between the 2 groups (19.2% in the LRT group and 20.5% in the no LRT group) and median OS was also similar between the groups (18.8 and 20.5 months in the LRT vs the no LRT groups, respectively). Local control was much improved in the LRT arm (89% and 47.5% in the LRT and no LRT arms, respectively; HR, 0.16), though distant progression-free survival was improved in the no LRT arm (28.3% and 47.5% in the LRT and no LRT arms, respectively; HR, 1.42; P=.01).[29]

There were a number of limitations to the study, the most notable of which was that the 99 patients reported to have disease characterized by HER2 overexpression did not receive HER2-targeted therapy, nor was analysis stratified by HER2 status. It is well recognized that the use of HER2-targeted therapy dramatically improves the survival of patients with HER2-positive disease,[31] so the omission of this therapy could have affected the results of this study. Namely, improvements in systemic therapy might obliterate any gains made with locoregional therapy, or conversely, women may now remain alive long enough to reap the benefits of such therapy. As shown by the study conducted at Memorial Sloan Kettering Cancer Center,[13] women with ER-/PR-positive and/or HER2 overexpressing disease had significant improvement in survival with resection of metastatic disease. It is possible that the benefit of surgery is greatest in the presence of effective systemic targeted therapy.

Soran and colleagues[30] presented early results from the phase 3 MF07-01 study from the Turkish Federation of Breast Diseases Societies (NCT00557986), which randomly assigned 278 women with de novo metastatic breast cancer and an intact primary breast tumor to either up-front systemic therapy with chemotherapy or endocrine therapy (no LRT), or LRT followed by systemic therapy. In this study, LRT could be either mastectomy or breast-conserving surgery with radiation therapy. All patients with clinically positive or sentinel node–positive disease underwent axillary clearance followed by radiation therapy, and free surgical margins had to be achieved. All women with hormone receptor–positive disease received hormonal therapy, and all those with HER2 immunohistochemical 3+ or fluorescence in situ hybridization (FISH)-amplified breast cancer received trastuzumab (Herceptin, Genentech).

With median follow-up of 21 months and only 32% of study participant deaths, the median OS was 4 months longer in the LRT group, but this difference was not statistically significant (median OS in the LRT and no

LRT groups was 46 and 42 months, respectively; *P*=.20). Additionally, a nonsignificant trend toward increased survival was seen in the surgery vs no surgery groups in patients with bone-only metastasis (39.1 vs 32.0 months, respectively; *P*=.13). Of note, patients with solitary bone-only metastasis who received surgery had significantly improved survival compared with patients who did not receive surgery and those with multiple bone metastases (median OS not reached in the LRT group vs 42 months in the no LRT group; *P*=.03). Contrastingly, in the small subgroup with multiple liver and pulmonary metastases (n=29), a statistically significant detriment in survival was seen in the up-front LRT group (median OS, 16 months in the LRT group vs not reached in the no LRT groups, respectively; *P*=.02).[30]

One notable limitation of this trial was that only about one-half of the patients with solitary bone metastases had biopsy-proven metastatic disease. This suggests that some of these patients might not have stage IV disease, and therefore may have had disease that was curable with locoregional and systemic therapy. Additionally, it is unclear if these results are generalizable to patients who first receive systemic therapy because the patients in this study received up-front LRT.

Four other randomized trials are currently underway. In 2010, an Austrian study called POSYTIVE (Primary Operation in Synchronous Metastasized Invasive Breast Cancer) began enrollment (NCT01015625). This study plans to randomly assign 254 patients with primary metastatic breast cancer to early local therapy consisting of surgery, axillary dissection, and possibly radiation therapy vs systemic therapy followed by delayed local therapy only if clinically necessary. First-line chemotherapy is allowed and is a stratification factor for the arms. In 2011, a 410-patient study by the Japan Clinical Oncology Group (JCOG 1017) began. In this study, patients with metastatic breast cancer have a 3-month lead-in phase of systemic therapy; those whose tumors do not progress are randomly assigned to primary tumor resection plus systemic therapy plus systemic therapy or to systemic therapy alone. In 2011, the SUBMIT (Systemic Therapy With or Without Upfront Surgery in Metastatic Breast Cancer) trial from the Dutch Breast Cancer Trialists' Group was initiated (NCT01392586). With a planned accrual of 516 patients, this trial is randomizing patients with de novo metastatic breast cancer to breast tumor surgery followed by systemic therapy, or to systemic therapy followed by delayed local treatment of the breast tumor if clinically indicated. Early in 2011, the E2108 trial from the Eastern Cooperative Oncology Group opened in the United States and Canada (NCT01242800). The E2108 trial aimed to register 880 women with primary metastatic breast cancer with an intact breast tumor. This trial allows up-front systemic therapy at the discretion of the treating oncologist, then randomly assigns women with stable disease or response to one of 2 groups. The first group receives definitive local therapy consisting of either breast-conserving surgery or mastectomy with appropriate axillary staging (similar to women with nonmetastatic disease) and the second group receives continued systemic therapy at the discretion of the treating oncologist, with palliative local therapy only if needed. Owing to poor accrual, the E2108 trial was amended to reduce accrual to 368 patients, with a goal to randomly assign 258 women who exhibit response or stable disease to either early local therapy or continued systemic therapy as noted above.

Conclusions

The role of local therapy in patients who present with de novo metastatic breast cancer remains controversial. The bulk of the larger retrospective studies suggest a benefit to such an approach, although smaller, single-institution studies suggest that, when one controls for tumor- and treatment-related factors, there are no benefits from locoregional therapy. Two randomized trials recently have been presented that shed further light on this topic and find no overall benefit from locoregional therapy in this setting, although the Turkish trial suggested a possible benefit in those with bone-only disease. Neither of the recently presented international trials both maintained the primacy of systemic therapy (ie, giving systemic therapy upfront, then selecting patients who do not progress for consideration of locoregional therapy) and administered modern systemic therapies. The current controversy surrounding this topic supports the continued accrual to ongoing trials in both the United States and other countries. Now more than ever, we should have equipoise on this issue, and we should redouble our efforts to complete the ongoing randomized studies on this topic.

Disclosures

The authors have reported no relevant financial disclosures.

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