Occult Breast Cancer

Introduction

Occult breast cancer (OBC) is defined as clinically recognizable axillary metastatic carcinoma from an undetectable primary breast tumor. In 1907, Halsted was the first to report 3 cases of “cancerous axillary glands with non-demonstrable cancer of the mamma.”¹ The disease is rare, with 0.3% to 1.0% of all patients who present with breast cancer.²,³ The American Joint Committee on Cancer Staging classifies OBC as T0N1/2M0 stage II. Other adenocarcinomas metastasize to the axilla as well; these most commonly include lung, thyroid, gastrointestinal, ovary, and uterus.⁴,⁵ However,
when metastatic adenocarcinoma presents with isolated axillary nodes, the occult primary is most likely to be an ipsilateral breast cancer.\textsuperscript{6,7}

**Diagnosis**

Patients with OBC typically present with a persistent axillary mass. A thorough history and physical examination should be taken, followed by bilateral mammography, ultrasound, and chest radiograph.\textsuperscript{8} Once these preliminary studies are negative for tumor pathology, fine-needle aspiration versus core needle biopsy of the axillary mass should be undertaken; core needle biopsy is preferred because it will provide the pathologist with an adequate tissue sampling for immunohistochemical staining receptor positivity.\textsuperscript{8} Ultrasound-guided biopsy of the axillary mass is another valid option.

With negative preliminary imaging modalities and a biopsy-confirmed tissue diagnosis of metastatic adenocarcinoma in the axilla, the patient is now classified as having an occult cancer with unknown primary. As noted earlier, metastatic adenocarcinoma in the axilla with unknown primary is most likely an ipsilateral breast cancer.\textsuperscript{6,7} Magnetic resonance imaging (MRI) of the breast has proven a useful imaging modality in OBC. Buchanan and colleagues\textsuperscript{9} identified 55 patients with OBC with stage II disease. MRI revealed suspicious lesions in 76\% of patients (42 of 55). In this subgroup, 62\% of the time MRI revealed the occult primary tumor with a false-positive rate of 29\%, and 58\% of these patients received breast conservation therapy. Although recently criticized for high false-positivity rates in routine breast cancer diagnoses, MRI clearly has a place in the diagnostic dilemma of OBC.

**Surgery**

Beginning in 1909, the standard treatment for OBC was a blind radical or modified radical mastectomy\textsuperscript{10}; however, one-third of patients who undergo blind mastectomy will not have any pathologic evidence of carcinoma on serial sectioned analysis.\textsuperscript{2} When this is taken into consideration, along with increased sensitivity of imaging modalities, such as ultrasound and MRI, a discussion of breast conservation is warranted. In 1982, Vilcoq and colleagues\textsuperscript{11} treated 11 patients with OBC conservatively with whole-breast radiotherapy. At 5 years, only 3 of the 11 patients had local breast recurrences that were managed with salvage mastectomy. In an even larger study by Vlastos and colleagues,\textsuperscript{12} 45 patients with OBC were treated with either mastectomy or breast conservation with whole breast radiotherapy. When comparing mastectomy to breast conservation, there was no significant difference in locoregional recurrence (15\% vs 13\%), distant metastases (31\% vs 22\%), or 5-year survival (75\% vs 79\%). Breast conservation is a valid surgical option for OBC, and an informed discussion with the patient regarding surgical options is mandatory.

Management of the axilla does not differ from patients with breast cancer with clinically palpable nodes. All of these patients should undergo an axillary lymph node dissection for locoregional control and staging. The most important determinant of survival in OBC is the number of positive axillary nodes. In the study by Vlastos and colleagues,\textsuperscript{12} 5-year overall survival was 87\% with 1 to 3 positive nodes compared with 42\% with more than 4 positive nodes (P<.0001).

**Adjuvant Therapy**

With regard to systemic therapy, patients with OBC should be treated systemically as any other patient with stage II/II breast cancer. There are no specific prospective data on survival benefit with systemic therapy for OBC; however, most investigators agree
in recommending adjuvant chemotherapy and hormonal therapy for estrogen receptor/progesterone receptor (ER/PR)-positive.8,12,13

**Summary**

OBC accounts for fewer than 1% of all breast cancers. Although other cancers metastasize to the axilla, the most common primary source of metastatic adenocarcinoma in the axilla is an ipsilateral breast cancer. Core needle biopsy is preferred for tissue sampling in the axilla for hormone receptor evaluation. MRI is warranted for diagnosis of the primary occult cancer. Surgical therapy has traditionally centered on mastectomy; however, breast conservation with whole-breast radiotherapy followed by axillary lymph node dissection has shown equivalent results. The axilla should be managed as in any patient who presents with clinically palpable disease, and an axillary lymph node dissection should be undertaken for all patients with OBC. Systemic therapy follows guidelines similar to stage II/III breast cancers.

**BREAST CANCER IN PREGNANCY**

**Introduction**

Pregnancy-associated breast cancer (PABC) is defined as breast cancer diagnosed either during pregnancy or within 1 year postpartum. With women increasingly deferring to have children later into their third and fourth decades, there has been a recent increase in the incidence of PABC. After cervical cancer, breast cancer has become the second most common malignancy in pregnancy.14 The incidence of PABC has been reported as 0.2% to 3.8% of all breast cancers or 2.4 per 100,000 deliveries.15,16 Because termination of pregnancy does not improve maternal outcome, clinicians need to be familiar with effectively and safely treating PABC.17

**Diagnosis**

A conundrum associated with PABC remains a delayed diagnosis. Because of estrogen and progesterone surges, the physiologic changes in the breast during pregnancy include glandular hypertrophy, and increased size and density.18 These changes act to either obscure a new lesion or to provide a false explanation for a newly appearing lesion that needs to be investigated. Older studies from the 1960s to 1970s quote a 6-month diagnostic delay.19,20 More recent studies by Tretli and colleagues,21 however, found a delay in diagnosis of 2.5 months in pregnancy and 6 months during lactation.

Clinical presentation in PABC is similar to that in nonpregnancy breast cancer—a painless, palpable mass. The imaging modality of choice in PABC is ultrasonography followed by mammography. Patients with PABC have dense breast tissue, not only because of the physiologic changes in pregnancy alluded to earlier, but also because of the patients’ younger age. Ultrasonography is the imaging modality of choice in the workup of dense breast tissue in PABC.22,23

If ultrasonography is inconclusive, or if magnification of both breasts is desired, mammography in pregnancy may be indicated. With proper fetal shielding, fetal radiation exposure has been estimated to be 0.4 mrad; the literature quotes a 5.0-rad level to be linked to fetal malformations.24,25 If a suspicious mass is noted on either ultrasonography or a 1-view oblique mammogram, cranio-caudal and mediolateral views of both breasts help rule out bilateral or multifocal disease. MRI of the breasts with gadolinium should be reserved until after pregnancy; gadolinium has been shown to cross the placenta and has the potential for fetal abnormalities.26
Biopsy/Pathology

Core needle biopsy is the gold standard with a sensitivity rate of 90%. Invasive ductal carcinoma is the most common histologic type in PABC. Pathology and hormone receptor status is similar to age-matched controls. Patient age and not pregnancy determines the biologic activity of tumors in PABC. Estrogen and progesterone receptors are typically absent; whereas HER2/Neu receptors are positive 28% to 58% of the time.

Staging

Appropriate staging of patients with PABC focuses on major sites of metastasis: liver, lung, and bone. Guidelines for staging indicate an MRI of the spine without contrast, chest radiograph with fetal shielding, and liver ultrasound. Sentinel lymph node biopsy has recently been accepted as a safe and accurate means of staging the axilla. Because of the risk of anaphylactic shock in the mother, the use of blue dye to aid in identification of the sentinel lymph should be avoided in pregnant patients; however, the use of technetium 99m-labeled sulfur colloid has been proven a safe means for sentinel node identification. With technetium 99m sulfur colloid-guided sentinel lymph node (SLN) biopsy, Keleher and colleagues reported a radiation exposure dose of 4.3 mGy, which is below the estimated safe fetal threshold of 0.1 to 0.2 Gy.

Surgery

After appropriate diagnosis and staging, surgery should not be delayed. If delivery is planned within 2 to 4 weeks, surgical treatment can be delayed. The principles that guide breast cancer surgery in nonpregnant patients should also be followed in PABC. Both modified radical mastectomy and breast conservation surgery, followed by sentinel node biopsy/axillary lymph node dissection, are viable options. At the M.D. Anderson Cancer Center, Dominici and colleagues treated 67 patients with PABC with either mastectomy or breast conservation surgery; they concluded that both surgeries are viable options with low postoperative complications in PABC.

Radiation Therapy

For patients who pursue breast conservation, radiation therapy remains a mainstay of their treatment. The optimal timing for radiotherapy after breast conservation is 12 weeks or less. Thus, when the diagnosis of PABC is made in the third trimester, delay of radiation treatment until after delivery is an accepted course. The dilemma of radiotherapy in PABC centers on women who pursue breast conservation in the first and early second trimesters. Some of these women will go on to receive either neoadjuvant/adjuvant chemotherapy, and thus their radiotherapy may be delayed until after completion of surgery and systemic therapy. In these patients, the timing is favorable to delay radiotherapy. The dilemma really focuses on a small subset of patients in the first and early second trimesters who pursue breast conservation but will not need systemic chemotherapy. In this circumstance, a thorough discussion with the patient should ensue. The patient should weigh the risk of fetal exposure to radiation with a risk of local recurrence if outside the 12-week window eluded to earlier.

Chemotherapy

Systemic chemotherapy should be avoided in the first trimester of pregnancy because of its detrimental effects on organogenesis and possible fetal death. Chemo-therapy has been proven safe in the second and third trimesters of pregnancy.
Cardonick and colleagues\textsuperscript{17} reported a fetal malformation rate of 3.8% in PABC treated with chemotherapy after the first trimester; this malformation rate is not higher than that observed in the general population. To avoid complications from the hematopoietic nadir associated with systemic chemotherapy, a 3-week interval from the last cycle of chemotherapy until delivery should be undertaken.\textsuperscript{32}

**Trastuzumab**

Trastuzumab is not recommended for PABC. It has been associated with oligohydramnios, anhydramnios, and fetal death.\textsuperscript{42}

**Tamoxifen**

Endocrine therapy is not recommended during pregnancy. Tamoxifen has been associated with craniofacial defects and abnormalities of the urogenital tract.\textsuperscript{43,44} Aromatase inhibitors are not appropriate because of the patients’ premenopausal age.

**Summary**

Patients with breast cancer in pregnancy can be safely and effectively treated. The termination of pregnancy does not improve outcomes. Given a patient’s pregnancy trimester and stage of breast cancer, a clinician must be able to guide therapy accordingly.

Treatment guidelines for PABC should closely follow established breast cancer treatment protocols. Patients typically present with a painless palpable mass that can be further imaged with ultrasound. With fetal shielding, mammographic views are possible; MRI without gadolinium can be used in select cases in which ultrasound or mammography are inconclusive. Core needle biopsy is the gold standard for tissue diagnosis.

Breast surgery should proceed with either mastectomy or breast conservation with radiation therapy. Sentinel node biopsy with technetium sulfur colloid is an effective means to stage the axilla. If breast conservation is chosen, a discussion with the patient regarding the risks of radiation to the fetus should be undertaken. Patients with PABC who are in their third trimester can delay radiotherapy until after delivery; patients with PABC who are in their first or second trimester will often need systemic chemotherapy and the timing of delaying radiation until after delivery maybe favorable.

Systemic therapy guidelines differ from patients with breast cancer who are not pregnant. During the first trimester, chemotherapy should not be administered; however, it has been proven a safe means of systemic treatment in the second and third trimesters. Neoadjuvant chemotherapy is a viable option for systemic treatment in the second and third trimesters. Both hormonal therapy and trastuzumab are contraindicated in pregnancy.

**MALE BREAST CANCER**

**Introduction**

In 2012, the National Cancer Institute estimated 226,870 newly diagnosed female breast cancers and 2190 newly diagnosed male breast cancers.\textsuperscript{45} Male breast cancer is rare; it accounts for 0.7% of all breast cancer diagnoses.\textsuperscript{46} Because of the rarity of the disease, few prospective clinical trials are available; most of the surgical literature is dependent on retrospective reviews. Treatment algorithms for male breast cancer have been derived from the treatment of female breast cancer.

The mean age for male breast cancer diagnosis is 67 years; this is approximately 5 years older than the mean age diagnosis for women.\textsuperscript{47} More than 50% of male breast cancers are stage II or greater at the time of initial diagnosis; this compares
less favorably to 35% of female breast cancers that are diagnosed as stage II or greater.\textsuperscript{47,48} When 5-year survival rates for stages I to IV male breast cancers (96%, 84%, 52%, and 24% respectively) are compared with stages I to IV female breast cancers, there is no significant difference.\textsuperscript{47}

**Risk Factors**

BRCA 1 and BRCA 2 are tumor suppressor genes that aid in regulating cell cycle control. Unregulated cell proliferation leads to tumorigenesis. BRCA 2 mutations occur more frequently in men with breast cancer than women. It is estimated that 4% to 16% of male breast cancers are associated with a BRCA 2 mutation.\textsuperscript{49} These patients with BRCA 2 mutations often present at a younger age, and have bilateral disease and a poorer survival.\textsuperscript{49,50} BRCA 1 mutations are associated with male breast cancer to a much lesser extent.

Hormonal imbalances may also play a role in male breast cancer. Klinefelter syndrome (XXY) is strongly associated with male breast cancer.\textsuperscript{51,52} This results from the relative imbalance of high estrogen/androgen ratio. Hultborn and colleagues\textsuperscript{53} determined that a man with Klinefelter syndrome has a 49% risk of developing breast cancer. With increased estrogen levels, obese men (body mass index >30) have been shown to have double the risk of developing breast cancer compared with nonobese men.\textsuperscript{48} Gynecomastia is the enlargement of breast glandular tissue in men. In men older than 50, it is caused by hormonal imbalances centering on a decline in serum testosterone while maintaining estradiol levels. However, the rates of male breast cancer in men with versus without gynecomastia do not appear to differ.\textsuperscript{54} Testicular abnormalities are other risk factors for the development of male breast cancer, specifically those disorders that cause a paucity of androgen production.\textsuperscript{55,56} These disorders include congenital inguinal hernia, undescended testes, testicular injury, orchiectomy, or orchitis.

**Pathology**

Male breast tissue is predominately composed of undeveloped ductal components encircled by connective, adipose, and subcutaneous tissues. As a result of this, lobular carcinoma is extremely rare in male breast cancer. Ninety percent of male breast cancers are invasive ductal carcinomas; 10% are ductal carcinoma in situ of the papillary or cribriform type.\textsuperscript{57} Male breast cancers have high rates of estrogen and progesterone receptor positivity. About 90% of men express positivity for the estrogen receptor, and 80% of men express positivity for the progesterone receptor\textsuperscript{47}; however, male breast cancers express HER2/Neu positivity less often than female breast cancers (5% vs 15%).\textsuperscript{58,59}

**Diagnosis**

Male breast cancer typically presents as a painless subareolar mass. Acceptable imaging modalities include mammography and ultrasound. Mammography has a sensitivity and specificity for diagnosing male breast cancer of 92% and 90%, respectively.\textsuperscript{60} If a lesion is discovered, stereotactic or ultrasound-guided biopsy should be used.

**Surgery**

Although for many years radical mastectomy was the standard treatment for male breast cancer, modified radical mastectomy followed by SLN biopsy/axillary lymph node dissection has become the standard surgical therapy.\textsuperscript{48,61} Because of the
paucity of male breast tissue and the central location of male breast tumors, breast conservation therapy is rarely an option.

Axillary staging consists of SLN biopsy followed by axillary lymph node dissection if indicated. The first case of SLN biopsy in male breast cancer was in 1999. A retrospective review of the Memorial Sloan-Kettering Cancer Center SLN biopsy database from 1996 to 2005 revealed 78 (1%) of 7315 SLN biopsies performed in men. Of the 78 performed, the SLN was found in 76 (97%) patients. In 37 (49%) of 76 patients displaying node positivity, axillary lymph node dissection was completed either at the initial operation or at a subsequent surgery with no axillary recurrences at a median follow-up of 28 months.

At the M.D. Anderson Cancer Center from 1999 to 2005, Boughey and colleagues compared their SLN experience of 30 men versus 2784 women. In men, the SLN was found in 100% of the cases. Interestingly, the male tumors were larger than women’s ($P = .04$), and the incidence of positive SLN in men was higher (although not statistically significant) than in women, at a rate of 37.0% versus 22.3%. In male breast cancers with a positive SLN, the investigators found a non-SLN positivity rate in 62.5% of the cases, with 20.7% of the female cohort ($P = .01$). SLN biopsy can safely and effectively be used as a means to accurately stage the axilla in men with breast cancer.

**Adjuvant Therapy**

Because of the rarity of male breast cancer, randomized prospective trials on adjuvant therapy for male cancer is scarce. Typically male patients with breast cancer follow adjuvant therapy guidelines similar to female patients with breast cancer. In one of the largest retrospective trials, Giordano and colleagues evaluated 51 of 156 male patients with breast cancer who received adjuvant systemic therapies (both cytotoxic and hormonal) and found a 43% lower risk of death than in those who did not receive any systemic therapy. Statistically significant improvement was seen in time to disease recurrence and overall survival with respect to adjuvant hormonal therapy. Adjuvant chemotherapy was associated with lower risk of disease recurrence and death, although this was not statistically significant.

Extrapolating the effectiveness of systemic chemotherapy in female breast cancers and adding to that the retrospective evidence referred to previously, chemotherapy is indicated in male breast cancer. Giordano, at the M.D. Anderson Cancer Center, suggests chemotherapy for breast cancers larger than 1 cm or with positive lymph node involvement. Given the high incidence of ER/PR positivity, tamoxifen should be used as adjuvant hormonal therapy in all ER/PR-positive male breast cancers. In male patients with breast cancer with stage II or III disease, administration of tamoxifen resulted in a 56% 5-year disease-free survival versus 28% in historical controls.

Postmastectomy radiotherapy (PMRT) guidelines for male breast cancer also follow female breast cancer guidelines. Yu and colleagues retrospectively analyzed 75 male patients with breast cancer; 29 did not receive PMRT and 46 completed PMRT. PMRT did not demonstrate a benefit to overall survival; however, it did confer better local recurrence-free survival ($P < .0001$). The investigators site node positivity, advanced stage, or surgical margin smaller than 2 mm as risk factors for male patients with breast cancer who may show an improvement in locoregional recurrence with PMRT.

**Summary**

Male breast cancer remains a rare diagnosis. Although many characteristics of male breast cancer are similar to female breast cancer, there are a few important differences. Men are typically diagnosed at a later age and stage than women with breast
cancer. Male breast cancer risk factors show strong association with BRCA 2 mutations, as well as Klinefelter syndrome. Histologic characteristics show a strong predilection for invasive ductal carcinoma as well as ER/PR receptor positivity.

Surgical treatment centers on modified radical mastectomy followed by SLN biopsy. If the SLN is positive, an axillary lymph node dissection is indicated. Systemic therapy focuses on hormonal and chemotherapy. With male breast tumors correspondingly high estrogen/progesterone positivity rate, tamoxifen is the gold standard for adjuvant hormonal therapy. Radiation therapy should be considered in those patients with risk factors for local regional failure.

**PRIMARY BREAST SURGERY IN STAGE IV BREAST CANCER**

**Introduction**

In the United States, approximately 6% of newly diagnosed women with breast cancer present with stage IV disease. Median survival for patients with stage IV disease has improved to 29 months. Classic breast oncologic dictum has preferred systemic therapy as the mainstay of treatment for stage IV disease. Surgical therapy of the primary tumor has been reserved for palliation. However, several retrospective reviews evaluating the efficacy of surgical treatment of the primary breast cancer in the metastatic setting have shown an increased survival advantage. Critics point to selection bias and stage migration in these retrospective reviews. Prospective randomized controlled trials are lacking. Is there a specific subgroup of patients with stage IV disease who may benefit from surgical treatment of the primary breast tumor?

**Retrospective Reviews**

Several single-institution and population-based retrospective reviews have proclaimed an increased survival advantage for primary breast surgery in patients with stage IV breast cancer. The largest retrospective study by Khan and colleagues evaluated 16,023 patients from the National Cancer Database from 1990 to 1993 who were diagnosed with stage IV disease. A total of 9162 women (57%) underwent either partial or total mastectomy. Using a Cox proportional model on multivariate analysis, the investigators identified the following covariates as independent prognostic indicators of patient outcomes: surgical resection of primary tumor, type of metastatic disease, and the number of metastatic sites. Three-year survival rates were 17% with no surgery, 28% for partial mastectomy, and 32% for mastectomy.

Evaluating the Surveillance, Epidemiology, and End Results (SEER) database, Gnerlich and colleagues analyzed 9734 patients with stage IV breast cancer; 47% underwent extirpation of the primary tumor. Median survival was longer in the surgical cohort versus the nonsurgical cohort in patients alive during the study period (36 vs 21 months, \( P < .001 \)), as well as for women who died during the study period (18 vs 7 months \( P < .001 \)).

A single-institution retrospective study from the University of Texas M.D. Anderson Cancer Center evaluated 224 patients with stage IV breast cancer from 1997 to 2002. Eighty-two patients underwent either a partial mastectomy (48%) or total mastectomy (52%) for local control of their primary breast tumor. The surgical cohort was associated with a trend toward improved overall survival (\( P = .12 \)) and an improved metastatic progression-free survival (\( P = .0007 \)).

**Selection Bias**

Even though only 3 articles are referenced touting increased survival for patients with stage IV breast cancer with extirpated primary tumors, there is a plethora of literature...
with the same claims; however, there is inherent selection bias in many of these retrospective single-institution studies. Patients were not randomly assigned to cohorts; rather, surgical candidates were selected by the treating physician.

Cady and colleagues\(^{75}\) performed a matched pair analysis in an attempt to analyze potential bias in selecting patients for primary site surgery in metastatic breast cancer. Of 622 patients analyzed, 388 (62%) had no surgery and 234 (38%) underwent surgery. Once again, the surgery cohort was associated with an improved survival (\(P < .0001\)); however, on case-matched control analysis, the timing of systemic chemotherapy played a significant role in survival. Patients who received preoperative chemotherapy followed by surgery had a 90% survival at 2 years; this differed markedly from those patients who received chemotherapy and surgery simultaneously, as well as those patients who received chemotherapy postoperatively. And thus, Cady and colleagues\(^{75}\) suggest selection bias can explain much of the survival advantage evident in the previously mentioned nonrandomized retrospective reviews. This calls for randomized prospective trials to evaluate the efficacy of primary site surgery in patients with stage IV breast cancer.

**Stage Migration**

Bafford and colleagues\(^{76}\) performed a retrospective review from the Dana Farber Cancer Institute at the Brigham and Women’s Hospital and the Massachusetts General Hospital evaluating the effect of surgery in patients with stage IV disease. From 1998 to 2005, 148 women presented with stage IV cancer; 61 (47%) underwent mastectomy or lumpectomy. On univariate and multivariate analyses, the surgery cohort versus the nonsurgical cohort had superior overall survival of 3.52 years versus 2.36 years (\(P = .093\)) and 4.13 years versus 2.36 years (\(P = .003\)), respectively. However, in those patients undergoing surgery, 36 patients (59%) were diagnosed with metastatic disease postoperatively and 25 patients (41%) were diagnosed with metastatic disease preoperatively. Median survival in the patients with postoperatively discovered metastatic breast cancer was 4.0 years; however, median survival in the preoperatively detected metastatic disease group undergoing surgery versus the nonsurgical cohort differed very little: 2.40 years versus 2.36 (\(P = .18\)). This clearly demonstrates stage migration bias.

**Targeted Molecular Therapy**

Although acknowledging the aforementioned retrospective reviews, Neuman and colleagues\(^{77}\) sought to identify subsets of patients who would benefit from surgical resection of the primary tumor in stage IV disease. They examined the relationship between tumor molecular subtype in combination with targeted molecular therapy and surgery. During 2000 to 2004, 186 patients with stage IV disease and an intact primary tumor were treated at the Memorial Sloan-Kettering Cancer Center. Sixty-nine (37%) patients’ primary tumors were treated surgically: 34 patients with unknown metastatic disease at the time of surgery, 15 patients for local control, 14 patients for palliation, and 6 patients to obtain tissue. On univariate analysis, there was a trend toward improved survival in patients treated surgically of 40 months compared with nonsurgically treated patients of 33 months. This trend was also evident in the previously discussed retrospective reviews. On further analysis, however, Neuman and colleagues\(^{77}\) identified tumor molecular subtype as the most significant prognostic factor for surgery as an adjunctive to multimodality therapy in patients with stage IV disease with an intact primary tumor. Surgery of the primary tumor was associated with improved survival in patients who were ER/PR-positive and HER2/Neu-positive (\(P = .004\)); however, no survival benefit was seen in patients who were triple negative.
who underwent resection of the primary tumor. This proposes that the influence of local control is most effective in the presence of appropriate targeted molecular therapy.

**Summary**

Stage IV breast cancer has classically been treated with systemic therapy. Traditionally, surgical therapy in stage IV breast cancer has been relegated to palliative control of an ulcerated breast wound. However, several retrospective trials have associated a survival advantage with primary site tumor extirpation in the setting of stage IV breast cancer. Selection bias and stage migration may be contributors to improved survival seen in retrospective reviews of single-institution or population-based trials arguing for primary site surgery in metastatic breast cancer. A subset of patients with stage IV breast cancer who underwent targeted molecular therapy may benefit the most from local control of the primary tumor. Prospective randomized controlled trials are needed to obviate selection bias.

**REFERENCES**