Inflammatory breast cancer (IBC) is a rare and aggressive form of invasive breast cancer accounting for 2.5% of all breast cancer cases. It is characterized by rapid progression, local and distant metastases, younger age of onset, and lower overall survival compared with other breast cancers. Historically, IBC is a lethal disease with less than a 5% survival rate beyond 5 years when treated with surgery or radiation therapy. Because of its rarity, IBC is often misdiagnosed as mastitis or generalized dermatitis. This review examines IBC’s unique clinical presentation, pathology, epidemiology, imaging, and biology and details current multidisciplinary management of the disease, which comprises systemic therapy, surgery, and radiation therapy.
A Medical Dilemma: Clinical and Pathological Diagnosis of IBC

Because of the rapid progression of IBC, accurate diagnosis is critically important—aggressive multimodal therapy can significantly improve outcome when instituted early enough. Thus, it is unfortunate that IBC is frequently misdiagnosed as an infective process, which results in having some patients receiving antibiotics for extended periods before the correct diagnosis is reached.

The aggressive course of IBC, together with accumulating data on its unique molecular and epidemiological characteristics, lends support to the hypothesis that IBC may in fact be a distinct biological entity rather than a subtype on the spectrum of locally advanced breast cancers (LABC). To this end, it is important to distinguish 2 distinct clinical varieties of IBC that are commonly cited in the literature. The term “primary IBC” is used to describe the de novo development of IBC in a previously normal breast. In contrast, “secondary IBC” describes the development of inflammatory skin changes that mimic primary IBC either in a breast that already had cancer or on the chest wall after a mastectomy for non-IBC.

Clinical diagnosis combines observations of the physical appearance of the affected breast, a careful medical history, physical examination, and pathological findings from a skin biopsy and/or needle or core biopsy to confirm the diagnosis of carcinoma.

Clinical Signs and Symptoms of Primary Inflammatory Breast Cancer

Physical Appearance of the Breast

One of the most frequently described changes associated with IBC is erythema, where the skin overlying the breast shows a pink or mottled pink hue (Fig. 1A). The erythema may be associated with a sensation of heat in the affected breast and increase in size secondary to edema. The edema is associated with exaggerated hair-follicle pits, causing a characteristic peau d’orange (orange peel) appearance of the skin (Fig. 1B). The rapid progression, along with diffuse erythema of more than one-third of the skin overlying the breast, distinguishes IBC from neglected LABC with skin involvement. In more advanced and aggressive cases, the color can demonstrate dramatic changes from pinkish to dark red or purple in a few days and can spread diffusely over the entire breast. Blockage of lymphatic channels can cause wheals or ridging of the skin in the breast mound and may be accompanied by a generalized induration of the breast.

FIGURE 1. Clinical signs of IBC are depicted. (A) This IBC patient presented with erythema and breast enlargement. (B) This IBC patient presented with breast edema associated with nipple retraction.
Primary IBC can present bilaterally (Fig. 2A). Typically, synchronous bilateral IBC is associated with minimal breast edema and predominant erythema, with skin changes that may progress quickly to nodules and ulceration.

It is important to recognize that there are variations in presentation. In African American women, for example, increase in breast size and peau d’orange frequently occur with minimal redness or sometimes without detectable erythema (Fig. 2B), contributing to the difficulty of and delay in clinical diagnosis. In this situation, it must be emphasized that the description of the clinical symptoms together with the rapidity of the changes in the breast and skin can provide criteria to support a clinical diagnosis of IBC.

Medical History
Inflammatory breast cancer is most frequently characterized by a very rapid onset of clinical signs and symptoms. Because of the possibility of mistaking IBC for a benign bacterial infection such as mastitis, it is important to note that IBC is not a true inflammatory process and is generally not associated with symptoms such as fever, localized pain, or leukocytosis. A careful medical history typically contributes important information for discriminating the clinical signs of IBC, particularly the acute onset of breast enlargement and heaviness.

Physical Examination
In the majority of patients with IBC, no discrete mass is palpable on clinical examination. Rapid breast enlargement and changes in the skin overlying the breast are usually the first manifestations of the disease that bring patients to the attention of a physician (Fig. 1A). Because IBC is relatively rare, some physicians might interpret the lack of a palpable tumor as excluding a diagnosis of breast cancer. Furthermore, skin changes may vary in both color and pattern of distribution depending on the extent of disease at presentation (Fig. 1B). Early erythematous discoloration of the skin can further progress to intense red or purple color involving the entire breast. Specifically associated skin manifestation is the peau d’orange or orange peel appearance attributed to underlying skin edema.

From 55% to 85% of patients present with metastases to the axillary or supraclavicular lymph nodes that may be detectable on clinical examination. Fixed,
palpable, ipsilateral, axillary nodes are a common finding.\textsuperscript{3} As with non-IBC, the presence of lymph node involvement is a crucial piece of information in the staging of the disease and provides important prognostic information. In the seventh edition of the American Joint Committee on Cancer (AJCC) staging guidelines for breast cancer, IBC is classified as Stage IIIB, IIIC, or even IV, depending on nodal status and evidence of distant metastasis.\textsuperscript{5}

Although nipple involvement is not described as a diagnostically defining clinical feature of IBC, flattening, retraction, crusting, or blistering may be frequently apparent. It is usual to photograph the condition of the breasts during the examination, as response to treatment can be monitored by reduction of erythema and edema.

Secondary IBC can be associated with disease manifestation in the breast or chest wall that was previously affected by a non-inflammatory disease. The secondary IBC can present as a diffuse chest wall rash or as nodules that can quickly become ulcerated (Fig. 3A, B). Saltzstein described a rare and controversial presentation reported as a clinically “occult,” variant of IBC identified in 4 patients with aggressive breast cancer.\textsuperscript{6} Those cases were characterized by lack of clinical evidence of inflammation, despite the presence of tumor emboli in the dermal lymphatics on histologic examination.

### Differential Diagnosis

Few conditions are considered in the differential diagnosis of IBC, and those typically can be excluded on the basis of an accurate medical history and diagnostic biopsy. Bacterial infection, including mastitis and abscess, is a common misdiagnosis. However, such infections are rare in nonlactating women. Uncommon presentations of other cancers can mimic some or all of the clinical signs of IBC but can be ruled out by biopsy results. Postradiation dermatitis, another cause of erythema, is sharply demarcated, whereas the erythema characteristic of IBC shows a diffuse distribution. Congestive heart failure is a rare cause of unilateral breast edema, which should resolve when the underlying condition is appropriately treated. Primary lymphomas of the breast, mostly non-Hodgkin disease, are an extremely rare condition that may mimic IBC and will be excluded on the bases of histopathological features.

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**FIGURE 3.** Clinical presentation of secondary IBC is depicted. (A) This IBC patient presented with a chest-wall rash. (B) An IBC patient has ulcerated nodules.
Inflammatory breast cancer is a rare and aggressive variant of LABC. Although the disease is characterized by specific clinical manifestations already described, it is not a specific histological subtype of mammary carcinoma. The presence of pertinent histopathological findings in the mammary parenchyma and overlying skin, however, in conjunction with the characteristic clinical history, can allow the pathologist to suggest a diagnosis of IBC.

The pathognomonic feature that distinguishes IBC from the commonly encountered “not otherwise specified” LABC type is the presence of numerous dermal tumor emboli in the papillary and reticular dermis of the skin overlying the breast (Fig. 4). Many of the spaces in the dermis that contain tumor emboli do not contain red blood cells and are, therefore, considered to be lymphatic spaces.

The cells that compose the emboli are usually of high nuclear grade with a ductal phenotype. Generalized dermal lymphatic dilatation is also seen (Fig. 5). Although lymphovascular tumor emboli may also be encountered in patients with noninflammatory types of LABC, the emboli in patients with IBC are generally more numerous and often larger in size. There is, however, no direct relation between the number of lymphatic tumor emboli or the extent of vascular distension and the skin manifestations in patients with IBC.

The presence of dermal lymphovascular tumor emboli can be demonstrated by obtaining at least 2 skin-punch biopsies of 2 mm to 8 mm in diameter from the most prominent area of breast skin discoloration. The microscopic pathology of the skin varies greatly among patients with inflammatory carcinoma. Samples of skin from within and outside the zone of erythema and edema may appear histologically identical, with lymphatic tumor emboli detectable in areas that appear clinically uninvolved. Although tumor emboli in dermal lymphovascular spaces are one of the most consistent pathological findings in IBC, they may not be demonstrable in the skin-punch biopsies in every patient. Despite adequate sampling of the skin, including evaluation of multiple levels of the tissue block, dermal tumor emboli may be identified in no greater than 75% of patients with the clinical manifestations of IBC. Therefore, whereas the presence of dermal lymphovascular tumor emboli is useful in confirming the clinical diagnosis of IBC, their absence does not negate a diagnosis of IBC in patients who present with the characteristic skin findings and demonstrate invasive carcinoma in the underlying breast.

Mild to moderate lymphoplasmacytic infiltration may be noted around some of the lymphovascular spaces containing tumor emboli. There is no correlation between extent of this infiltration and severity and distribution of the cutaneous manifestations of the disease. Because of increased collagen deposition and edema of the reticular dermis, the skin thickness may measure up to 8 mm, which is substantially more than the normal thickness of 1 mm ± 0.2 mm over the upper outer quadrant or 1.5 mm ± 0.4 mm over the areola. There is generally no evidence of skin ulceration, Paget’s disease of the nipple, or nipple discharge in these patients.

In patients with IBC, the breast contains invasive mammary carcinoma (most often of ductal phenotype and high histologic and nuclear grades), which may or may not form a distinct mass. The invasive tumor is usually not associated with a distinct intraductal component and often infiltrates the stroma diffusely, making accurate assessment of the size and extent of tumor difficult on gross pathological examination. The invasive carcinoma is usually distributed as several
foci of various sizes with adjacent uninvolved parenchyma studded with lymphovascular tumor emboli, rather than as a uniform continuous infiltration of the stroma by invasive tumor (Figs. 6).

Evaluation of skin margins in surgically excised specimens may not be useful because of the possibility of finding emboli in grossly unremarkable skin as well as in the skin beyond the extent of the invasive tumor in the breast. The frequency of involvement of axillary and supraclavicular lymph nodes in different studies of IBC patients has ranged from 60% to 85%.17

Distinguishing some cases of LABC from IBC may be problematic because of overlapping clinical and pathological findings. Direct extension of the invasive tumor to the overlying skin in some patients with LABC can result in localized erythema mimicking the clinical presentation of IBC.18 In such cases, however, the skin does not show extensive edema or as many dermal emboli as are usually observed in IBC. Other tumors that may be confused with IBC include any poorly differentiated invasive neoplasm that is associated with extensive lymphovascular invasion in the breast and overlying skin and clinical manifestations characteristic of IBC. Such mimickers include tumors such as high-grade non-Hodgkin lymphoma, acute leukemia, melanoma, angiosarcoma, and metastatic poorly differentiated carcinomas from other organ sites.10,19,20 These tumors can usually be excluded easily by morphological and immunohistochemical findings.

An Epidemiological Dilemma: Establishing Risk Factors for IBC

Inflammatory breast cancer is the most aggressive and fatal form of invasive breast cancer. The median overall survival duration among women with IBC is less than 4 years even with multimodality treatment options.21 According to the Surveillance, Epidemiology, and End Results (SEER) registries of the National Cancer Institute, the incidence of breast cancer decreased significantly in 2003 and has leveled off since then.22,23 The American Cancer Society (ACS) estimates that 209,060 new cases of breast cancer will be diagnosed this year and more than 40,230 persons will die from the disease.24 Given the estimation that IBC encompasses 2.5% of all incident breast cancer cases in the United States, we can expect approximately 5000 possible new cases each year. However, it is difficult to determine the incidence rate trends specifically for IBC because of the debatable case definitions that are used to diagnose this disease. In a previous report that used a comprehensive case definition with both clinical and pathological features, IBC cases in the United States occurred at significantly higher rates in African American women than in white women.25 Furthermore, IBC was diagnosed in African American women at a much earlier age, which further emphasizes the considerable racial disparities among patients with IBC compared with those with other non-T4 breast cancers.

At present, there are few established risk factors for IBC. However, many distinguishable epidemiologic characteristics of IBC have been studied (Table 1). The risk factors with the strongest associations with IBC include the higher incidence evident in African American ethnicity, high body mass index (BMI), and younger age at disease onset. African American women were found to have an incidence of IBC at least 50% higher than white women, to be diagnosed at younger ages, and to have decreased survival times.26 IBC shows a prominent geographic pattern. North African countries reported a greater percentage of IBC cases than other regions, with the most studied and documented cases reported in Tunisia.27

The University of Texas M. D. Anderson Cancer Center established a multinational IBC registry in April 2007 with the intent of establishing defined risk factors and prognostic factors by prospectively collecting epidemiological, clinical, and imaging data from patients with IBC (Table 2).28 As of December 2009, approximately 85 patients had been enrolled in the registry, and registration is continuing to increase as additional sites are added. The mean age of the registry patients is 55 years, which corroborates the previously noted younger age at diagnosis for IBC.
More than half exhibit estrogen receptor (ER)-negative tumors; approximately 33% of those present as triple-negative tumors. There is also growing evidence in the literature that high BMI may be positively associated with a diagnosis of IBC more frequently than with non-IBC. Interestingly, an overwhelming 50% of registry patients at M. D. Anderson Cancer Center have a BMI of 30 or higher, marking them as obese. More than two-thirds of the women in the registry are postmenopausal at time of diagnosis. The risk association does not vary by menopausal status, which differs from breast cancer in general, showing high BMI associated with decreased risk of premenopausal breast cancer but increased risk of postmenopausal breast cancer.29

A Tunisian study reported that rural residence was related to a rapid progression of breast cancer in both premenopausal and postmenopausal women, and a mother’s early age (18 years or younger) at her first child’s birth was a factor in 14 of 15 premenopausal women with IBC.15 The significance of the associations could not be completed because of a lack of information. However, Chang et al did not report similar findings in their research conducted in the United States.29 In the future as the size of the registry and duration of enrollment increases, the research program at M. D. Anderson will investigate rural residence and its relation to disease progression as well as the association of a mother’s young age at first birth with age at onset.

Several other risk factors have shown some indication of being associated with a diagnosis of IBC, but further studies are warranted.

**TABLE 1. Selected Risk Factors for Inflammatory Breast Cancer**

| SELECTED RISK FACTORS                     | ASSOCIATION |
|------------------------------------------|-------------|
| Probable risk factors                    | ++          |
| Younger age at diagnosis                 | ++          |
| Younger age at menarche                  | +           |
| Younger age at live first birth          | +           |
| High BMI (≥30)                           | ++          |
| Oral contraceptive use                   | +           |
| Ever pregnant                            | ++          |
| Longer duration of breast feeding        | +           |
| White vs African American ethnicity      | ++          |
| Negative hormone receptor status         | +           |
| Residence in Northern African countries  | ++          |
| Proposed risk factors (too few studies to assess consistency) | — |
| Family history of breast cancer          | —           |
| Carrier of HHV/HPV viruses               | —           |
| Smoking status                           | —           |
| Alcohol use                              | —           |
| NSAID use                                | —           |

++ indicates relative risk >3; +, relative risk >1 and <3

More than half exhibit estrogen receptor (ER)-negative tumors; approximately 33% of those present as triple-negative tumors. There is also growing evidence in the literature that high BMI may be positively associated with a diagnosis of IBC more frequently than with non-IBC. Interestingly, an overwhelming 50% of registry patients at M. D. Anderson Cancer Center have a BMI of 30 or higher, marking them as obese. More than two-thirds of the women in the registry are postmenopausal at time of diagnosis. The risk association does not vary by menopausal status, which differs from breast cancer in general, showing high BMI associated with decreased risk of premenopausal breast cancer but increased risk of postmenopausal breast cancer.29

Large epidemiological studies have not reported a true familial link for IBC, nor have prospective studies properly evaluated this possible genetic trait. However, a matched case-control study of Pakistani women suggested that a family history of breast cancer was significantly more prominent in IBC cases than in non-IBC cases.30 Approximately 40% of the M. D. Anderson registry patients reported having a family history of some form of breast cancer, with 18% reporting an affected first-degree relative. These numbers are very similar to those for non-IBC breast cancer patients at M. D. Anderson, with 36% reporting a family history of breast cancer and 17% reporting an affected first-degree relative. A small number of extremely rare male IBC cases have been reported, dating back to 1953.31

Advances in Diagnostic Imaging of Inflammatory Breast Cancer

The key roles of imaging in IBC are to 1) identify a primary breast tumor and facilitate image-guided diagnostic biopsy to enable the optimal evaluation of biomarkers, 2) stage locoregional disease, 3) diagnose distant metastases, and 4) evaluate tumor response to neoadjuvant therapy.

Standard breast-imaging modalities, such as mammography and ultrasound, are still the mainstay for diagnosis, clinical staging, and therapeutic monitoring of breast cancer, but newer modalities such as magnetic resonance imaging (MRI) and hybrid positron emission tomography/computed tomography (PET/CT) are being used more frequently. In addition to these modalities, others (eg, functional MRI, cone-beam breast CT, 3-dimensional [3D] ultrasound, and optical imaging) are being developed explicitly to take advantage of the special properties and morphology of breast tumors versus normal breast parenchyma. In this section, we review the current and emerging modalities for imaging IBC.
Mammography

Mammography, the gold standard for breast imaging, has been largely unsuccessful in achieving the above-stated roles for imaging IBC. Despite their median age of older than 51 years, more than 90% of women with IBC have nonfatty breast tissue, which may contribute to poor observation of IBC features on mammography, including breast masses or nodules and skin changes.\(^32\) Mammographic breast abnormalities associated with IBC include a mass, architectural distortion, and global skin and trabecular thickening, usually described when already associated with overt clinical findings (Fig. 7).\(^32-34\) Calcifications, a less common feature in IBC, were noted in 33 (41%) of 80 patients in a recent series and in 47% of patients from a survey of 9 published studies.\(^32-34\) Global skin and trabecular thickening are the most frequent mammographic abnormalities in IBC patients, but are nonspecific, as they can also be associated with mastitis and LABC. There are currently no available data on early mammographic changes before clinical diagnosis.

Ultrasonography

Ultrasonography is a cheap and rapid alternative imaging method that has shown success in delineating focal breast parenchymal lesions in patients with IBC, facilitating tissue diagnosis of invasive cancer and permitting evaluation of tumor markers.\(^32-34\) On an ultrasound image, IBC most frequently appears as an area of heterogeneous infiltration of the breast parenchyma or as a conglomerate of masses within the breast with overlying skin and subcutaneous edema (Figs. 8A, B).\(^32,33\) In a recent report, ultrasonography enabled detection of up to 93% of ipsilateral axillary nodal involvement and up to 50% of infraclavicular, internal mammary, or supraclavicular nodal involvement (N3 disease in the TNM classification system) in IBC patients (Fig. 8C).\(^32\) These findings are useful for delineating regional nodal metastases and may affect locoregional therapeutic planning that is based on initial disease involvement.\(^35,36\) Furthermore, ultrasonography is extremely useful in evaluating response to induction chemotherapy of axillary nodes, with possible impact on timing of local therapy.

### TABLE 2. Selected Demographic Factors from the M. D. Anderson Inflammatory Breast Cancer Registry\(^a\)

| DEMOGRAPHIC FACTORS      |  |  |  |
|--------------------------|---|---|---|
| **Age at diagnosis**     |  |  |  |
| Overall                  |  |  |  |
| White                    |  |  |  |
| Hispanic                 |  |  |  |
| African American         |  |  |  |
| Hormonal factors         |  |  |  |
| ER+ / PR+                |  |  |  |
| ER- / PR+                |  |  |  |
| ER+ / PR-                |  |  |  |
| ER- / PR-                |  |  |  |
| HER2/neu+                |  |  |  |
| Triple negative          |  |  |  |
| Body mass index          |  |  |  |
| Normal (<25)             |  |  |  |
| Overweight (24-29)       |  |  |  |
| Obese (>30)              |  |  |  |
| Lifestyle factors        |  |  |  |
| Ever smoked              |  |  |  |

SD indicates standard deviation; ER, estrogen receptor; PR, progesterone receptor; OCP, oral contraceptive pill.

\(^a\) \(n=70\) at time of data analysis.

\(b\) Parous women only.
Magnetic Resonance Imaging

Dynamic contrast-enhanced (DCE) magnetic resonance imaging (MRI), a multiplanar imaging technique that exploits the presence of angiogenesis in malignant tumors, depicts cancers by producing images of characteristic contrast uptake patterns and kinetics. Although published data on MRI findings in patients with IBC are limited, MRI has been shown to be the most accurate test for detecting a primary breast lesion in patients with IBC. From 1997 to 2008, only 9 studies described MRI findings in the diagnosis and staging of IBC and the role of MRI in the monitoring of response to therapy. The majority of those studies were retrospective trials, with small sample sizes ranging from 15 to 80 patients.

MRI results frequently found in patients with IBC include diffuse skin thickening associated with breast enlargement, edema, and a breast mass or abnormal parenchymal enhancement (Fig. 9). A breast parenchymal lesion was noted in 41% to 98% of cases in several series. As reported in a retrospective study of 48 patients with IBC and 52 patients with LABC, the IBC masses were...
Inflammatory Breast Cancer

Asymmetric nonmass-like enhancement is more frequently associated with IBC than with non-IBC, a finding concordant with the clinically aggressive and infiltrative behavior observed in this disease and with the tendency for this carcinoma to be multifocal and multicentric in its distribution. The initial MRI peak-signal intensity seen immediately after administration of intravenous contrast is usually greater than 100% and has been reported to be higher in patients with IBC than in those with mastitis or LABC.

Other MRI findings that are predominantly related to the inflammatory components of IBC, such as dilated lymphatic ducts, breast edema, or chest wall edema, are best observed on a fat-suppressed T2-weighted sequence. The diffuse edematous pattern has been observed more commonly in IBC than in LABC, whereas the focal peritumoral edematous pattern has been reported in both. Skin abnormalities can be associated with mastitis, LABC, or IBC. Whereas normal skin thickness measures 3 mm or less on mammography and MRI, the thickness in patients with IBC frequently measures up to 13 mm.

DCE MRI has been used to monitor tumor response to chemotherapy. Some reports have shown that, in LABC, tumor size after neoadjuvant chemotherapy, as observed on MRI, correlated better with actual residual disease than did measurements by clinical examination, mammography, or ultrasonography. Only 2 published studies have evaluated the role of breast MRI in monitoring response to chemotherapy in IBC, and the sample sizes for both retrospective trials were small (19 and 24 patients).

Positron Emission Tomography

Positron emission tomography (PET) is a molecular imaging technique that is sensitive to functional or metabolic changes in tissues. Because functional changes precede anatomical changes, fluorine-18 fluorodeoxyglucose PET (F18-FDG PET) has the potential to detect viable tumor tissue early through its level of glucose metabolism, which is higher than that in surrounding normal tissues. Whole-body PET/CT has the potential to clearly demonstrate—in a single functional study—the extent of the disease, the most likely sites for staging biopsies, and whether a given therapy is achieving its goal. Increasingly, F18-FDG PET is being used as a staging imaging modality in women with LABC, and it has been shown to be useful in detecting involvement of internal mammary lymph nodes that is predictive of recurrence. A recent retrospective review on the role of PET/CT in the initial staging of IBC reported encouraging preliminary results in the diagnosis of locoregional and distant disease: 17% of 41 patients were shown to have unsuspected distant metastases at staging. Moreover, the conventional method of assessing response to therapy in IBC is measuring tumor size. Because functional changes precede morphological changes in tumors, much research has focused on the role and efficacy of functional techniques in measuring response to therapy. Preliminary data on the monitoring of primary chemotherapy in LABC show that FDG uptake is reduced after the first cycle of treatment and that this decrease is a marker that may be valuable in predicting treatment response, and it will likely be able to correlate with overall prognosis. In IBC, the absence of clinically identified masses to measure and track over time makes an overall functional approach even more appealing for assessing response and managing therapy.

FIGURE 9. (A) A 44-year-old woman has IBC (invasive ductal carcinoma). An axial T1-weighted VIBRANT MR image demonstrates multiple parenchymal breast masses, with a large central dominant mass (arrows). (B) A 49-year-old woman has IBC (invasive ductal carcinoma and ductal carcinoma in situ). An axial contrast-enhanced T1-weighted VIBRANT MR image demonstrates abnormal nonmass-like parenchymal enhancement (arrows).
In routine imaging for breast cancer, basic requirements include the capability of detecting tumors smaller than 1 cm, a practice that has been problematic when using whole-body PET scanners, which have a maximal spatial resolution of approximately 6 mm. The PEM (positron-emission mammography) Flex device (Naviscan, San Diego, Calif) has been approved by the US Food and Drug Administration as a high-resolution PET scanner, and FDG has been approved as a contrast agent for imaging cancers with a PEM device. Preliminary studies that used FDG-PEM reported 90% sensitivity, with depiction of 10 of 11 (91%) cases of ductal carcinoma in situ and 33 of 37 (89%) invasive breast cancers, including 5 of 8 (62.5%) invasive cancers sized 1 cm or smaller.63 Considering its higher resolution, PEM may have a role in monitoring early response to targeted therapy of LABC and IBC.

### Multimodality Imaging: Overview and Advanced Use for Diagnosis and Staging

Multimodality imaging is defined as the process of registering and fusing data sets that have been produced by distinct modalities at different time points.70-76 Registration identifies the 3D geometric transformation of one data set in the spatial reference system of another data set. Fusion combines the registered information to provide combined functional and anatomic information on one image. Ideally for the registration process, the patient is in an identical position and physiological state across modalities and time points, which is seldom achieved but can still be reasonably mitigated in many cases.71,74 Figure 12 demonstrates such real-life registration and fusion of a parametric MRI scan and an FDG-PET/CT scan that were performed separately on the same patient with breast cancer.

In summary, the primary imaging tools for patients with IBC include mammography and sonography, which in combination can help direct a targeted breast biopsy for histological diagnosis and delineate disease extent, including regional nodal status, for baseline characterization to facilitate monitoring of tumor response and planning of imaging modalities) may be possible, including optical, ultrasound, and MRI-based probes.64-68 Tumor hypoxia, an important factor mediating cancer aggressiveness and therapeutic resistance, has been widely studied by imaging; some recent studies in breast cancer have used PET imaging and the agent 18F-fluoromisonidazole.69 The potential advantages offered by these modalities will likely benefit evaluation of IBC patients in the near future.

### Recent and Emerging Imaging Modalities

A wide range of pharmaceuticals has been developed into tracers for imaging diverse aspects of breast cancer biology.64 For imaging requiring larger molecules such as monoclonal antibodies and fragments (eg, human epidermal growth factor receptor 2 [HER2] imaging), a wide range of probes (and, therefore,
radiation therapy. Magnetic resonance imaging and PET/CT have evolving roles in mapping locoregional disease and documenting distant metastases. Molecular imaging offers a powerful tool for transforming basic science research into clinical applicability by providing a way to assess and quantify pathways in animal models and patients to verify that the pathways are similar in both scenarios.64–68

**Evolving Concepts in the Biology of Inflammatory Breast Cancer**

**Molecular Subtype of IBC**

Breast tumors are categorized into specific subtypes on the basis of the presence or absence of estrogen receptors and progesterone receptors (ER/PR), the level of expression of claudins, the presence and extent of amplification of the *Her2* oncogene, and the differential production of cytokeratins 5/6 and/or cytokeratins 8/18. Although IBCs may possess any combination of hormone receptors and oncogenes, they are most often classified within the *Her2*-amplified, basal-like, breast cluster and may also be low in claudin. This classification of IBC tumors is consistent with previous gene expression studies reporting that IBC tumors commonly lack ER/PR and have *Her2* oncogene amplification.77 Other characteristics of IBC tumors include high expression of the tumor suppressor *p53* and overexpression of the epidermal growth factor receptor (EGFR), which are both associated with poor prognosis.78,79

Molecular subtyping of breast cancers has provided a tool to determine the potential utility of targeted therapeutics such as those that target *Her2* and/or EGFR. Results of clinical trials have reported a high response rate (39%) and efficacy of the dual tyrosine kinase inhibitor lapatinib (Tykerb), which targets both HER2 and EGFR in IBC patients with *Her2*-positive tumors. Although promising, the response of IBC patients to lapatinib is not durable, with disease progression within 12 months and development of resistance. Studies are underway to identify the mechanisms of lapatinib resistance and to identify agents that may be combined with lapatinib to provide a durable response for IBC patients. Examples of other targeted therapeutics being evaluated for their effects in IBC include the anti-EGFR humanized monoclonal antibody panitumumab and the EGFR tyrosine kinase inhibitor erlotinib. Because many poorly differentiated non-IBC breast tumors also express HER2 and EGFR, it is probable that significant advances in prolonging overall survival of IBC patients will require identification of classes of therapeutic agents that target molecules other than ER/PR, HER2, and EGFR.

**NFκB Activation, Proinflammatory Cytokines, and Chemokine Receptors in IBC**

Pioneering gene-expression profiling studies were the first to report that ER-negative IBC tumors are characterized by overexpression of multiple nuclear factor kappa beta (*NFκB*) target genes.80 While *NFκB* activation and stimulation of associated target genes is known to be involved in tumor progression, there are currently no selective pharmacologic agents that target *NFκB*. Curcumin and analogs of this natural product derived from the Indian spice turmeric as well as the proteosomal degradation inhibitor bortezomib (Velcade®) have been evaluated for their ability to inhibit *NFκB*-mediated events. Studies have demonstrated correlation among *NFκB* activation, Toll-like receptors, and hyperactivation of the mitogen-activated protein kinase (MAPK) signaling pathways, which may be linked to overexpression of EGFR and/or HER2. Other studies have demonstrated the coexpression of EGFR and the chemokine receptor CXCR4 in IBC patients, which was associated with significantly decreased overall survival.81 These signaling pathways potentially offer new therapeutic targets for development of inhibitors of IBC.

**Rho C GTPase and the Molecular Signature of IBC**

The majority of IBC studies have used the SUM149 cell line, which was developed from a primary IBC tumor.82 Differential display analysis was used to identify genes in this cell line and compare them to human mammary epithelial cells and normal lymphocytes; this approach identified 17 genes of interest, 8 expressed in normal but not tumor tissue and 9 expressed only in SUM149 cells. One of the most highly upregulated genes in IBC was the transforming oncogene Rho C GTPase,83,84 which encodes a member of the ras homology (Rho) GTPase family of proteins involved in cytoskeletal reorganization during invasion as well as regulation of angiogenic growth factors and production of inflammatory cytokines. Rho C GTPase was overexpressed in 90% of IBC tumors.
examined. Interestingly, the IBC phenotype associated with Rho C GTPase is blocked by a farnesyl transferase inhibitor, which led to clinical studies that are currently evaluating the effects of the farnesyl transferase inhibitor tipifarnib (Zarnestra®) in a phase 2 clinical trial in patients with stage IIB-IIIC breast cancer.

Loss of WISP3/CCN6 and Cross Talk With Insulin-Like Growth Factor Signaling Pathways

Other studies using the SUM149 IBC cell line identified the loss of Wnt-inducible signaling protein 3 (WISP3/CCN6; LIBC [lost in inflammatory breast cancer]). WISP3/CCN6 is a secreted protein with tumor suppressor functions that is a member of the CCN protein family. Interestingly, CCN6 contains a binding motif similar to one in insulin-like growth factor (IGF) binding protein-related peptides (IGFBP-rp9). High levels of circulating IGF, with loss of IGF binding proteins, have been associated with increased risk for development of multiple tumor types, including breast cancer. Microarray analysis of differential gene expression in IBC tumors compared with non-IBC tumors revealed a distinct IBC molecular signature that includes genes involved in IGF signaling, loss of IGF-binding genes, and increase in expression of genes belonging to the Rho guanyl-nucleotide exchange factor activity, consistent with the observations of a gain of Rho-GTPase and loss of WISP3/CCN6 as a signature of IBC. Insulin-like growth factor 1 stimulates production of the inflammatory cytokines interleukin-8 and interleukin-6 through activation of extracellular signal-regulated kinases (ERKs) and MAPK, suggesting that alterations in IGF-1 signaling in IBC have important consequences in regulation of a "proinflammatory microenvironment," which may be sensitive to inhibitors of ERKs and MAPK. Furthermore, clinical and epidemiological evidence indicates an important link between insulin resistance, hyperinsulinemia, diabetes, and poor prognosis in breast cancer patients. These observations are consistent with the clinical observations that there is a significant association between BMI and poor prognosis among patients with LABC, including IBC. There are currently multiple agents targeting the IGF-1 signaling pathway that have been evaluated in preclinical studies and are now in clinical trials, including anti-IGF-1 receptor antibodies and small molecule inhibitors of the IGF-I receptor tyrosine kinase. Furthermore, recent reports indicated that administration of the antidiabetic agent metformin results in significantly greater frequency of pathologic complete response to chemotherapy in diabetic breast cancer patients than in those not treated with metformin. The mechanism of action of metformin includes activation of the energy-sensing kinase adenosine monophosphate-activated protein kinase and blockade of protein translation regulated by the p70S6 kinase1/mammalian target of rapamycin. Moreover, metformin blocks activation of the phosphoinositide 3-kinase (PI3K)/Akt pathways involved in survival and proliferation and abrogates activation of ERKs. All of these pathways are known to be dysregulated in breast cancer, and inhibitors and/or antagonists are available for many of them. These studies, as well as other studies reporting the convergence of insulin signaling with EGFR, ERKs, MAPKs, and proinflammatory cytokines, suggest that these pathways may be crucial targets to explore for their relevance in regulating the aggressive phenotype of IBC.

Cyclooxygenase-2 and Prostanoid Receptors as Molecular Regulators of IBC Invasion and Metastasis

Studies using the SUM149 and SUM190 IBC cell lines document a role for prostaglandin endoperoxide synthase 2, also known as cyclooxygenase-2 (COX-2), in the invasive and angiogenic phenotype of IBC, which confirms previously reported results from gene-expression and tissue-microarray studies which were the first to identify Cox-2 overexpression in IBC tumors. Overexpression of Cox-2 and elevated levels of its enzymatic product prostaglandin E2 (PGE2) is a characteristic of invasive human breast cancers and is detectable at early stages of tumorigenesis. Cox-2 also directly regulates the P450 Cyp19A1 aromatase enzyme, thereby regulating estrogen production, and interacts with both HER-2 and EGFR. Cox-2 is one of a group of genes that mediate tumor extravasation, survival, and reinitiation at distant sites during metastasis. Although nonsteroidal anti-inflammatory agents and the coxibs, a class of selective Cox-2 inhibitors, showed promise as therapeutic and chemopreventive agents, the association with cardiotoxicity in some individuals led to discontinuation of the use of rofecoxib and reduction in the use of celecoxib.
Our studies demonstrate that antagonists of the prostanooid receptor EP4, which block binding of PGE₂, effectively inhibit the robust invasion and aberrant angiogenesis exhibited by IBC tumor cells.97 Interestingly, a study in canine inflammatory mammary carcinoma reported that the nonselective nonsteroidal anti-inflammatory drug (NSAID) piroxicam, used as a single agent, significantly increased the mean overall progression-free survival interval compared with treatment with doxorubicin-containing regimens.98 The roles of Cox-2 and the associated PGE₂ prostanooid receptor family in the metastatic phenotype of IBC are currently under active investigation and represent important therapeutic targets in IBC.

ERBB2 Tyrosine Kinase Family of EGFRs
Another IBC cell line (KPL-4) that was isolated from the pleural effusion of an IBC patient has been characterized as overexpressing multiple members of the ERBB2 tyrosine kinase family of EGFRs.99 The KPL-4 cell line and the KPL-4 xenograft model have been used primarily to evaluate the efficacy of agents that target these pathways, including the HER1/EGFR tyrosine kinase inhibitor erlotinib; a HER2-specific recombinant, humanized, monoclonal antibody, pertuzumab (Omnitarg™), which prevents heterodimerization of HER2 with other HERs; and the dual inhibitor of EGFR and ErbB2 kinase, MP-412 (AV-412).100 Although both the SUM149 and KPL-4 cell lines can be injected into immunocompromised mice and form primary tumors, with development of metastatic lesions (primarily to the lung), there are currently only 2 in vivo xenograft models of IBC, the Mary-X and the WIBC-9 models that recapitulate the tumor emboli that are the signature of human IBC.

Overexpression of E-cadherin as a Molecular Signature of IBC
The first clinical signs of IBC are the rapidly progressing changes in the skin that are presumed to be secondary to the presence of florid lymphovascular invasion. These changes in the skin have a unique microscopic appearance and occur as compact clumps of tumor cells that are retracted from the endothelial cell layer that lines the lymphovascular spaces of the dermis. The subsequent plugging of the lymphovascular spaces by tumor emboli is believed to contribute to the tenderness, reddening, and swelling of the breast as well as to the changes in skin texture that are the initial signs of IBC, although the association of these observations in terms of cause and effect has never been subjected to rigorous scientific evaluation. As one of the classical histopathological findings in IBC, tumor emboli within the skin are skin lesions that have escaped the confines of the underlying breast. Whereas most human xenografts grow in mice as nodules without obvious lymphovascular invasion, the Mary-X xenograft model of IBC exhibits lymphovascular tumor emboli present in the skin overlying the breast, turning the skin of the mouse bright red, thereby providing an appropriate model with which to study this phenomenon, one of the most well-characterized signatures of IBC. Studies using IBC tumor spheroids in vitro and IBC tumor emboli in vivo are providing insight into molecular pathways and therapeutic targets that are vitally important to the invrasation and rapid metastasis exhibited by IBC. Furthermore, tumor emboli that are the result of lymphovascular invasion can be used as a therapeutic endpoint if the Mary-X model of IBC is used.

Mary-X has a molecular subtype characteristic of the majority of IBC tumors: it is ER/PR/HER-2 null but expresses both p53 and EGFR.101 It is characterized by aberrant overexpression of the calcium-dependent transmembrane glycoprotein E-cadherin, one of the hallmarks of IBC tumors and tumor emboli, which is also present on the surface of circulating tumor cells isolated from IBC patients.102,103,104 Interestingly, the tumor emboli of Mary-X overexpress E-cadherin with the concomitant loss of sialyl-Lewisx/a (sLex/a). An overactive intact E-cadherin/alpha,beta-catenin axis mediates homotypic aggregation of the cells comprising the tumor emboli, while sLeα/a mediates binding of the tumor emboli to the endothelium through E-selectin. The gain of E-cadherin and loss of sLeα/a results in tight aggregation of cells within the tumor emboli while simultaneously preventing tumor emboli from binding to the surrounding endothelium. E-cadherin expression has been associated with a normal breast cell phenotype, whereas loss of E-cadherin and gain of N-cadherin have been reported to occur during the epithelial–mesenchymal transition (EMT) associated with tumor progression and metastasis.105 Inflammatory breast carcinoma is a notable exception to the common association between the loss of E-cadherin and subsequent acquisition of an EMT phenotype.102,104 This anomalous overexpression of E-cadherin by the most aggressive and metastatic of
all breast cancers is provocative in light of the current thinking that loss of E-cadherin is a requirement for the process of EMT, which is associated with acquisition of a metastatic phenotype. This may represent a unique mechanism by which tumor cells that have molecular plasticity undergo metastatic progression, or alternatively it may represent a survival mechanism for cells within the tumor emboli.

Studies focused on E-cadherin as a potential therapeutic target have demonstrated that blockade of E-cadherin by using anti-E-cadherin antibodies results in loss of homotypic aggregation of Mary-X spheroids in vitro. When injected via the intravenous route into animals bearing Mary-X tumors with known pulmonary metastasis, anti-E-cadherin antibodies induced dissolution of the metastatic lesions. In vitro, Mary-X spheroids containing a dominant-negative E-cadherin mutant (H-2K[d]-E-cad) lacking the extracellular binding domain but retaining the \( \beta \)-catenin binding domain similarly resulted in loss of homotypic aggregation. In mice, these dominant-negative mutant constructs were only weakly tumorigenic and did not form tumor emboli. Other studies using the SUM149 IBC cell line demonstrated that the presence of dominant negative E-cadherin (H-2kd-E-cad) cDNA blocked the robust invasion of SUM149 cells in vitro, which was associated with decreased expression of the matrix metalloprotease (MMP) enzymes MMP-1 and MMP-9. These studies suggest that the process of invasion and intravasation by IBC tumor emboli was mediated by both E-cadherin and enhanced proteolytic enzyme activity. In support of the role of E-cadherin and related molecules in IBC are recent studies demonstrating that blockade of p120-catenin, which anchors E-cadherin, or inhibition of the translation initiation factor eIF4G1, which regulates translation of specific mRNAs such as p120, results in loss of integrity of SUM149 tumor spheroids.

These findings collectively suggest that the E-cadherin molecule is central to the intravasation of IBC tumor emboli and represents an important target for effective treatment of IBC.

**Angiogenesis, Lymphangiogenesis, and Vasculogenic Mimicry in IBC**

In studies using real-time quantitative reverse transcriptase polymerase chain reaction, IBC tumors were demonstrated to have significant levels of gene expression of multiple genes associated with angiogenesis and lymphangiogenesis, compared with non-IBC breast tumors. These same studies validated the presence of angiogenic growth factors and the associated receptors, by using tissue microarray and immunohistochemistry, and validated the presence of increased lymphatic endothelial cell proliferation, suggesting that lymphangiogenesis has an important role in IBC tumors.

In addition to the classic angiogenic pathways associated with endothelial migration, proliferation, and organization to form new vessels, driven primarily by vascular endothelial growth factor (VEGF) and its receptors, IBC tumors exhibit vasculogenesis, which is the de novo formation of vessel-like structures that allow the flow of oxygen and nutrients in the absence of endothelial cells. The ability of tumor cells to form tube-like structures is defined as vasculogenic mimicry (VM) and was first described in uveal malignant melanoma. In addition to being a characteristic of embryonic stem cells, VM is a hallmark of very aggressive tumor types that display phenotypic plasticity. Studies in melanoma suggest that tumor cells capable of undergoing VM exhibit the ability to undergo epigenetic reprogramming and can remodel their microenvironment. The observations that IBC tumors exhibit VM are consistent with observations that IBC tumors are more angiogenic, lymphangiogenic, and vasculogenic than non-IBC breast tumors and that IBC tumor cells express genes associated with survival under hypoxic conditions, even in a normoxic environment.

The WIBC-9 xenograft model was used to first demonstrate a role for VM in IBC. The Mary-X model of IBC also exhibits a type of VM, whereby mesenchymal stem cells form vascular channels that encircle tumor emboli in dermal lymphatics (unpublished observations, S. H. Barsky). Studies in dogs with inflammatory mammary carcinoma have also reported that these tumors are highly angiogenic, exhibit lymphangiogenesis, and contain capillary-like structures. Evaluation of molecules and pathways that are known to regulate lymphangiogenesis and vasculogenesis as well as pathways that regulate tumor hypoxia through hypoxia-inducible factor-1 alpha represent new opportunities for understanding the spectrum of angiogenic pathways that are crucial to the distinct molecular signature of IBC.
Cancer Stem Cells and IBC

Some of the most exciting opportunities in IBC research come from converging evidence from the areas of stem cell biology, developmental biology, and cancer biology, which suggest that aggressive metastatic tumor types exhibit phenotypic plasticity and are enriched for a subpopulation of cells that have unique characteristics consistent with their activities as “tumor-initiating” or cancer stem cells (CSCs). In a manner similar to embryonic stem cells, CSCs can undergo self-renewal, providing a means of limitless replication, and are multipotent, giving rise to more differentiated cells of other lineages. Established breast cancer cell lines contain CSCs that can be cultivated by using specific culture conditions, providing the foundation for developing in vitro models to evaluate the role and function of CSCs. SUM149 IBC cells were documented to express the putative stem cell surface markers CD44+/HCD24−/low and to have aldehyde dehydrogenase (ALDH-1) enzyme activity, believed to be a marker of tumor-initiating activity. CSCs that possess both CD44+/HCD24− and ALDH-1 activity have been demonstrated to be highly tumorigenic when injected into mice, whereas bulk tumor cells that lack these stem cell markers have lower tumorigenic potential. CSCs are relatively quiescent and undergo replication very slowly and, thus, are defined as label-retaining cells. This characteristic renders CSCs less susceptible to the cytotoxic effects of conventional chemotherapeutic agents, which primarily target actively proliferating cells. CSCs also express cassettes of multidrug transporters responsible for the rapid efflux of lipophilic and chemotherapeutic drugs, which provide additional mechanisms for CSCs to resist effects of cytotoxic therapies used to treat the majority of breast cancers. CSCs have also been shown to activate survival pathways, such as the PI3K/Akt signaling pathway, that mediate resistance to ionizing radiation.

By using the Mary-X model of IBC, tumor spheroids were found to express surface markers CD44+/HCD24−/low, to have ALDH-1 activity and, most uniquely, to express CD133, which is consistent with Mary-X having characteristics of CSCs.

Evidence that IBC tumors may be enriched for CSCs could provide an explanation for the observations that targeting proliferation of IBC tumors has not been successful in terms of increasing the durations of disease-free survival and overall survival of IBC patients. Signaling pathways, transcription factors, and molecules that regulate survival, self-renewal, and multipotency of CSCs, which in some cases overlap with those used by normal stem cells including the Notch, Wnt, and hedgehog signaling pathways, are currently being evaluated for their utility as targets for development of effective therapeutics for IBC.

IBC and the Epithelial-Mesenchymal Transition

Further support for the potential role of CSCs in the aggressive phenotype of IBC comes from observations that CSCs are linked to tumor progression through their ability to undergo the process of epithelial-mesenchymal transition (EMT). This ability is regulated by transcription factors that also orchestrate critical steps of organ development during embryogenesis. The EMT is associated with a change in cancer cells from epithelial morphology to acquisition of mesenchymal morphology with an associated gain of motility. Recent studies demonstrate that breast cancer cells that undergo EMT acquire characteristics of CSCs. There is currently great interest in agents and molecular strategies that reverse the EMT process, which would result in the loss of invasive and metastatic potential. One study demonstrated that the SUM149 IBC cell line, which expresses high levels of EGFR and undergoes EMT, was sensitive to the inhibitory effects of either EGFR small interfering RNA or erlotinib, an inhibitor of the EGFR tyrosine kinase. Targeting EGFR through the ERK1/2 pathway blocked SUM149 invasion in vitro; interestingly, low doses of erlotinib, which had no effect on primary tumor growth, inhibited development of pulmonary metastases. These results suggest that EGFR and the associated ERK signaling pathway may be important targets in the strategy of reversing the process of EMT in IBC.

New Tools to Elucidate the Biology of IBC

New technologies will prove invaluable for unraveling the complexities of the biology of IBC. Next generation sequencing, for example, will provide first-time definition of single nucleotide polymorphisms, deletions/insertions, translocations, and copy-number variations in IBC tumors and cell lines. Coupled with
these studies, global methylation and acetylation studies will lead to a comprehensive characterization of the epigenetic alterations in IBC tumors. The use of proteomics platforms such as reverse-phase protein arrays and mass spectrometry/microsequencing will identify the phosphorylation status of proteins within multiple signaling cascades as well as post-translational modifications, including the glycosylation status of IBC tumors that may provide the first IBC-specific biomarkers. Another very exciting area of opportunity in IBC research is the emerging search for a role for noncoding and microRNAs in metastasis. The link between small RNAs and cancer metastasis has led to the coining of the term “metastamir” as a description of microRNAs that regulate tumor progression. Thus far, there have been no reports of an IBC-specific microRNA or a noncoding RNA signature, but there is little doubt that the microRNA and non-coding RNAs involved in IBC will soon be elucidated, and these, in turn, may provide clues to cancer gene targets that are the molecular drivers for the aggressive phenotype of IBC.

**Multimodality Approach to Treatment of IBC**

Studies and changes in practice over the past 2 decades have led to the consensus that patients with primary IBC should receive systemic chemotherapy (including trastuzumab and hormonal therapy when indicated), followed by surgery and radiation therapy. This current standard for management of primary IBC is based on the evidence detailed below.

**Standard Treatment of Primary IBC**

The standard multimodality approach to treating primary IBC is summarized in Figure 13. Despite limited data on them, each treatment modality has unique aspects that need to be considered when managing IBC.

**Systemic Therapy**

Because of the rarity of the disease, there is insufficient definitive evidence from prospective randomized clinical trials for an optimal chemotherapy for IBC. Historically, IBC has been excluded from most prospective chemotherapy-related randomized trials because of its unique biological outcome and poor prognosis. Several retrospective trials have explored the efficacy of the chemotherapy used to treat non-IBC.

One series covering a 20-year period at M. D. Anderson demonstrated the efficacy of anthracycline-based chemotherapy in IBC. One hundred seventy-eight patients with IBC were treated at M. D. Anderson with anthracycline-containing regimens as induction chemotherapy followed by local treatment with radiation, with or without mastectomy. The overall survival rates were 40% at 5 years and 33% at 10 years. In a cohort study of 68 patients with IBC from 2 prospective randomized trials, treatment with either 3 cycles of CAF (cyclophosphamide, doxorubicin, and 5-fluorouracil) or CEF (cyclophosphamide, epirubicin, and 5-fluorouracil) followed by surgery, adjuvant therapy, and radiation therapy resulted in overall survival rates of 44% at 5 years and 32% at 10 years. These results indicate that anthracycline-containing primary systemic therapy resulted in a survival benefit for patients with IBC.

As is the case in non-IBC, integration of taxanes into combination chemotherapy has shown efficacy in the neoadjuvant treatment of IBC. Initially, among a
series of 44 patients with IBC, investigators from M. D. Anderson noted that 7 of 16 patients who had crossover treatment from anthracycline-based induction chemotherapy to paclitaxel achieved a partial response and were able to undergo mastectomy.  

With this experience, the same investigators compared a cohort of 178 patients with IBC who received CAF alone with 62 patients who received CAF followed by paclitaxel. Patients who received paclitaxel had a higher pathologic complete response rate (25% vs 10%; \(P = .012\)), median overall survival rate, and progression-free survival rate than patients who did not receive paclitaxel. Thus, combination of a taxane with an anthracycline increased the response rate to primary systemic chemotherapy and improved prognosis.

It is important to note that, in these preoperative chemotherapy studies, the response to preoperative chemotherapy was the most important prognostic factor. In evaluating a cohort of 372 patients with LABC (including IBC) who were enrolled in 2 prospective trials, investigators at M. D. Anderson observed significantly better outcomes in the group of patients who achieved a pathologic complete response than in the patients with residual disease (5-year overall survival rates, 89% vs 64%, respectively; 5-year disease-free survival rates, 87% vs 58%, respectively). In a retrospective study with a long-term outcome for 54 patients with IBC, patients who achieved a pathologic complete response had a longer 10-year survival rate than patients with residual disease (45% vs 31%, respectively; \(P = .09\)). In a study of 61 IBC patients with cytologic confirmed axillary lymph node metastases treated with neoadjuvant anthracycline- and taxane-based chemotherapy, patients who had a pathologic complete response in the axillary lymph nodes had better overall survival and disease-free survival rates than patients with residual axillary disease (overall survival rates, 82.5% vs 37.1%, respectively; disease-free survival rates, 78.6% vs 25.4%, respectively). Taken together, these data demonstrate that primary systemic therapy plays an important initial role and that tumor response to that therapy defines the long-term outcome for patients with IBC.

Trastuzumab is a humanized monoclonal antibody targeted against the HER2 protein that has been shown effective in combination with chemotherapy for breast cancer in the neoadjuvant, adjuvant, and metastatic settings. Trastuzumab has been investigated in 5 prospective trials with systemic chemotherapy for LABC, including IBC. In that study of the combination of neoadjuvant docetaxel, cisplatin, and trastuzumab, 48 patients with HER2-positive LABC, including IBC, had a 17% pathologic complete response. Among those who had a pathological response, 4-year progression-free and overall survival rates were 100%. In a second study, 22 patients (9 with IBC) were treated with neoadjuvant docetaxel and trastuzumab, 31 patients with HER2-amplified cancers, including IBC, had clinical and pathological response rates of 94% and 34%, respectively. In a pilot study of the combination of paclitaxel and trastuzumab, 40 patients (6 with IBC) had complete clinical and pathological response rates of 30% and 18%, respectively. The largest series of patients with IBC was reported in the preliminary data from the NOAH (neoadjuvant trastuzumab) phase 3 trials. In 76 patients with HER2-positive IBC, a significantly higher pathologic complete response rate (54.8%) was noted in women who received standard doxorubicin, paclitaxel, and cyclophosphamide chemotherapy with trastuzumab than in women who received standard therapy without trastuzumab (19.3%). These investigations, demonstrating the success of trastuzumab in combined systemic chemotherapy regimens for HER2-positive breast cancer, suggest that trastuzumab may be an essential drug in such regimens for patients with HER2-positive IBC. Further study is warranted in a large cohort of patients with IBC to confirm this efficacy and to find the most effective combination of chemotherapy plus trastuzumab in IBC.

Surgery

Surgery plays an important role in the multimodality treatment of IBC. Historically, mastectomy alone failed to achieve any survival benefit as a primary treatment. In contrast, however, several retrospective studies have shown that surgery improved the local control rate and survival duration for patients whose disease responded well to primary chemotherapy. The optimal surgical procedure for those whose
disease responds to neoadjuvant chemotherapy is mastectomy with axillary lymph node dissection. Data showing poorer prognosis for patients with positive margins than for those with negative margins indicate that surgery should aim for complete resection of residual gross disease with negative surgical margins. Axillary lymph node involvement at the time of presentation is noted in about 55% to 85% of patients with IBC. Lymph node status remains an important prognostic indicator; thus, complete axillary lymph node dissection is the standard of care for IBC patients.

The surgeon must exercise careful judgment in determining which patients will benefit from mastectomy. In one study, patients who had a complete or partial clinical response to primary chemotherapy derived local control and survival benefits from mastectomy (followed by radiation therapy), whereas patients whose disease did not respond to induction chemotherapy derived no such benefits. Patients whose disease does not respond to induction chemotherapy should be considered for radiation therapy and then re-evaluated for operability.

**Radiation Therapy**

As a standard approach, most IBC patients who require radiation therapy have undergone mastectomy after primary chemotherapy. The chest wall and the lymph nodes within the axillary, infraclavicular, supraclavicular, and internal mammary regions are targeted for radiation therapy. For patients with IBC, the most important field is the chest wall, so enough coverage of potential tumor emboli within dermal lymphatics is assured. To achieve broad chest-wall coverage and minimize intrathoracic organ risk, a combination of electron and photon tangent fields or matched electron fields is used.

It is vitally important to have comprehensive pretreatment images, including mammograms, sonograms, medical photographs, and MRI scans, to correlate with postchemotherapy and/or postsurgery CT scans for radiation treatment planning. Areas with pretreatment skin involvement also should be considered for radiation treatment because there is a high risk of local recurrence. Radiation treatment planning, including the design of fields and the choice of dose, should take into account the degree of treatment response and extent of surgical resection. This treatment strategy requires that patients be seen by all multimodality team members before initiation of treatment.

Radiation treatment schedules (once or twice daily) and treatment doses vary among institutions. At M. D. Anderson, a treatment schedule of twice a day and a total dose of up to 66 Gy has been our standard approach to IBC for about 15 years. We have recently identified lower risk IBC subgroups for whom standard dose and fractionation of radiation may be sufficient (see the section on accelerated hyperfractionated radiation therapy). Outside M. D. Anderson, once daily radiation is typical. Although not much comparative information is available about dose, a total dose of 55 Gy to 66 Gy can be used.

**Standard Treatment of Metastatic IBC**

There are currently no standard IBC-specific treatments for patients with advanced disease; therefore, enrollment in available clinical trials, including those of novel targeted therapies, is strongly recommended for IBC patients.

One area of controversy is whether patients with newly diagnosed metastatic IBC should undergo local resection. As standard care, locoregional management of metastatic disease is challenging and plays a limited role. There is some anecdotal evidence that debulking the primary tumor will prolong overall survival. Whether this concept truly applies for IBC is completely unknown. Therefore, we generally recommend that patients with metastatic IBC undergo systemic therapy first and then local therapy (radiation and/or surgery) for palliative purposes. A prospective study is needed to address whether local therapy is indicated in the IBC setting, and its impact on prolongation of disease control.

**Novel Local and Systemic Therapies**

For the 70% of patients with IBC who present with distant metastatic disease during the course of their disease, there is a strong need for novel approaches. Approaches that have been or are currently being evaluated for IBC include targeted systemic therapy and novel approaches to surgery and radiation therapy.

**Targeted Systemic Therapy**

Several potential molecular targets have been identified for the treatment of IBC. It is important to recognize that the novel and unique targets that drive
IBC in a clinical setting have not yet been established. While HER-targeted therapy has been investigated largely on the basis of clinical hypotheses, recent extensive work with experimental models and molecular profiling has identified additional genes and pathways potentially involved in the development of IBC and/or responsible for the rapid progression of this disease.

**Therapy Targeting HER2**

Targeted therapy against HER2—trastuzumab and lapatinib—is one promising strategy for treatment of IBC, and it has been extensively investigated in the clinic. The success of trastuzumab in breast cancer, described in detail already, has led to investigations of lapatinib in breast cancer. Lapatinib is an oral, dual, tyrosine kinase inhibitor against EGFR and HER2. Inflammatory breast cancer is known to overexpress HER2 frequently; furthermore, EGFR expression is associated with poor prognosis. Clinical trials have shown that lapatinib is effective in HER2-positive breast cancer and has efficacy similar to that of trastuzumab in such patients.

The preliminary results from a phase 2 trial of lapatinib and paclitaxel as neoadjuvant therapy in patients with newly diagnosed IBC showed that 95% of HER2-positive cases had a clinical response. In a phase 2 trial of lapatinib monotherapy for heavily treated patients with IBC, the response rate was 50% among the 30 patients with HER2-positive tumors but only 7% among the 15 patients with HER2-negative/EGFR-positive tumors. Currently, the European Organization for Research and Treatment of Cancer (EORTC) is conducting a randomized phase 1/2 trial of doxorubicin and docetaxel with bevacizumab in combination with doxorubicin and cyclophosphamide followed by weekly carboplatin and paclitaxel with bevacizumab for HER2-negative large or inflammatory breast tumors, 3 of 10 patients in the study had a pathologic complete response.

Semaxanib (SU5416), a small-molecule inhibitor of VEGFR-2, was investigated in a phase 1 trial combining doxorubicin and cyclophosphamide and paclitaxel in combination with bevacizumab. Decreased tumor blood flow after treatment was shown on DCE MRI. Unfortunately, 4 (22%) of the 18 patients experienced a significant decrease in cardiac function after completion of treatment. These adverse events precluded further investigation of this combination.

**Therapy Targeting Vasculolymphatic Pathways—Angiogenesis, Lymphangiogenesis, and Vasculogenesis**

Molecular targets in vasculolymphatic processes—angiogenesis, lymphangiogenesis, and vasculogenesis—have shown greater potential in IBC than in non-IBC.

**Angiogenesis.** Angiogenesis, the formation of new vessels from pre-existing vessels, is necessary for tumor growth and metastasis. Bevacizumab, a human monoclonal antibody against VEGF, was evaluated in a pilot trial in combination with neoadjuvant doxorubicin and docetaxel in 21 previously untreated patients with LABC, 20 of whom had IBC. The overall response rate was 67%, and a significant decrease in the level of phosphorylated VEGF receptor-2 (VEGFR-2) in tumor cells was noted after a single cycle of bevacizumab. This result might indicate that anti-VEGF therapy could have not only an antiangiogenic effect but also a direct antitumoral effect through VEGFR-2. In a preliminary report of a phase 2 trial of dose-dense doxorubicin and cyclophosphamide followed by weekly carboplatin and paclitaxel with bevacizumab for HER2-negative large or inflammatory breast tumors, 3 of 10 patients in the study had a pathologic complete response.

**Lymphangiogenesis and vasculogenesis.** Lymphangiogenesis can lead to tumor cell dissemination through lymph vessels. Tumors can induce formation of a new lymph vessel network, a process called tumor-induced lymphangiogenesis, and thereby promote tumor spread. Vasculogenesis is the formation of new vascular channels due to de novo production of endothelial cells by tumor cells. Although lymphangiogenesis and vasculogenesis is one potential mechanism for tumor progression, both mechanisms must be studied further before vasculogenesis can be confirmed as a potentially useful target for treatment of IBC.

**Therapy Targeting Overexpression of RhoC GTPase and Loss of WISP3**

RhoC is an important player in signal transduction as a member of the Ras superfamily and is involved in regulation of the cytoskeleton. Farnesyl...
transferase inhibitor treatment to modulate RhoC expression has been investigated in the preclinical setting. Although further investigation is required in the clinical setting, farnesyl transferase inhibitors may be a potential novel targeted therapy for tumors that overexpress RhoC, including IBC. Just recently, a phase 2 clinical trial of the farnesyl transferase inhibitor tipifarnib combined with doxorubicin and cyclophosphamide for LABC, including IBC, was completed. Results are eagerly awaited.

High-Dose Chemotherapy
Several investigators have tried high-dose chemotherapy (HDCT) with autologous stem cell support to improve response in patients with IBC. Although the use of HDCT for breast cancer remains controversial, recent studies show encouraging results in IBC. Although HDCT has produced some better responses than conventional chemotherapy in patients with IBC, HDCT is associated with more toxicity and poorer quality of life. The definitive benefit of HDCT has not been established yet, and a large clinical trial is warranted to assess its efficacy and safety for patients with IBC. At M. D. Anderson, we are currently conducting a HDCT study in which circulating tumor cells are removed by using a CD34-positive selection process during apheresis.

Surgery
Two approaches to surgery have been evaluated recently for patients with breast cancer, but they are not recommended for patients with IBC.

Sentinel Lymph Node Biopsy
Although sentinel lymph node biopsy (SLNB) has been accepted as the standard of care for evaluating axillary lymph node status in patients with early breast cancer, it is not recommended for patients with IBC. One significant reason is that lymphatic blockage by tumor cells is a feature of IBC, and such blockage could prevent the dye or radioactive isotope used for this procedure from being carried to sentinel lymph nodes. There has also been a concern that SLNB after neoadjuvant therapy would not be reliable for evaluating axillary lymph node involvement.

Skin-Sparing Mastectomy with Immediate Reconstruction
Skin-sparing mastectomy is not recommended for patients with IBC. This disease's high rate of dermal lymphatic invasion can make it difficult to achieve the negative margins that are so important in IBC, as discussed already. Moreover, because postmastectomy radiation therapy is required in patients with IBC, immediate reconstruction is not recommended.

Radiation Therapy

Accelerated Hyperfractionated Radiation Therapy
Accelerated hyperfractionation has been investigated to achieve better local control than standard radiation therapy for this aggressive disease. One reason that tumors develop resistance to standard radiation therapy is the rapid repopulation of IBC tumor cells between radiation doses. To circumvent this rapid cell growth, an accelerated hyperfractionated schedule has been studied.

To evaluate the effect of a higher radiation dose, outcomes for 32 patients treated with twice-daily radiation to a total dose of 60 Gy were compared with outcomes for 39 patients treated twice daily to a total dose of 66 Gy. Significantly better rates of locoregional control were achieved in the high-dose group than in the standard-dose group (84% vs 58% at 5 years, 77% vs 58% at 10 years; \( P = .04 \)). Although data have demonstrated the effectiveness of postmastectomy accelerated hyperfractionated radiotherapy, an updated review of this approach showed that the benefit appeared highest in cases at high risk of recurrence: those that have a poor response to chemotherapy, those with close or positive surgical margins, those involving 4 or more nodes after neoadjuvant chemotherapy, and those in patients younger than age 45 years. In the same analysis, short-term and long-term toxic reactions to this treatment were examined. Although the degree of acute skin reaction is thought to correlate with local disease control, such reactions were significant and sometimes required analgesics. A higher risk of developing grade 3 to 4 late complications was observed in the high-dose group than in the standard-dose group (29% vs 15%, respectively; \( P = .08 \)). As such, this approach is reserved for patients with features suggesting high risk of recurrence.

Preoperative Radiation Therapy
In other malignancies, radiation therapy has been investigated as a preoperative modality. Although this strategy has not been thoroughly explored in breast cancer, there may be a benefit in the aggressive IBC. In an M. D. Anderson review of preoperative
radiation treatment in 42 patients with IBC, the 5-year local control and distant metastasis-free survival rates were 75% and 20%, respectively, and 8 patients survived without distant metastasis for more than 40 months (unpublished data). However, higher complication rates have been reported in patients who received preoperative radiation than in those who did not. One study reported wound necrosis in 6 (21%) of 29 patients with IBC who received preoperative radiation at a dose between 44.2 and 50.4 Gy.\textsuperscript{165} With these results in mind, until the safety and efficacy of preoperative radiation therapy have been demonstrated, surgical candidates should undergo surgery before radiation therapy.

Concurrent preoperative chemoradiation has not been used as effectively in breast cancer as in other cancers. At M. D. Anderson, concurrent capecitabine and radiation therapy resulted in 91% of “inoperable” breast cancers becoming operable. The clinically complete response and overall response rates were 33% and 22%, respectively.

### Summary

Inflammatory breast cancer has proven to be distinct from LABC and is managed as such. Clinical presentation of IBC consists of acute onset of diffuse erythema, edema, breast induration, and pain. Although dermal lymphatic invasion is a pathological hallmark of IBC, it is not required for diagnosis.

Epidemiological observations have suggested geographic differences in the incidence of IBC but have not resulted in identification of risk factors. An ongoing international prospective registry is being conducted at The University of Texas M. D. Anderson Cancer Center that will further elucidate the etiology and risk factors for IBC.

The descriptions of advanced imaging approaches and modalities herein are not exhaustive and are not necessarily specific to IBC, but they are based on our current experience and represent some promising areas for improving the characterization and multidisciplinary management of this complex disease.

The ability to identify new therapeutic targets that regulate the aggressive phenotype of IBC will be crucial. There are currently new classes of agents that display novel mechanisms of action, and early experiments suggest that these drugs may be effective in IBC. Emerging concepts in the areas of stem cell biology and cancer biology may revolutionize our understanding of the molecular basis of IBC while providing opportunities to discover new molecular targets and useful diagnostic biomarkers for IBC.

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