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Breast Cancer

Inflammatory Breast Cancer: What We Know and What We Need to Learn

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ABSTRACT

Purpose. **We review the current status of multidisciplinary care for patients with inflammatory breast cancer (IBC) and discuss what further research is needed to advance the care of patients with this disease.**

Design. **We performed a comprehensive review of the English-language literature on IBC through computerized literature searches.**

Results. **Significant advances in imaging, including digital mammography, high-resolution ultrasonography with Doppler capabilities, magnetic resonance imaging, and positron emission tomography–computed tomography, have improved the diagnosis and staging of IBC. There are currently no established molecular criteria for distinguishing IBC from noninflammatory breast cancer. Such criteria would be helpful for the diagnosis and development of novel targeted therapies. Combinations of neoadjuvant systemic chemotherapy, surgery, and radiation therapy have led to an improved prognosis; however, the overall 5-year survival rate for patients with IBC remains very low (~30%). Sentinel lymph node biopsy and skin-sparing mastectomy are not recommended for patients with IBC.**

Conclusion. **Optimal management of IBC requires close coordination among medical, surgical, and radiation oncologists, as well as radiologists and pathologists. There is a need to identify molecular changes that define the pathogenesis of IBC to enable eradication of IBC with the use of IBC-specific targeted therapies.** ***The Oncologist*** 2012;17:891–899

INTRODUCTION

Inflammatory breast cancer (IBC) is a very aggressive type of locally advanced breast cancer with a poor prognosis. Patients present with rapid onset of erythema and edema of the breast skin (i.e., peau d'orange) [1]. In the U.S., IBC is a very rare disease, with a frequency in the range of 1%–6% [1]. The first description of IBC in the scientific literature was published in 1814 by Sir Charles Bell [2]. In 1938, the terms "primary IBC" and "true IBC" were established to distinguish what is now considered to be IBC from "secondary IBC," which was defined as secondary changes in the breast resulting from noninflammatory locally advanced breast cancer or breast cancer recurrence [2]. In current clinical practice, we routinely distinguish the skin changes of IBC (T4d) from the skin changes as-

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sociated with a neglected noninflammatory breast tumor (T4a–c). Therefore, "secondary IBC" is currently defined as a recurrence associated with clinical features such as erythema, edema, or skin changes in the breast of a patient with a previous history of noninflammatory breast cancer (non-IBC).

Historically, single-modality treatment to cure IBC was not successful; >90% of patients developed recurrent and/or metastatic disease within 2 years, and the 5-year survival rate was <5%. Combinations of neoadjuvant systemic chemotherapy, surgery, and radiation therapy have led to an improved prognosis. However, the overall 5-year survival rate for patients with IBC is still very low, at ~30% [3]. A molecular definition of IBC has not yet been developed, which has limited the identification of molecular targets for treatment of this disease. Optimal management of IBC requires close coordination among medical, surgical, and radiation oncologists, as well as radiologists and pathologists. In this article, we review the current status of combined-modality management of IBC and discuss what further research is needed to advance the care of patients with this disease (Table 1).

We performed a review of the English-language literature on IBC over the past 30 years. Articles for review were identified through computerized literature searches of MEDLINE. Unpublished observations of results of ongoing research projects by investigators who specialize in IBC are also presented as appropriate.

What Are the Diagnostic Criteria for IBC?

Currently, there are no definitive molecular or pathological diagnostic criteria for IBC. Therefore, the diagnosis is based on clinical findings: rapid onset of symptoms and signs, erythema and edema of the skin of the breast (peau d'orange), and ridging. The absence of definitive diagnostic criteria and the rarity of this disease make delayed diagnosis a common, costly mistake (Fig. 1).

In 1956, the first diagnostic criteria for IBC were established by Haagensen on the basis of clinical findings [4]. One of the important clinical characteristics of IBC is lymphatic blockage caused by tumor emboli. Because one series indicated that patients with dermal lymphatic involvement had a poor prognosis, dermal lymphatic involvement was considered a definitive diagnostic criterion for IBC [5]. However, proving dermal lymphatic involvement requires a skin punch biopsy, which is not commonly performed. Further, sampling error may lead to a missed diagnosis of dermal lymphatic involvement. Reports indicate that dermal lymphatic involvement is confirmed in <75% of IBC cases, even with a comprehensive examination for such involvement [6]. Currently, dermal lymphatic involvement is not required for the diagnosis of IBC.

Clinical Criteria

Current consensus is that clinical criteria are important for the diagnosis of IBC [7]. Signs and symptoms required for a diagnosis of IBC include erythema occupying at least one third of the breast, edema and/or peau d'orange of the breast, and/or a warm breast, with or without an underlying palpable mass. The onset of these signs and symptoms should be rapid; the duration of signs and symptoms at initial presentation should be ≤3 months.

Because of its clinical signs and symptoms, sometimes IBC is misdiagnosed as a bacterial infection. It also may be misdiagnosed as mastitis, abscess of the breast, metastasis from another cancer, postradiation dermatitis, or even breast edema from congestive heart failure. Presumptive diagnosis of cellulitis or mastitis and treatment with a trial of antibiotic therapy is the leading cause of delay in diagnosis and treatment of IBC and can be deadly. IBC is not an infectious process, and it does not cause fever and leukocytosis.

Some reports indicate that the incidence of IBC is much higher in North Africa and the Middle East than in Europe and North America [8]. Differences in diagnostic criteria may be responsible for at least some of this apparent difference in incidence. The shorter overall life expectancy in North Africa than in Europe and North America results in a higher proportion of breast cancer occurring in younger women. Therefore, a higher proportion of aggressive breast cancers may result because of the more aggressive biological characteristics of breast cancers occurring in young women.

Pathological Criteria

IBC is not considered to be a specific histological subtype of breast carcinoma, and there are no special pathological diagnostic criteria for IBC. However, the combination of pertinent histopathological findings in the breast and the overlying skin in conjunction with characteristic clinical findings can be used to suggest a diagnosis of IBC. Patients with IBC most often have ductal tumors with high histological grades; there may or may not be a distinct mass.

The most striking histopathologic finding in patients with IBC is the presence of many lymphovascular tumor emboli in the papillary and reticular dermis overlying the breast. Although skin emboli are sometimes noted in the skin of patients with non-IBC, emboli in patients with non-IBC are usually less numerous and smaller than the skin emboli in patients with IBC. There is no direct correlation between the presence, number, or size of emboli and the degree of skin redness in patients with IBC.

Although pathological evidence of dermal lymphatic involvement is not considered a definitive diagnostic criterion for IBC, a skin punch biopsy is recommended in cases of suspected IBC as an aid to diagnosis. To avoid sampling errors, the area of the affected breast with the most significant skin changes can be targeted, and a 6-mm punch can be used. However, as previously noted, even with adequate sampling and pathological evaluation of the skin with punch biopsies, dermal lymphovascular involvement is noted in <75% of patients with IBC [9]. Therefore, the absence of dermal emboli does not rule out a diagnosis of IBC.

Molecular Criteria

There are no established molecular criteria for distinguishing IBC from non-IBC. Several studies have suggested IBC-specific molecular signatures [10–14]. However, because of small

Table 1. Inflammatory breast cancer research: the known and the questions

	What is known	Questions that need to be answered
Diagnosis		
Clinical criteria	IBC diagnosis is based on clinical criteria, including rapid onset of inflamed skin, peau d'orange, edema, or a warm breast with or without an underlying palpable mass.	Does the duration of clinical signs and symptoms at the time of diagnosis have to be ≤3 months?
		Does erythema have to involve more than one third of the breast?
Pathological criteria	Invasive breast cancer should be confirmed pathologically.	Is dermal lymphatic involvement a requirement for the diagnosis of IBC?
	Skin punch biopsy is recommended.	
Molecular criteria	Molecular subtypes of IBC are similar to molecular subtypes of non-IBC.	Can we identify molecular criteria for a definitive diagnosis of IBC?
Imaging		
Overall	There are no radiological findings that definitively indicate IBC.	Can we identify radiological findings specific to IBC by exploring molecular imaging?
	CT or bone scan is required for systemic staging.	
Mammography	Mammography is currently the imaging modality of choice for patients with suspected IBC.	
	Skin thickening and trabecular distortion may be subtle early findings in IBC.	
Ultrasonography	Ultrasonography is useful for guiding biopsy of a primary breast lesion and evaluation of axillary lymph nodes.	
MRI	MRI may be useful when a breast parenchyma lesion is not identified on mammography and ultrasonography.	Does functional MRI have a role in monitoring response of IBC to neoadjuvant chemotherapy?
PET–CT		What is the appropriate role of PET–CT in systemic staging of patients with IBC?
Treatment		
Chemotherapy	Neoadjuvant chemotherapy including anthracyclines or taxanes is standard.	What is the role of nonanthracycline-based or nontaxane-based chemotherapy?
Targeted therapy	Anti–HER-2 therapy should be used for HER-2^+ IBC.	Can we establish an IBC-specific targeted therapy?
	Hormonal agents should be used for estrogen receptor–positive IBC.	
Surgery	Modified radical mastectomy is recommended.	What is the role of sentinel lymph node biopsy? Is immediate reconstruction appropriate?
Radiation therapy	Postmastectomy radiation therapy should be given.	Which patients should undergo accelerated hyperfractionated radiation therapy?
		Does preoperative radiation therapy have a role?
		Can concurrent chemoradiation improve outcomes?
Treatment of metastatic disease	Treatment of metastatic IBC is currently the same as treatment of metastatic non-IBC.	Does metastatic IBC differ biologically from metastatic non-IBC?
	Clinical trials should be considered, including phase I trials if appropriate.	Can we establish a targeted therapy or immunotherapy for metastatic IBC?

Abbreviations: HER-2, human epidermal growth factor receptor 2; IBC, inflammatory breast cancer; MRI, magnetic resonance maging; PET–CT, positron emission tomography–computed tomography.

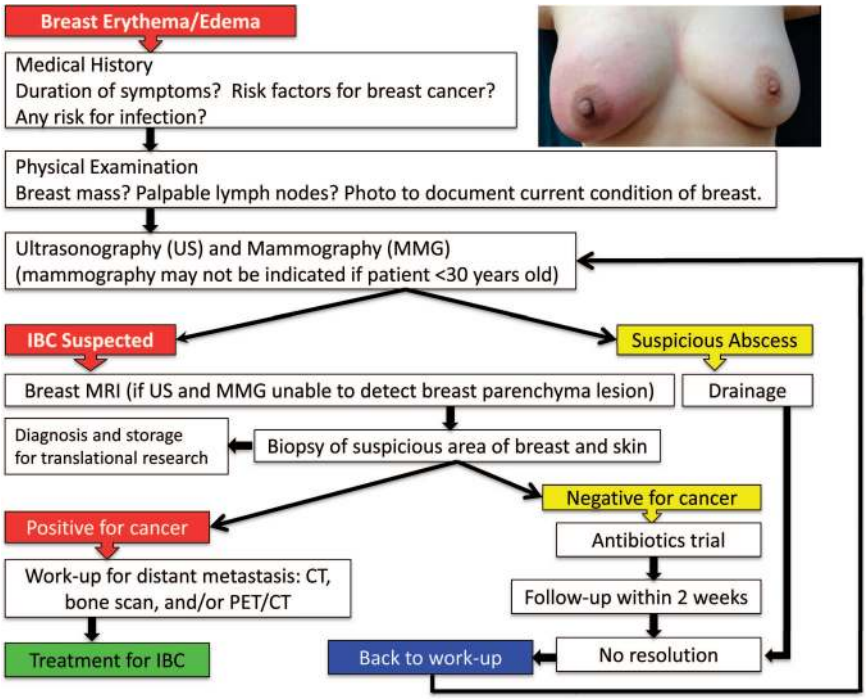

Figure 1. Workup for inflammatory breast cancer.

sample sizes and the molecular heterogeneity of IBC, none of these findings can be considered conclusive [15]. An effort is underway to combine microarray data to define the molecular characteristics of IBC. Other studies revealed that the frequency of hormone receptor positivity is lower in IBC than in non-IBC, that patients with estrogen receptor–negative IBC have a poorer prognosis than patients with estrogen receptor–positive IBC [1, 16], and that the molecular subtypes of IBC are similar to those of non-IBC [17]. These molecular subtypes may have important clinical and molecular differences. Thus, future studies involving IBC should consider the various molecular and clinical subtypes separately [18].

There is a need for more detailed molecular dissection of IBC through microdissection and comparing the genome in tumor versus nontumor areas, tumor emboli versus the dominant tumor mass, and skin versus the primary tumor. Microarray investigations of skin lesions may produce more significant results than histological examinations. Because breast skin changes are one of the most prominent clinical features of IBC, investigations focused on skin lesions seem worthwhile. Furthermore, because IBC cells (like stem cells) are very aggressive, there should be more investigation of whether or not IBC cells have stem cell characteristics [19, 20].

How Should We Use Imaging for IBC?

The challenge in imaging women with suspected or confirmed IBC is to identify a primary breast tumor to facilitate image-guided biopsy so that the receptor and biomarker status can be established and appropriate neoadjuvant chemotherapy can be initiated. It is well established that 20%–30% of women with newly diagnosed IBC have distant metastasis at the time of diagnosis; imaging may also be useful in identifying such distant metastases [21]. Another use of imaging in women with IBC is to evaluate the response to therapy [7].

Significant advances in imaging techniques, including digital mammography, high-resolution ultrasonography with Doppler capabilities, magnetic resonance imaging (MRI), and positron emission tomography–computed tomography (PET–CT), have improved the diagnosis and staging of IBC. CT and whole-body scintigraphy play a role in the staging of IBC, as they do in the staging of non-IBC.

Mammography

As in other types of breast cancer, mammography in women with IBC may reveal a mass, architectural distortion, or calcifications. Skin thickening and trabecular distortion are seen in 80% of patients with IBC; these findings may suggest the diagnosis of IBC but are nonspecific [22, 23]. In women with IBC, the rate of identification of a primary tumor on mammography is very low. A retrospective review in patients with confirmed IBC demonstrated that a primary tumor was found in only 15% of cases; the most common radiologic sign was trabecular distortion [23]. The better contrast resolution of digital mammography allows visualization of skin thickening, trabecular and stromal thickening, and diffuse increased breast density—findings that are frequently associated with IBC [22, 23]. A focal mass lesion or a group of suspicious calcifications is less common in IBC than in non-IBC [23]. Therefore, it is recommended that women with suspected IBC undergo bilateral mammography, which will provide screening of the contralateral breast.

Breast Ultrasonography

Ultrasonography is useful for identifying suspicious areas to be biopsied to confirm the diagnosis of breast cancer. In women with suspected or confirmed IBC, high-resolution ultrasonography identifies a focal breast abnormality (mass or architectural distortion) in >90% of cases and can be used to facilitate image-guided biopsy to confirm the diagnosis of breast cancer or gather additional information about the tumor. Ultrasonography can also provide valuable information about the regional lymph nodes, including the nodes in the axillary, supraclavicular, infraclavicular, and internal mammary nodal basins. It is especially important to identify involved regional lymph nodes before systemic chemotherapy so that postmastectomy radiation therapy can be planned to adequately target unresected involved nodal basins [23].

MRI

MRI is an emerging imaging technique that has high sensitivity in the detection of primary breast parenchymal lesions and global skin abnormalities. Findings on MRI may help guide skin punch biopsies for a high diagnostic yield in cancer. On MRI, skin thickening and enhancement are seen in 90%–100% of patients with IBC; thus, MRI may be a useful tool for differentiating patients with IBC from patients with locally advanced non-IBC. In a study from the University of Texas MD Anderson Cancer Center of patients with IBC, breast MRI identified all breast parenchymal lesions, mammography identified 80% of breast parenchymal lesions, and ultrasonography identified 95% of breast parenchymal lesions [23].

On MRI, IBC appears as multiple masses with irregular margins and heterogeneous internal enhancement, breast edema (high T2-weighted signal throughout the affected breast), ipsilateral breast enlargement, and asymmetric breast enhancement. Because of its high sensitivity, MRI may be recommended in patients with suspected IBC when mammography and ultrasonography reveal no breast parenchymal lesion. MRI, especially functional MRI (i.e., magnetic resonance spectroscopy), may be a valuable method for monitoring the response of IBC to chemotherapy. A technique that is useful for patients with IBC is diffusion-weighted MRI. Diffusion-weighted MRI is an in vivo imaging technique that may enhance the diagnosis of breast cancers without the need for contrast material administration through exploitation of the microstructural properties of tissues related to water diffusion. Diffusion has been shown to decrease in highly cellular tissue including malignant tumors and is quantified by the apparent diffusion coefficient. Breast cancers show low apparent diffusion coefficient values compared with normal breast tissue, although there is some overlap between benign and malignant lesions [24, 25]. Further investigation is required of this role of MRI for IBC.

PET–CT

Although its use is controversial, PET–CT is routinely used for patients with IBC because early detection of distant metastasis may facilitate control of metastatic disease. In addition, detection of advanced regional nodal disease as well as contralateral regional involvement is relatively common in IBC, and prechemotherapy cross-sectional imaging of the neck is of great value in radiation planning if comprehensive radiation therapy is ultimately appropriate.

Regarding PET–CT imaging of the primary tumor itself, one retrospective study evaluated PET for 41 patients with IBC [26]. Diffuse hypermetabolic skin thickening and hypermetabolic breast uptake were observed with axillary lymph node involvement. In that study, seven patients (17%) not known to have metastases at initial staging had distant metastasis diagnosed at staging PET–CT [26].

Not surprisingly, a recent study suggested that superior long-term outcomes of patients with IBC screened with PET–CT could be a result of a stage migration effect [27]. Stage migration is to be expected with the addition of any staging procedure that increases the detection of advanced disease and can have a dramatic effect on outcome reporting in any disease if not considered. In many cancer sites, PET–CT response has been incorporated into treatment and prognosis algorithms. However, of 32 patients with IBC and fluorodeoxyglucose-avid axillary nodes who achieved a PET complete response after neoadjuvant chemotherapy, only 26% also achieved a pathological complete response (W.A. Woodward, T.A. Buchholz, unpublished observations). There is a need for additional investigation to determine the role of PET–CT for monitoring the early response to neoadjuvant systemic therapy.

What Is the Optimal Treatment for IBC?

Historical results support multimodal treatment of IBC. Before the era of chemotherapy, IBC was treated with surgery and/or radiation therapy, and <5% of patients survived >5 years [28]. In the 1950s, a study of 29 patients with IBC treated with radical mastectomy reported a mean survival time of only 19 months; none of the patients survived 5 years [29]. In a study from the Joint Center for Radiation Therapy, treatment of IBC with definitive radiation therapy produced 5-year relapse-free and overall survival rates of only 17% and 28%, respectively [30]. The combination of surgery followed by radiation therapy resulted in better locoregional control than with surgery alone or radiation therapy alone, but it had no impact on survival outcomes.

In the 1970s, neoadjuvant doxorubicin-based chemotherapy was integrated into the treatment of IBC. Prospective trials proved the efficacy of neoadjuvant chemotherapy followed by surgery and radiation therapy [31–34]. Subsequently, neoadjuvant taxane-containing regimens were investigated in the treatment of IBC, and results showed that taxanes combined with anthracyclines led to a better response [35, 36].

Today, the general consensus is that patients with IBC without evidence of distant metastases at the time of diagnosis should receive systemic chemotherapy followed by surgery followed by radiation therapy. For patients with human epidermal growth factor receptor (HER)2^+ disease, trastuzumab (an antibody targeting HER-2) is indicated; this option is discussed in more detail in the Targeted Therapy section. For patients with hormone receptor–positive disease, hormonal therapy is indicated.

Chemotherapy

A report on a 20-year experience at MD Anderson showed that anthracycline-based chemotherapy in patients with IBC resulted in overall survival rates of 40% at 5 years and 33% at 10 years [31]. In addition, several retrospective studies have explored the efficacy of anthracycline-based chemotherapy regimens typically used to treat non-IBC [31–34]. One cohort study of 68 patients with IBC treated with three cycles of either cyclophosphamide, doxorubicin, and 5-fluorouracil or cyclophosphamide, epirubicin, and 5-fluorouracil followed by surgery, adjuvant therapy, and radiation therapy in two prospective randomized trials showed overall survival rates of 44% at 5 years and 32% at 10 years [37].

An initial report from investigators at MD Anderson showed that taxane-based combination chemotherapy was as effective as neoadjuvant treatment for IBC [35]. In a cohort of 178 patients with IBC, the same investigators demonstrated a benefit from the addition of paclitaxel to fluorouracil, doxorubicin, and cyclophosphamide [36]. The benefit was more pronounced in patients with estrogen receptor–negative IBC. Currently, the sequence of taxane-based chemotherapy followed by anthracycline-based chemotherapy is the cornerstone of primary systemic therapy for IBC at MD Anderson.

Targeted Therapy

Several molecular candidates for targeted therapy for IBC have been investigated; so far, therapies targeted to HER-2 and epidermal growth factor receptor (EGFR) have proven to be clinically beneficial.

HER-2 is overexpressed or amplified in 36%–60% of cases of IBC [38–40]. Trastuzumab in combination with systemic chemotherapy for locally advanced breast cancer, including IBC, has been investigated in several prospective trials [41–45]. The results of these trials suggested that combinations of trastuzumab and systemic chemotherapy have a role in the treatment of IBC.

Lapatinib is an oral dual tyrosine kinase inhibitor of EGFR and HER-2. Clinical trials showed that lapatinib has efficacy similar to that of trastuzumab in patients with HER-2^+ breast cancer. Lapatinib is used for the treatment of IBC, which has a rate of HER-2 positivity higher than that of non-IBC [40]. Preliminary results from a phase II trial of lapatinib and paclitaxel as neoadjuvant therapy in patients with newly diagnosed IBC showed that 95% of the HER-2^+ patients had a clinical response [46]. Currently, the European Organization for Research and Treatment of Cancer is conducting a randomized phase I/II trial of lapatinib and docetaxel as neoadjuvant therapy in patients with HER-2^+ locally advanced breast cancer, IBC, or resectable breast cancer [47]. At MD Anderson, a phase II study of neoadjuvant lapatinib plus systemic chemotherapy (sequential 5-fluorouracil, epirubicin, and cyclophosphamide and paclitaxel) in patients with HER-2^+ IBC is in progress [48]. Further, the combination of a histone deacetylase inhibitor and an aromatase inhibitor plus a tyrosine kinase inhibitor of insulin-like growth factor is currently being tested.

Molecular targets in vasculolymphatic processes—angiogenesis, lymphangiogenesis, and vasculogenesis—have shown greater potential for IBC than for non-IBC [49]. High expression of angiogenic factors has been observed in IBC, and antiangiogenesis therapies (bevacizumab and semaxanib) have shown some clinical effect in clinical trials [50, 51]. Lymphangiogenesis may play an important role in the early spread of disease to lymph nodes in patients with IBC. Vasculogenesis might be related to hematogenous metastasis in IBC and has been extensively investigated in a human IBC mouse xenograft model.

Comparison of gene expression between human IBC and stage-matched non-IBC tumor samples revealed overexpression of RhoC and loss of WISP3 in IBC [52]. RhoC is a member of the Ras superfamily and is involved in cytoskeleton regulation [53]. The use of farnesyltransferase inhibitors to modulate RhoC expression has been investigated in preclinical studies and has potential as a novel targeted therapy for tumors that overexpress RhoC, including IBC [54, 55]. Neoadjuvant chemotherapy with the farnesyltransferase inhibitor tipifarnib in combination with doxorubicin and cyclophosphamide was tested in a phase II trial and was associated with a 25% rate of pathological complete response accompanied by decreasing farnesyltransferase enzyme activity [56].

E-cadherin expression has been observed to be high in IBC. Generally, E-cadherin expression decreases when cancer progresses, and loss of E-cadherin expression is related to epithelial–mesenchymal transition [57–61]. This unique pattern of E-cadherin expression in IBC could make E-cadherin a target for treatment of IBC, and this strategy has been investigated in IBC xenografts [58]. *EIF4G1*, recently discovered to be the target gene of eukaryotic translation initiation factor 4γ, may be related to the role of E-cadherin in IBC [62]. Overexpression of this gene was observed more frequently in IBC tumors (80%) than in normal cells and non-IBC cells.

Surgery

Surgery plays an important role in the multimodal treatment of IBC. Historically, mastectomy as the sole treatment failed to produce any survival benefit in patients with IBC; 5-year survival rates after surgery alone were 0%–10% [63]. In contrast, several retrospective studies have shown that surgery results in higher local control rates and better survival outcomes for patients who respond well to neoadjuvant chemotherapy [64]. The optimal surgical procedure for patients who respond to neoadjuvant chemotherapy is mastectomy with axillary lymph node dissection. The goal of surgery should be complete resection of residual gross disease with negative surgical margins; a better prognosis has been reported for patients with negative margins [65, 66]. The most appropriate candidates for surgery are patients for whom negative margins are anticipated.

Axillary lymph node involvement is noted in 55%–85% of patients with IBC at the time of presentation [21]. Axillary lymph node status is a predictor of survival outcome; therefore, complete axillary lymph node dissection is standard of care for IBC patients. Although sentinel lymph node biopsy (SLNB) has been accepted as the standard of care to evaluate axillary lymph node status in patients with early breast cancer, SLNB is not recommended for patients with IBC because of lymphatic

blockage by tumor cells and the unreliability of the SLNB procedure after neoadjuvant therapy. In one study, eight patients with IBC underwent SLNB after neoadjuvant chemotherapy. The rate of identification of SLNs was 70% and the false-negative rate was 40% [67]. This unacceptably high false-negative rate demonstrates the unreliability of SLNB in IBC.

Skin-sparing mastectomy is not recommended for patients with IBC. This disease has a high rate of dermal lymphatic involvement, which could prevent achievement of negative margins.

Whether or not immediate reconstruction should be encouraged for patients with advanced breast cancer, including IBC, remains controversial [68]. The cosmetic outcomes of patients who undergo chest wall irradiation after breast reconstruction are poor, even with recent technical developments. One series reported that there was no delay in diagnosis in six patients who developed local recurrence among 10 patients with IBC who underwent delayed breast reconstruction with myocutaneous flaps, suggesting that delayed reconstruction is not absolutely contraindicated in IBC patients [69].

Radiation Therapy

When mastectomy is feasible after neoadjuvant chemotherapy, the standard approach for patients with IBC is to deliver postmastectomy radiation therapy. Treatment fields are designed to target the chest wall and any undissected draining lymphatics, including the infraclavicular, supraclavicular, and internal mammary lymphatics. Critical objectives include generous coverage of the chest wall to effectively treat any tumor infiltration of the dermal lymphatics, adequate skin dose, and full coverage of all involved regional nodal basins and at-risk nodal regions. Anecdotally, chest wall recurrences in the medial aspect of the scar have been seen when the medial scar coverage has been limited in an effort to avoid the contralateral breast. Generous medial coverage therefore seems prudent, and preoperative communication with the surgeon to optimize scar extent to permit ideal radiation coverage can be helpful. Oligometastatic (M1) regional nodal disease (i.e., mediastinal extension from the internal mammary nodes, bilateral internal mammary lymph node involvement, contralateral lymph node involvement) is not uncommon; when coverage can be achieved with acceptable normal tissue constraints, it is reasonable to use radiation to treat such disease. Several radiation therapy regimens have been shown to result in acceptable local control with either dose escalation or aggressive approaches to maximize skin dose [66, 70].

Technical parameters should be carefully considered and optimized for each patient. Combinations of electron and photon tangent fields or matched electron fields are used to obtain broad chest wall coverage and minimize the risk to intrathoracic organs. Tissue equivalent material is placed over the chest wall during delivery of some or all fractions of radiation to ensure adequate doses to the skin [66, 70].

Comprehensive pretreatment imaging, including cross-sectional imaging through all involved nodal basins, is critical. The pretreatment images should be correlated with postchemotherapy and/or postsurgery radiation-planning CT scans. Prechemotherapy PET–CT scans are extremely useful in patients with infraclavicular, internal mammary, or supraclavicular nodal disease. When these areas are involved, careful dose escalation is required, and prechemotherapy cross-sectional imaging allows dose escalation to be tailored to the nodes involved to limit damage to surrounding normal tissue. The extent of pretreatment skin involvement also is an important consideration for radiation treatment because IBC frequently infiltrates the dermal lymphatics of the breast skin; such involvement is associated with a high risk for local recurrence. Prechemotherapy medical photography and examinations are extremely beneficial for radiation treatment planning; when feasible, prechemotherapy radiation referral is beneficial. Radiation treatment planning, including field design and choice of dose, should be done with consideration for the degree of response to neoadjuvant therapy and extent of surgical resection [71].

Treatment dose varies by institution. Accelerated hyperfractionated radiation therapy may be used to achieve better local control than what has historically been achieved for this aggressive disease if the risks for short-term and long-term toxic effects are judged to be reasonable [70]. Currently, accelerated hyperfractionated radiation therapy should be reserved for patients with significant residual disease after chemotherapy, patients with close or positive surgical margins, and patients aged <45 years [72].

Trials from preoperative radiation therapy showed that complication rates are higher in patients who receive preoperative radiation therapy than in those with no preoperative radiation therapy, and the risk for operative complications is dose dependent [73]. The use of concurrent radiation therapy and capecitabine (825 mg/m^2 twice daily on the days when radiation is received) is currently being investigated at MD Anderson Cancer Center. In the absence of new data, candidates for surgery should undergo surgery before radiation therapy.

Future Directions

Because of the rarity of IBC, it is important for institutions to collaborate by establishing a tumor registry for collecting data and tissue from patients with IBC worldwide and by sharing resources to confront this deadly disease.

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