Original Study

# Inflammatory Breast Cancer Management in the National Comprehensive Cancer Network: The Disease, Recurrence Pattern, and Outcome

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## Abstract

**IBC is a unique entity with aggressive clinical features, predictable recurrence patterns, and poor prognosis. The high rate of recurrence, especially in the CNS, suggests that new strategies for surveillance and follow-up are needed for earlier detection or prevention of brain metastases.**

**Background:** Inflammatory breast cancer (IBC) is an uncommon clinicopathologic entity characterized by rapid progression and aggressive behavior. We used the National Comprehensive Cancer Network (NCCN) Outcomes Database to characterize recurrence patterns and outcomes. **Methods:** Patients with newly diagnosed IBC treated between 1999 and 2009 at 12 NCCN institutions were identified, and baseline characteristics were obtained. Patients had multimodality therapy if they received 2 of 3 treatments: surgery, perioperative (neoadjuvant or adjuvant) chemotherapy, or perioperative radiation. The first site of recurrence/metastatic diagnosis was identified. Overall survival was calculated on the basis of stage at diagnosis and receipt of multimodality therapy. **Results:** We identified 673 patients, of whom 195 (29%) had metastatic disease at presentation. Median follow-up was 29 months. Of patients in stage III, 82% received > 1 treatment modality. Among 203 patients in stage III with recurrence, the most frequent sites of first recurrence were bone (28%), central nervous system (CNS), lung, and liver (all 21%). Human epidermal growth factor receptor 2 positive and triple negative subtypes had higher rates of CNS recurrence ($P = .001$). Median survival was 66 months (95% confidence interval [CI], 54-107) for stage III and 26 months (95% CI, 22-33) for stage IV. Among 82% of patients in stage III receiving multimodality therapy, the median survival was 107 months (95% CI, 71 to not reached). **Conclusions:** This large, retrospective, multi-institutional study confirms the aggressive clinical features, unique recurrence patterns, and adverse prognosis of IBC. The high rate of CNS recurrence among high-risk subtypes, despite the inflammatory nature of the breast cancer, suggests that new strategies are needed for earlier detection or prevention of brain metastases to improve long-term prognosis.

*Clinical Breast Cancer,* Vol. 15, No. 1, 1-7 © 2015 Elsevier Inc. All rights reserved.

**Keywords:** Brain metastases, Inflammatory breast cancer, Metastatic breast cancer, Multimodality therapy, Triple negative breast cancer

## Introduction

Inflammatory breast cancer (IBC) is an uncommon entity that affects approximately 2.0% to 2.5% of women diagnosed with breast cancer.[1,2] The clinical presentation consists of diffuse erythema, rapid enlargement of the breast, skin ridging, and a characteristic peau d'orange appearance of the skin secondary to dermal lymphatic tumor involvement.[3] Compared with patients with non-IBC, these patients often present with a more aggressive clinical course. Population-based data suggest that 25% of patients with IBC have distant disease at diagnosis.[4] Overall survival is also shorter than with non-IBC; single institution series suggest a 5-year and 15-year survival of approximately 40% and 20%, respectively.[4-7]

Given the uncommon presentation and frequent misdiagnosis of IBC, most data regarding clinical outcomes are from small single institution series and describe a predictable pattern of recurrence despite appropriate multidisciplinary treatments. Although larger, population-based studies have been aimed at defining survival and

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Submitted: Feb 10, 2014; Revised: May 7, 2014; Accepted: May 27, 2014; Epub: Jun 23, 2014

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http://dx.doi.org/10.1016/j.clbc.2014.05.005

incidence rates, overall and by race, age, and other factors,[4-7] they lack detailed clinical information, such as symptoms at presentation, baseline clinical-pathologic characteristics, and patterns of relapse. In this study, we used data from the multi-institutional National Comprehensive Cancer Network (NCCN) Breast Cancer Outcomes Database to characterize the presentation, treatment, and outcomes for patients with IBC treated at academic centers across the United States.

## Materials and Methods

### *Data Source*

Since 1997, the NCCN Breast Outcomes Database has prospectively collected diagnoses, treatments, and outcomes data for patients with newly diagnosed localized or metastatic breast cancer who receive care at one of the participating NCCN member institutions. The eligibility criteria and data collection procedures for the database have been described.[8-10] Briefly, patients are eligible to be entered into the database if they receive some or all of their primary oncologic care (surgery, chemotherapy, or hormonal therapy) at an NCCN institution. Patients who receive a second opinion or radiation therapy only are not eligible. Clinical, treatment, and recurrence information are abstracted from medical records by dedicated, trained clinical research associates at each site. Rigorous data quality assurance processes were in place to validate the accuracy of the data used in this study. These included initial and follow-up data management training, online edit checking during web-based data entry, programmed logic checks against the pooled data repository, routine quality assurance reports to the centers for rectification by the data managers, and audits of a random sample of source documents against the submitted data, conducted within the first few months of data collection and repeated annually at each institution.

Twelve participating NCCN institutions contributed data to this analysis: City of Hope Cancer Center (Duarte, CA); Dana-Farber/Brigham and Women's Cancer Center (Boston, MA); Fox Chase Cancer Center (Philadelphia, PA); The University of Texas MD Anderson Cancer Center (Houston, TX); Roswell Park Cancer Institute (Buffalo, NY); The Ohio State University Comprehensive Cancer Center-James Cancer Hospital and Solove Research Institute (Columbus, OH); H. Lee Moffitt Cancer Center and Research Institute at the University of South Florida (Tampa, FL); Duke Cancer Institute at Duke University (Durham, NC); the Robert H. Lurie Comprehensive Cancer Center of Northwestern University (Chicago, IL); Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine (St Louis, MO); the Huntsman Cancer Institute at the University of Utah (Salt Lake City, UT); and Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance (Seattle, WA). The institutional review boards (IRBs) at each institution approved the data collection, transmission, and storage protocols. At centers where the IRB required signed informed consent for data collection, only patients who provided consent were included in the database; elsewhere, the IRB granted a waiver of signed consent.

## Patients

Patients with newly diagnosed IBC treated between 1999 and 2009 were identified at the 12 participating NCCN institutions. The clinical diagnosis of IBC was based on the American Joint Committee on Cancer definition in the 5th and 6th editions and staged as clinical T4d, N0-3, and M0-1. Baseline pathologic characteristics, including histologic type and estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2)/neu status, were available. HER2 status by IHC was added to the NCCN data as a routine element in 1999; HER2 status by fluorescence in situ hybridization (FISH) was added in 2001. Patients were classified as receiving multimodality therapy if they received 2 of the following 3 treatments: surgery (mastectomy), perioperative (neoadjuvant or adjuvant) systemic chemotherapy, or perioperative radiation therapy. In addition to pathologic characteristics, data collected included the demographics, the trigger event leading to diagnosis of IBC, and the site of first recurrence. Vital status and cause of death are collected via medical record, institutional tumor registry, and then verified biennially via the National Death Index for those who are deemed lost to follow-up when they have not visited the NCCN center for 2 or more years consecutively.

### *Definition of Recurrent/Metastatic Disease*

For patients with stage III disease, diagnosis of first site of recurrence was identified on the basis of the first date of diagnosis of recurrent disease. Because patients with metastatic disease may often have additional sites identified on subsequent imaging studies or biopsies, we also included sites detected within 2 weeks of the initial diagnosis of recurrent disease as a first site of recurrence. The NCCN Outcomes Database, as with other tumor registries, classifies patients as having stage IV metastatic disease at presentation if it is detected within 90 days of the breast cancer diagnosis. Therefore, for stage IV disease, we included all sites of disease that occurred within 90 days as being present at diagnosis.

### *Definition of Tumor Subtype*

To determine whether the site of metastatic disease varied according to tumor subtype, we classified patients into 1 of the following 4 distinct groups using their hormone receptor (HR) and HER2/neu status at the time of their initial diagnosis of breast cancer: HR+ if they were ER or PR positive and HER2 negative; HER2 + if they were HER2+ with any ER/PR; triple negative if they were ER negative, PR negative, and HER2 negative; or unknown. ER/PR and HER2 status determination are standard among NCCN institutions and follow American Society of Clinical Oncology/College of American Pathologists recommendations at the time data were obtained. ER/PR and HER2 status are entered into the database according to the classification on the available pathology report (positive vs. negative), so percent positivity and FISH ratio were not available. Tumor grade and Ki-67 are not collected if patients present with stage III disease or at the time of recurrence; they are collected only when patients present with de novo metastatic disease. Given the lack of consistent availability of grade and Ki-67 for the entire cohort, they were not used in the analysis.

### *Analysis*

Descriptive statistics were obtained for both patient demographic and tumor characteristic variables, as well as for distribution of first

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