HHS Public Access

Author manuscript

Clin Breast Cancer. Author manuscript; available in PMC 2016 February 01.

Published in final edited form as:

Clin Breast Cancer. 2015 February ; 15(1): 1–7. doi:10.1016/j.clbc.2014.05.005.

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

Jennifer M. Matro, MD[1], **Tianyu Li, MS**[1], **Massimo Cristofanilli, MD**[2], **Melissa E. Hughes, MSc**[3], **Rebecca A. Ottesen, MS**[4], **Jane C. Weeks, MD MSc**[3], and **Yu-Ning Wong, MD MSCE**[1]

[1]Fox Chase Cancer Center, Philadelphia, PA

[2]Thomas Jefferson University Hospital, Philadelphia, PA

[3]Dana Farber Cancer Institute, Boston, MA

[4]City of Hope Cancer Center, Duarte, CA

Abstract

Background—Inflammatory breast cancer (IBC) is an uncommon clinicopathologic entity characterized by rapid progression and aggressive behavior. We used the 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 obtained. Patients had multimodality therapy if they received two of three treatments: surgery, perioperative (neoadjuvant or adjuvant) chemotherapy, or perioperative radiation. First site of recurrence/metastatic diagnosis was identified. Overall survival was calculated based on stage at diagnosis and receipt of multimodality therapy.

Results—We identified 673 patients, of which 195 (29%) had metastatic disease at presentation. Median follow-up was 29 months. Of stage III patients, 82% received >1 treatment modality. Among 203 stage III patients who recurred, the most frequent sites of first recurrence were bone (28%), central nervous system (CNS), lung, and liver (all 21%). HER2 positive and triple negative subtypes had higher rates of CNS recurrence (p=0.001). Median survival was 66 months (95% CI 54-107) for stage III and 26 months (95% CI 22-33) for stage IV. Among 82% of stage III patients receiving multimodality therapy, median survival was 107 months (95% CI 71-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.

Corresponding Author: Jennifer Matro MD Fox Chase Cancer Center 333 Cottman Ave Philadelphia, PA 19111 Telephone: 215 728 3545 Fax: 215 728 3639 Jennifer.matro@fccc.edu.

D*isclosures*: All authors declare they have no conflict of interest.

Keywords

Inflammatory breast cancer; metastatic breast cancer; brain metastases; triple negative breast cancer; multimodality therapy

Inflammatory breast cancer (IBC) is an uncommon entity that affects about 2.0-2.5% 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 to non-IBC patients, these patients often present with a much more aggressive clinical course. Population-based data suggest that 25% of IBC patients 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 its uncommon presentation and the frequent misdiagnosis, most data regarding clinical outcomes are from small single institution series and describe a predictable pattern of recurrence in spite of appropriate multidisciplinary treatments. Although larger, population-based studies have been aimed at defining survival as well as 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.

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 previously[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 is 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 (IRB) 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 AJCC definition in the 5th and 6th editions and staged as clinical T4d, N0-3, M0-1. Baseline pathological characteristics, including histological type and estrogen receptor (ER), progesterone receptor (PR), and 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 two of the following three treatments: surgery (mastectomy), perioperative (neoadjuvant or adjuvant) systemic chemotherapy, or perioperative radiation therapy. In addition to pathological characteristics, data collected included demographics, the trigger event leading to diagnosis of IBC, and site of first recurrence. Vital status and cause of death are collected via medical record, institutional tumor registry, and then verified biennially via 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 based on the first date of diagnosis of recurrent disease. Since patients with metastatic disease may often have additional sites identified on subsequent imaging studies or biopsies, we also included sites detected within two weeks of the initial diagnosis of recurrent disease as a first site of recurrence. 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 if the site of metastatic disease varied based on tumor subtype, we classified patients into one of the following four distinct groups using their hormone receptor (HR) and HER2/neu status at time of their initial diagnosis of breast cancer: HR+ if they were either 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 (ASCO)/College of American Pathologists (CAP) recommendations at the time data was obtained. ER/PR and HER2 status are entered into the database according to the classification on the available pathology report (positive v. negative), so percent positivity or FISH ratio were not available. Tumor grade and Ki-67 is 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 site of recurrence or metastatic disease. Overall survival was defined as time from diagnosis to the date of last follow up or death. Kaplan-Meier estimation method was used to calculate both median survival and actuarial overall survival rates. Chi squared tests were used to determine if sites of metastatic disease varied based on tumor marker status. SAS 9.2 (Cary, NC) was used for analyses.

RESULTS

We identified 673 patients with newly diagnosed IBC who were treated between 1999 and 2009 at one of 12 participating NCCN institutions. The demographics and tumor characteristics of the 673 patients are shown in **Table 1**. The overall median follow-up time was 29 months. The median follow-up for patients who were censored was 39.8 months. The median age at presentation was 53 years (range 22-91 years). Caucasians comprised 79% of the cohort, African Americans 10%, and Hispanics 8%. Additionally, 41% of patients were post-menopausal at the time of diagnosis.

In a majority of cases, the trigger event leading to the diagnosis of IBC was a self-discovered breast lump (34%) or breast pain or discomfort (19%) **(Table 1)**. Only 7% presented with an abnormal screening mammogram. Most patients presented with clinical stage IIIB disease (57%) and positive lymph nodes (81% with clinical N1-N3). Stage IV disease was present in 195 patients (29%) at the time of diagnosis. Invasive ductal type comprised 84% of histologies. Biomarker assessment revealed estrogen receptor positivity (ER+) in 298 patients (44%), progesterone receptor positivity (PR+) in 229 patients (34%), and HER2 positivity in 213 patients (32%). There were 175 patients (26%) who were triple negative; the percentages of tumor subtype did not differ significantly among patients who presented with stage III disease versus stage IV disease (p=0.32). However, patients with triple negative disease were more likely to develop metastatic disease than the other tumor types (56% versus 40% among HER2+ and 33% among HR+; p=0.0074; data not shown). Lymphovascular invasion was documented in 53% of IBC patients.

Of the stage III patients, 76% received perioperative radiation, 82% received perioperative systemic chemotherapy and 71% underwent surgery. There were 82% who received at least one modality and 64% received all three modalities **(Table 1)**. Of the 203 patients with

HER2 positive disease, 161 (76%) received trastuzumab. 50 (79%) stage IV patients and 111 (74%) stage III patients received trastuzumab, the majority (86%) in the neoadjuvant setting (data not shown).

Sites of Metastases

Recurrences were documented in 203 of the 478 patients with stage III disease at diagnosis **(Table 2)**. Among them, the most frequent sites of first recurrence were bone (28%), central nervous system (CNS) (21%), lung/pleural effusion (21%), liver (21%), chest wall (16%) and regional lymph nodes (8%). Patients may have had their first recurrence noted at more than one site. Among the different tumor subtypes, 56% of patients with triple negative stage III disease subsequently developed metastases, compared with 43% of patients with HER2 positive disease and 35% with hormone receptor (HR) positive disease. There was a higher rate of first recurrence in the CNS **(Table 3)** among triple negative and HER2 positive patients, with 17% and 37% of patients developing CNS metastases, respectively, compared to only 10% of patients with HR positive disease (p=0.001). There was no significant difference in rate of CNS metastases among HER2 positive patients who did (44%) and did not (25%) receive trastuzumab (p=0.13; data not shown).

Of the 195 (29%) patients who initially presented with metastatic disease, the most common sites of disease involvement were bone (50%), liver (32%), and lung (29%) **(Table 2)**. In contrast to patients with stage III disease who developed recurrence, in stage IV patients the presence of CNS metastases at the time of diagnosis was rare, regardless of tumor subtype: 2% of triple negative patients, 0% of HER2 positive patients, and 3% of HR positive patients had CNS metastases at the time of diagnosis **(Table 3).** Information on routine head CT or brain MRI at the time of diagnosis was not available.

Outcomes

With a median follow-up of 30 months for stage III patients overall, the median survival was 66 months (95% CI 54-107). Among the 82% of stage III patients who received multimodality therapy (n=392), the median survival was 107 months (95% CI 71-Not Reached); the 5-year and 10-year overall survival (OS) was 62% (95% CI 55-67) and 47% (95% CI 37-55), respectively. Among stage IV patients, median follow-up was 20 months, with a median survival of 26 months (95% CI 22-33) (**Table 4**).

DISCUSSION

This large, retrospective, multi-institutional study confirms the aggressive clinical features, adverse prognosis and unusual, although predictable, recurrence pattern of IBC described in previous smaller institutional series. Consistent with other studies, most of the women in our cohort were diagnosed with locoregionally advanced disease[4] while almost a third of patients had already developed distant metastasis at the time of initial diagnosis. Moreover, Stage III patients who received aggressive multi-modality therapy in our cohort had 10-year survival of less than 50%. Among our patients with a documented subsequent recurrence, a large number developed CNS metastases as their site of first recurrence. This is in contrast

to those who presented with de novo metastatic disease, where CNS metastases were uncommon.

These findings add to the limited body of IBC literature because this multi-institutional data supports clinical observations that were previously reported only in smaller, single institution series and case reports[11-13]. Most prior studies have not routinely included the event or symptom that led to the diagnosis of IBC. The NCCN Outcomes Database collects data on the "triggering event" that led to diagnosis. Although we do not have information on all patients in this cohort since 28% reported "other event" as the triggering event, our findings confirm the aggressive nature of this disease at presentation. Only 7% of patients had an abnormal mammogram as the triggering event. However, we do not know how many women had undergone prior screening, and whether the tumor developed rapidly between screenings or if mammography itself is somehow less effective at detecting these tumors. The majority of cases were diagnosed after a self-discovered breast mass or pain, which suggests that women were cognizant of changes in their breasts and instrumental in bringing these changes to the attention of their physicians, ultimately leading to a diagnosis. Despite awareness of breast changes as evidenced by our data, most cases of IBC are diagnosed at an advanced stage. Over 80% of our patients had N1-N3 disease at diagnosis, a rate that is consistent with other reports that between 55% and 85% of patients will present with clinically detectable axillary or supraclavicular lymph nodes [14]. Because of the rapid pace of disease progression and atypical presentation, identification and recognition of the unique clinical presenting features described here is critical to allow for earlier diagnosis, which could potentially lead to better outcomes.

The poor overall survival even among patients with localized IBC compared to patients with other forms of breast cancer suggests that occult micrometastatic disease may be present in many patients with IBC at the time of diagnosis. Cristofanilli et al postulated that there is an initial "systemic phase" of IBC associated with early dissemination through breast lymphatics and blood vessels[5,15]. The distribution of microscopic disease is not random, but rather is a predictable, methodical multistep process, which may explain the unusual recurrence pattern that is unique in IBC.

Our study is one of only a few to examine this recurrence pattern and identify the specific site of first relapse; most studies discuss locoregional relapse rates or relapse-free survival rates without delineating specific sites of disease spread[16,17]. While only 2% of the patients in our cohort presented with CNS metastases at diagnosis, about 20% of the stage III patients with a documented recurrence developed metastatic disease in the CNS as one of their first sites of recurrence. Several prognostic factors have been shown to be associated with the development of CNS metastases in non-IBC patients. These include younger age, larger tumors, more aggressive histologic features, HR negativity, and HER2 positivity[18-22], characteristics that were also seen in our cohort. Among IBC patients, the CNS metastasis-free survival duration is shorter for patients with these characteristics (hormone receptor negative, high tumor grade)[23].

Our data suggests that different metastatic patterns may be seen in IBC depending on stage at diagnosis. For those women who present with de novo metastatic disease, the rate of CNS

metastasis at diagnosis was low (2%). However, in our cohort, women who were diagnosed with stage III disease and ultimately recurred had a much higher rate of CNS metastases as their first site of recurrence (21% in our cohort). Several studies have shown that there are high rates of CNS metastases among women with metastatic triple negative breast cancer (TNBC) and HER2+ breast cancer, ranging from 25-46% and 30-44% respectively[24-29]. The rate of CNS metastases as the site of first recurrence has been reported to be approximately 14% for TNBC and 8% for HER2 + breast cancer overall[26]. The rate of CNS metastases seen in our cohort is therefore similar to other aggressive breast cancers, and much higher than the less aggressive subtypes, namely hormone receptor positive disease, which has 15-year overall incidence of brain metastases of 2-5%[25].

Given the large number of patients in the study cohort who developed brain metastases, clinicians should have a high index of suspicion and low threshold for imaging in symptomatic IBC patients. In spite of the higher incidence of recurrence, the NCCN guidelines for breast cancer do not include surveillance recommendations specific to IBC. The clinical features outlined in our study and others, including unique, albeit predictable, relapse patterns, suggest that IBC is a distinct entity within breast cancer, and guidelines tailored to these features may be needed. Moreover, as biology and molecular subtyping are increasingly used to tailor individual breast cancer treatment, so too may the follow-up need to be individualized based on these characteristics. Routine brain imaging is not recommended in IBC (and most malignancies) in the absence of symptoms. The increased rate of CNS metastases among the high-risk subtypes raises the question: should there be different guidelines or recommendations for staging and surveillance based on breast cancer subtype? Earlier detection of brain metastases subsequently treated with radiation therapy or surgery may decrease local and distant CNS failure rates and increase time to CNS relapse, but there has been no impact seen on overall survival[30]. This suggests that screening for asymptomatic brain metastases may not improve overall survival, but highlights the need for research into strategies to prevent recurrence. Therefore, the prevention of metastatic disease through the eradication of “micrometastatic disease” with initial therapy should be a priority. Improving initial therapy, including the development of new targeted therapies, could decrease recurrence risk and improve survival. In addition, biomarker analysis of the primary tumor or of circulating tumor cells (CTCs) could potentially be used to detect micrometastatic disease and guide therapy [31,32]. Further characterization and study of biologic markers on the primary tumor could lead to improved prediction of disease recurrence and help guide the development of novel diagnostic and therapeutic strategies.

Our study has several strengths. Although the NCCN Outcomes Database Project is not a population-based sample, it does provide insight into the patterns of presentation, treatment and outcomes at centers across the country. Our results confirm the aggressive nature of this disease described in other smaller single institution studies. In addition, this dataset provides information about the “triggering event” and disease recurrence, data that are not readily available from other sources such as registry and claims data (e.g. SEER/Medicare) or commercial insurance data.

Several limitations in our study are worth noting. First, a greater proportion of patients in our IBC population had triple negative (26%) and HER2 positive (32%) disease than is seen

in non-IBC populations. Triple negative breast cancer accounts for approximately 10-20% of breast cancers[33-35], while 20-25% of breast cancers overexpress HER2[13,36]. Since CNS metastases are more common in triple negative and HER2 positive breast cancer in general, we cannot conclude that IBC itself imparts a greater risk of CNS metastases. It may be that the greater incidence of HER2 positive and triple negative breast cancer in our cohort drove the findings. Moreover, since we do not know if routine brain imaging was done at diagnosis of other sites of metastatic disease, there may be an underdiagnosis of brain metastases in the population. If this is the case, our estimates of CNS metastases are overly conservative and bias our conclusions toward the null, making it more likely that our findings are significant. Second, patients who are included in the NCCN Database are those who receive their primary breast cancer therapy at an NCCN institution. If patients leave the NCCN institution for subsequent treatment, they are only followed for survival, and data on recurrence may be incomplete. Therefore, while we were able to describe the pattern of relapse and overall survival, we did not present data on time to progression or progression-free survival. Moreover, while all patients received care at NCCN centers by breast cancer experts, we do not know why one third of patients with stage III disease in our cohort did not receive trimodality therapy. For example, only 71% of patients with Stage III disease underwent surgery. We do not have information about their response to initial therapy. It is possible that some progressed through initial treatment with chemotherapy and/or radiation and were, therefore, no longer surgical candidates. Finally, the method of recurrence detection is not recorded in the database, although it is not unreasonable to assume that it is based on standard diagnostic and clinical criteria. We used a timeframe of two weeks to identify sites of first recurrence among patients with stage III disease. If delays of more than two weeks occurred, we would potentially be undercounting sites of first recurrence.

CONCLUSION

In conclusion, this large retrospective multi-institutional study confirms the aggressive clinical features, recurrence patterns and adverse prognosis of IBC described in previous single institution series. Even with aggressive multimodal therapy, the long term survival of IBC is shorter than non-IBC. Future investigations are needed to address the aggressive biology of IBC, the role of local therapy in de novo metastatic disease, and to outline new strategies for staging and surveillance to improve diagnosis and detection of metastatic disease.

Acknowledgments

Funding provided by: Drs Cristofanilli and Wong and Ms. Li were supported by P30 CA006927 Dr. Wong was also supported by K07CA136995-01

Data collection was supported by P50 CA 89393 to Dana Farber Cancer Institute

References

1. Hance KW, Anderson WF, Devesa SS, Young HA, Levine PH. Trends in inflammatory breast carcinoma incidence and survival: the surveillance, epidemiology, and end results program at the National Cancer Institute. Journal of the National Cancer Institute. 2005; 97(13):966–975. [PubMed: 15998949]

2. Levine PH, Steinhorn SC, Ries LG, Aron JL. Inflammatory breast cancer: the experience of the surveillance, epidemiology, and end results (SEER) program. Journal of the National Cancer Institute. 1985; 74(2):291–297. [PubMed: 3856043]
3. Robertson FM, Bondy M, Yang W, et al. Inflammatory breast cancer: the disease, the biology, the treatment. CA: a cancer journal for clinicians. 2010; 60(6):351–375. [PubMed: 20959401]
4. Wingo PA, Jamison PM, Young JL, Gargiullo P. Population-based statistics for women diagnosed with inflammatory breast cancer (United States). Cancer Causes & Control. 2004; 15(3):321–328. [PubMed: 15090727]
5. Cristofanilli M, Valero V, Buzdar AU, et al. Inflammatory breast cancer (IBC) and patterns of recurrence. Cancer. 2007; 110(7):1436–1444. [PubMed: 17694554]
6. Low JA, Berman AW, Steinberg SM, Danforth DN, Lippman ME, Swain SM. Long-term follow-up for locally advanced and inflammatory breast cancer patients treated with multimodality therapy. Journal of clinical oncology. 2004; 22(20):4067–4074. [PubMed: 15483018]
7. Bertucci F, Tarpin C, Charafe-Jauffret E, et al. Multivariate analysis of survival in inflammatory breast cancer: impact of intensity of chemotherapy in multimodality treatment. Bone marrow transplantation. 2004; 33(9):913–920. [PubMed: 15004544]
8. Christian CK, Niland J, Edge SB, et al. A multi-institutional analysis of the socioeconomic determinants of breast reconstruction: A study of the National Comprehensive Cancer Network. Annals of surgery. 2006; 243(2):241. [PubMed: 16432358]
9. Weeks J. Outcomes assessment in the NCCN: 1998 update. National Comprehensive Cancer Network. Oncology (Williston Park, NY). 1999; 13(5A):69.
10. Weeks J. Outcomes assessment in the NCCN. Oncology (Williston Park, NY). 1997; 11(11A):137.
11. Dawood S, Ueno N, Valero V, et al. Identifying factors that impact survival among women with inflammatory breast cancer. Annals of oncology. 2012; 23(4):870–875. [PubMed: 21765048]
12. Owens MA, Horten BC, Da Silva MM. HER2 amplification ratios by fluorescence in situ hybridization and correlation with immunohistochemistry in a cohort of 6556 breast cancer tissues. Clinical breast cancer. 2004; 5(1):63–69. [PubMed: 15140287]
13. Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, McGuire WL. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science. 1987; 235(4785):177–182. [PubMed: 3798106]
14. Walshe JM, Swain SM. Clinical aspects of inflammatory breast cancer. Breast disease. 2006; 22(1):35–44. [PubMed: 16735785]
15. Van der Auwera I, Van den Eynden GG, Colpaert CG, et al. Tumor lymphangiogenesis in inflammatory breast carcinoma: a histomorphometric study. Clinical cancer research. 2005; 11(21):7637–7642. [PubMed: 16278382]
16. Baldini E, Gardin G, Evangelista G, Prochilo T, Collecchi P, Lionetto R. Long-term results of combined-modality therapy for inflammatory breast carcinoma. Clinical breast cancer. 2004; 5(5): 358–363. [PubMed: 15585073]
17. Rehman S, Reddy CA, Tendulkar RD. Modern Outcomes of Inflammatory Breast Cancer. International Journal of Radiation Oncology* Biology* Physics. 2012; 84(3):619–624.
18. Distefano A, Yap HY, Hortobagyi GN, Blumenschein GR. The natural history of breast cancer patients with brain metastases. Cancer. 1979; 44(5):1913–1918. [PubMed: 498057]
19. Boogerd W, Vos V, Hart A, Baris G. Brain metastases in breast cancer; natural history, prognostic factors and outcome. Journal of neuro-oncology. 1993; 15(2):165–174. [PubMed: 8509821]
20. Crivellari D, Pagani O, Veronesi A, et al. High incidence of central nervous system involvement in patients with metastatic or locally advanced breast cancer treated with epirubicin and docetaxel. Annals of oncology. 2001; 12(3):353–356. [PubMed: 11332148]
21. Stewart JF, King RJ, Sexton SA, Millis RR, Rubens RD, Hayward JL. Oestrogen receptors, sites of metastatic disease and survival in recurrent breast cancer. European Journal of Cancer (1965). 1981; 17(4):449–453.
22. Clark GM, Sledge G, Osborne CK, McGuire W. Survival from first recurrence: relative importance of prognostic factors in 1,015 breast cancer patients. Journal of Clinical Oncology. 1987; 5(1):55–61. [PubMed: 3806159]

23. Gonzalez-Angulo AM, Cristofanilli M, Strom EA, et al. Central nervous system metastases in patients with high-risk breast carcinoma after multimodality treatment. Cancer. 2004; 101(8): 1760–1766. [PubMed: 15386311]
24. Lim E, Lin NU. New insights and emerging therapies for breast cancer brain metastases. Oncology. 2012; 26:652–659. [PubMed: 22888567]
25. Kennecke H, Yerushalmi R, Woods R, et al. Metastatic behavior of breast cancer subtypes. Journal of clinical oncology. 2010; 28(20):3271–3277. [PubMed: 20498394]
26. Lin NU, Claus E, Sohl J, Razzak AR, Arnaout A, Winer EP. Sites of distant recurrence and clinical outcomes in patients with metastatic triple-negative breast cancer. Cancer. 2008; 113(10):2638–2645. [PubMed: 18833576]
27. Brufsky AM, Mayer M, Rugo HS, et al. Central nervous system metastases in patients with HER2-positive metastatic breast cancer: incidence, treatment, and survival in patients from registHER. Clinical Cancer Research. 2011; 17(14):4834–4843. [PubMed: 21768129]
28. Bendell JC, Domchek SM, Burstein HJ, et al. Central nervous system metastases in women who receive trastuzumab-based therapy for metastatic breast carcinoma. Cancer. 2003; 97(12):2972–2977. [PubMed: 12784331]
29. Stemmler H-J, Schmitt M, Willems A, Bernhard H, Harbeck N, Heinemann V. Ratio of trastuzumab levels in serum and cerebrospinal fluid is altered in HER2-positive breast cancer patients with brain metastases and impairment of blood-brain barrier. Anti-cancer drugs. 2007; 18(1):23–28. [PubMed: 17159499]
30. Somlo G, Lau SK, Frankel P, et al. Multiple biomarker expression on circulating tumor cells in comparison to tumor tissues from primary and metastatic sites in patients with locally advanced/inflammatory, and stage IV breast cancer, using a novel detection technology. Breast cancer research and treatment. 2011; 128(1):155–163. [PubMed: 21499685]
31. Cristofanilli M, Budd GT, Ellis MJ, et al. Circulating tumor cells, disease progression, and survival in metastatic breast cancer. New England Journal of Medicine. 2004; 351(8):781–791. [PubMed: 15317891]
32. Mehta M. The dandelion effect: treat the whole lawn or weed selectively? Journal of Clinical Oncology. 2011; 29(2):121–124. [PubMed: 21135269]
33. Foulkes WD, Smith IE, Reis-Filho JS. Triple-negative breast cancer. The New England journal of medicine. Nov 11; 2010 363(20):1938–1948. [PubMed: 21067385]
34. Perou CM, Sorlie T, Eisen MB, et al. Molecular portraits of human breast tumours. Nature. Aug 17; 2000 406(6797):747–752. [PubMed: 10963602]
35. Dawood S. Triple-negative breast cancer: epidemiology and management options. Drugs. Dec 3; 2010 70(17):2247–2258. [PubMed: 21080741]
36. Slamon DJ, Godolphin W, Jones LA, et al. Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. Science. 1989; 244(4905):707–712. [PubMed: 2470152]

CLINICAL PRACTICE POINTS

IBC is a rare, aggressive subtype of breast cancer that demands prompt diagnosis and interdisciplinary management. Despite recent advances in treatment, IBC remains difficult to cure. Multimodality treatment should include perioperative chemotherapy, radiation, and surgery. Our study, which presents new data from the NCCN in the form of a larger, multi-institutional study, supports clinical observations previously only reported in smaller, single institution series. A significant number of patients with IBC will have metastatic disease at the time of presentation, and these patients may have lower rates of CNS metastases. Many patients who present with limited stage disease will develop metastases, and the rates of CNS metastases are high, especially in the triple negative and HER2 positive subtypes. While guidelines do not recommend routine screening for CNS metastases, clinicians should have a high index of suspicion and a low threshold for requesting brain imaging in patients with new neurological symptoms, especially in patients with triple negative or HER2 positive IBC. Our observations suggest that new strategies for staging and surveillance are necessary to improve diagnosis and detection of metastases, and that prevention of metastases through the eradication of “micrometastatic disease” with initial therapy should be a priority.

Table 1

Demographics, Clinical and Pathologic Characteristics (N=673)

		Median	Range
Age at diagnosis (years)		53	22-91
Follow-up (months)		29	

		N	%
Race			
	Caucasian	534	79
	African American	65	10
	Hispanic	52	8
	Other/Unknown	22	3
Menopausal Status at Diagnosis			
	Postmenopausal	275	41
	Premenopausal	385	57
	Unknown	13	2
Clinical Stage			
	IIIB	384	57
	IIIC	94	14
	IV	195	29
Clinical Nodal Stage			
	N0	117	17
	N1	301	45
	N2,N3	240	36
Lymphovascular Invasion			
	Yes	359	53
	No	251	37
	Unknown	63	9
Estrogen Receptor Status			
	Positive[a]	298	44
	Negative	364	54
	Unknown/Missing	11	2
Progesterone Receptor Status			
	Positive[a]	229	34
	Negative	433	64
	Unknown	11	2
Her2-Neu Status			
	Positive[a,b]	213	32
	Negative/Low +	406	60

		N	%
	Unknown/Missing	54	8
Tumor Subtype			
	HR Positive	229	34
	HER2 Positive	213	32
	Triple Negative	175	26
	Unknown	56	8
Histology			
	Invasive Ductal[c]	567	84
	Invasive Lobular[d]	41	6
	Mixed	38	6
	Other[e]	27	4
Event Leading to Diagnosis			
	Breast lump, self-discovered	230	34
	Breast pain or discomfort	131	19
	Abnormal screening mammogram	45	7
	Inverted nipple	38	6
	Axillary Mass	19	3
	Lump in breast, MD discovered	13	2
	Lump in breast, unknown discovered	3	1
	Bloody nipple discharge	3	1
	Unknown or “Other”[f]	191	28
Treatments received by Stage III patients (N=478)			
	Systemic Chemotherapy[g]	392	82
	Radiation Therapy[g]	362	76
	Definitive Surgery	338	71
	Patients receiving >1 modality	392	82

[a] ER/PR and HER status are obtained from medical records or pathology reports and classified as either positive or negative (without further information on cut-offs).

[b] Includes IHC 3+, FISH +, and NOS

[c] Includes invasive ductal with and without extensive intraductal component.

[d] Includes invasive lobular with and without extensive intraductal component.

[e] Includes colloid (mucinous), papillary, and invasive ductal and lobular with extensive intraductal component.

[f] Other is not further classified in the NCCN database.

[g] Includes both neoadjuvant and adjuvant.

Table 2

Sites of first relapse among stage III patients who recurred (N=203), and of metastatic disease among patients with stage IV disease at diagnosis (N=195).[a]

Site	Stage III with recurrence		Stage IV	
	N	%	N	%
Bone/Bone marrow	57	28	97	50
Brain/CNS/Meninges	43	21	4	2
Lung/Pleural Effusion	43	21	56	29
Liver	42	21	62	32
Chest Wall	32	16	N/A	
Regional Lymph Nodes[b]	16	8	21	11
Contralateral locoregional Lymph Nodes[c]	10	5	28	14
Skin	9	4	8	4
Ipsilateral Breast	7	3	N/A	
Other[d]	40	20	69	35

[a] Totals may be greater than 100% as patients may have had more than one site of first recurrence.

[b] Includes ipsilateral axillary and supraclavicular lymph nodes

[c] Includes contralateral breast, contralateral supraclavicular lymph nodes

[d] Includes intraabdominal, other distant lymph nodes, other distant visceral, other distant non-visceral, and other.

Table 3

Sites of first recurrence (stage III) and of metastatic disease at diagnosis (stage IV), by tumor subtype.[a]

Site	Stage III with recurrence N=203				Stage IV N=195			
	Triple Negative N=72	HER2 + N=60	HR+ N=51	Unknown N=20	Triple Negative N=46	HER2 + N=63	HR+ N=74	Unknown N=12
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Bone/Bone marrow	17 (24)	10 (17)	25(49)	5 (25)	12 (26)	34 (54)	47 (64)	4 (33)
Brain/CNS/Meninges	12 (17)	22(37)	5 (10)	4 (20)	1 (2)	0	2 (3)	1 (8)
Lung/Pleural Effusion	18 (25)	9 (15)	11 (22)	5 (25)	15 (33)	19 (30)	21 (28)	1 (8)
Liver	17 (24)	13 (22)	11 (22)	1 (5)	14 (30)	28 (44)	16 (22)	4 (33)
Chest Wall	15 (21)	8 (13)	5 (10)	4 (20)	N/A	N/A	N/A	N/A
Regional Lymph Nodes[b]	10 (14)	3 (5)	3 (6)	0	4 (9)	8 (13)	4 (5)	5 (42)
Contralateral Locoregional Lymph Nodes[c]	5 (7)	4 (7)	0	1 (5)	11 (24)	6 (10)	11 (15)	0
Skin	4 (6)	2 (3)	2 (4)	1 (5)	5 (11)	1 (2)	2 (3)	0
Ipsilateral Breast	1 (1)	6 (10)	0	0	N/A	N/A	N/A	N/A
Other[d]	18 (25)	10 (17)	10 (20)	2 (10)	23 (50)	16 (25)	29 (39)	1 (8)

[a] Totals may be greater than 100% as patients may have had more than one site of first recurrence.

[b] Includes ipsilateral axillary and supraclavicular lymph nodes

[c] Includes contralateral breast, contralateral supraclavicular lymph nodes

[d] Includes intraabdominal, other distant lymph nodes, other distant visceral, other distant non-visceral, and other.

Table 4

Overall and median survival by stage and treatment.

	5 year (%) (95% CI)	10 year (%) (95% CI)	Median Survival (months) (95% CI)
Stage III	54% (48 - 59)	41% (33 - 48)	66 (54 - 107)
Stage III Multimodality[a]	62% (55 - 67)	47% (37 - 55)	107 (71 - Not Reached)
Stage IV	28% (20 - 35)	18% (11 - 26)	26 (22 - 33)

[a]Patients received “multimodality” therapy if they received >1 modality (surgery, chemotherapy, radiation)