

# Insights of Breast Cancer

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## Barriers to Early Diagnosis of Inflammatory Breast Cancer [Version 2, Approved]

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### Abstract

Inflammatory breast cancer (IBC), the most aggressive form of breast cancer, presents as redness, warmth and edema in the breast which is frequently misdiagnosed as an infectious process and the first treatment is often antibiotics. Primary care physicians including family practice, internal medicine and obstetricians-gynecologists are among the first contact physicians for women with these symptoms. Although apparently not the primary determinant of outcome, delay in diagnosis does appear to contribute to decreased survival. In this study, we describe the experience of patients in the IBC Registry (IBCR) maintained at The George Washington University and document some of the reasons for delay in diagnosis. Patients seeing a surgeon shortly after onset of symptoms had a shorter delay in diagnosis and improved survival compared to patients initially seeing primary care providers including OB/ GYN doctors.

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## Introduction

Inflammatory breast cancer (IBC) is the most aggressive form of breast cancer, accounting for approximately 2.5% of all breast cancer cases and 7% of all breast cancer-related deaths [1]. Although considered by some to be a relatively uncommon disease, approximately 4800 U.S. women develop IBC each year and it is twice as common as acute myelocytic leukemia and chronic myelocytic leukemia in U.S. women [2]. Due to improved treatment, 5-year disease free survival for IBC has increased from 3%-10% to 32% [3], but even with these newer treatments delay in diagnosis can negatively impact the patient outcome. Primary care physicians are usually the first medical point of contact for IBC patients and the young age of the patient with signs suggestive of infection can be misleading.

IBC is a rapidly growing, highly angiogenic/ angioinvasive breast cancer. IBC has a range of clinical presentations from mild erythema, swelling, and pain to an enlarged, swollen breast with "peau d' orange". It is characterized by an early age at diagnosis, poor nuclear grade, and often has a negative hormone receptor status. Typical of IBC is rapid onset, often within days or weeks but by definition within six months [4]. Familiarity on the part of clinicians for both common and uncommon clinical signs and symptoms of IBC is necessary as IBC is primarily a clinical diagnosis requiring urgent attention and follow up. The designation "inflammatory" stems from the clinical appearance that often resembles an acute infection, but this is somewhat of a misnomer as the appearance is due to lymphatic obstruction from tumor emboli and is not a true inflammation [5]. The diffuse nature of the disease renders mammograms less effective at detection with mammograms not revealing a mass in approximately 35% of cases [2]. A similar percentage does not have a discrete palpable mass on physical examination [6]. While an earlier study [7] indicated initial response to chemotherapy was the primary determinant of survival, physician delay in diagnosis also apparently has an impact on survival. The aim of this study is to examine patient as well as physician delays and the attitudes that result in delays in diagnosis and treatment.

## Methods and Materials

This prospective cohort study used the IBC Registry established at The George Washington University School of Public Health and Health Services, Department of Epidemiology and Biostatistics. This active registry was established June 1, 2002 to collect standardized clinical data and bio specimens from patients with IBC in the US and Canada [2], with the intention of studying the risk factors of IBC and molecular markers of the disease. Patients were recruited through the internet or through local oncologists and diagnosis was confirmed by examination of medical records.

This analysis utilized the patients reported in a previous study [7] which evaluated 155 IBC cases in the IBC Registry and focused on 137 women who underwent neoadjuvant che-

motherapy to determine which of several factors determined survival, including the response to chemotherapy and delay in diagnosis. Seven patients were removed from this analysis because a review of their epidemiologic category categorized them as "non-classic" cases, such as secondary inflammatory breast cancer (IBC occurring in the site of a previous non-IBC breast cancer) or breast cancer with invasion of dermal lymphatics without clinical signs. This first study only had examined the impact of physician delay and not patient delay and did not include the reasons for delay. This current study focused on both patient factors and some important physician characteristics that could be useful in reducing delay in diagnosis. The characteristics of the IBC patients in this study group, described in detail previously [7] included four subcategories: "classic IBC" where the patients had more than half of the breast clinically involved with redness, warmth and edema with or without dermal lymphatic invasion (categories 1 and 2 = 59), "pathologically defined IBC" where clinical manifestations occupied less than half of the breast but dermal lymphatic invasion was found on biopsy (category 3 = 36), and "atypical IBC" where the clinical manifestations occupied less than half of the breast and dermal lymphatic invasion was not documented (category 4 = 35) (Table 1).

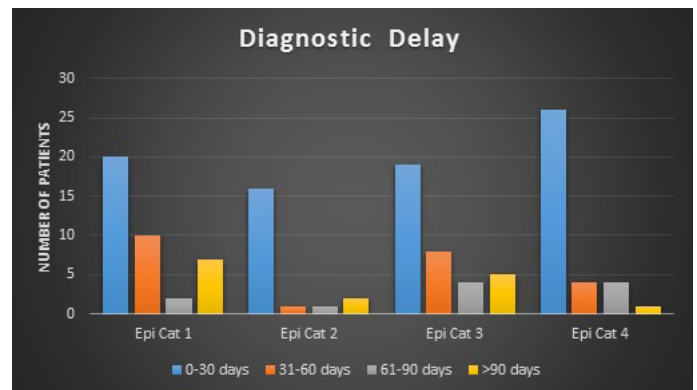


Figure 1: Diagnostic or Physician Delay: Interval between first medical consultation and pathological diagnosis of cancer.

Previous clinical and laboratory studies in Tunisia and in the United States have shown that the outcome and the biological characteristics of the patients in all three of our study groups are comparable [8-10]. Classic IBC was defined by the early case definition of the American Joint Committee on Cancer (AJCC) which required half of the breast to be clinically involved with redness, warmth and edema [11], or the early case definition of the Surveillance, Epidemiology and End Results (SEER) Program of the National Cancer Institute accepting less than half of the breast involved but requiring documentation of dermal lymphatic invasion of the skin with tumor emboli [12].

IBC cases were reviewed documenting the interval between the symptom onset to the date of first medical office visit i.e. patient delay time and the interval between the first medical contact and a pathological diagnosis of breast cancer i.e. physician or diagnostic delay time. Where this interval was

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60 days or more, the case notes were reviewed for reasons of patient/ physician delay. The patient's first medical contact person, the clinical impression of signs and symptoms on the patient's first visit and the clinical diagnosis, the assessment process, the results of mammography and /or ultrasonography examination, the findings on needle biopsy and the principal causes of delay were identified.

Statistical Methods: Initial visit with a physician was classified into two categories: surgeon (any) or non-surgeon. There were only 11 surgeons in the spreadsheet and 119 non-surgeons. Due to the small number of surgeons in this sample a 2-sided wilcoxon exact test was performed due to the non-parametric nature of the data.

## Results

Our final study group of 130 patients, which consisted of patient categories 1-4 including 59 classic (categories 1-2), 36 "pathologically defined IBC" (category 3) and 35 atypical (category 4) cases, had a mean (SD) age at diagnosis of 47.9 years. The time from symptom onset to first physician visit was categorized into periods of less than or equal to 30 days, 31 to 60 days, 61 to 90 days and more than 90 days (Figure 1 and 2). Less than 60 days was considered a short delay and 60 days or greater was considered a long delay. The majority of women (62.3%, n=81) had a pathological diagnosis within 30 days and 80% (n=104) were within 60 days. Long delays (61- 90 days) were seen in 11 women (8.5%) with 15 (10.9%) having a delay of >90 days.

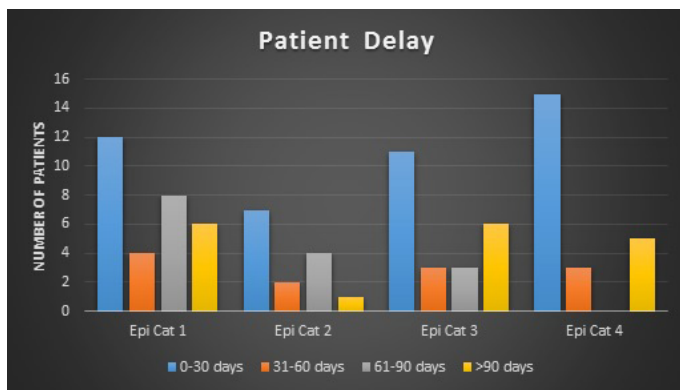


Figure 2: Patient Delay: Interval between first symptom of IBC and first medical visit.

Eleven of the 130 patients were initially seen by a surgeon and the other 119 were seen by non-surgeons (Ob-gyn doctors were included with the non-surgeons as they were the patients primary caregivers). All 11 patients initially seeing surgeons were diagnosed within 60 days, 10 of the 11 patients (90.9%) diagnosed within 30 days. In contrast, 26 of the 119 patients (21.85%) initially seen by a non-surgeon had a delay of more than 60 days, 15 (9.24%) having a delay >90 days. 71 (59.7%) of this group received a diagnosis within 30 days and 11 (9.2%) be-

tween 30-60 days. The two-sided Wilcoxon exact test yielded a p value of 0.0422 but the statistical value was considered not generalizable to the entire population and therefore unreliable for major conclusions.

Overall, there were no important differences between the women with the long delay and those with shorter delay in terms of age or race/ethnicity. In regard to clinical presentation, while 35 (25%) of the 130 patient group had clinical involvement of less than half of the breast, 19 (58%) of the 33 patients with a long patient delay (Figure 2) and 12 (46%) of the 26 patients with long physician delay (Figure 1) had classic IBC involving more than half of the breast. The reasons for patient delay were diverse. The most common was attributing the symptoms to minor health problems such as normal physiologic changes e.g. menses, weight gain, or pregnancy or an allergic reaction/ bug bite. Others included a prior history of fibrocystic disease, difficulties with insurance, concurrent stressful life events, or work related constraints, or persuasion by a significant other in appraising a breast symptom, e.g. the patient's mother said 'breast cancer doesn't hurt'.

In the diagnostic delay category, the major reason for delay was the diagnosis of infection and prolonged antibiotic medication, many physicians believing pain and the absence of a discrete lump in a young woman ruled out breast cancer as a diagnosis. The absence of a discrete mass on mammogram also contributed to delayed diagnosis in some patients.

## Discussion

The well-documented aggressiveness of IBC supports the importance of rapid diagnosis and initiation of treatment, usually combination chemotherapy to reach and hopefully eliminate disseminated micro metastases. Our earlier study [7] suggested that initial response to chemotherapy was a more important determinant of outcome than delay in diagnosis in IBC but delay in diagnosis also definitely affected survival. The reason for the diverse response to chemotherapy, possibly influenced by genetic predisposition, is currently beyond patient and physician control but delay in diagnosis, also affecting survival, is subject to improvement with improved patient and physician awareness.

It is of interest that the IBC patients with categories 3 and 4 (less than half the breast clinically involved) were more likely to have a rapid diagnosis than those with more significant breast involvement, the limited clinical picture perhaps less suggestive of an infectious process. Reasons for patient delay of greater than 60 days were due to: attribution of symptoms to normal physiologic changes e.g. menses, weight gain, pregnancy; an allergic reaction/ bug bite; prior history of fibrocystic disease; insurance related issues; concurrent stressful life events; work-related constraints, or outside advice.

Diagnostic delay appears to have at least two major contributing factors, both resulting from the unusual appearance

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of IBC clinically for a malignancy. First, most cancers appear as a lump whereas IBC often presents as an infiltrating lesion and therefore no discrete lump can be palpated on physical examination and no discrete lesion may be seen on mammography. Second, the invasion of the dermal lymphatics often produces acute breast swelling, pain and redness which to the average clinician raises the likelihood of an acute infectious process requiring antibiotics and certainly not a surgical procedure. As IBC is a relatively unusual manifestation of breast cancer, most primary care providers are unlikely to see more than one case in his/her career. Therefore the most important message emerging from this study is that primary care physicians need to be alerted as to the importance of having an unresolved breast disorder referred to a breast specialist, usually a surgeon. A short delay is understandable as primary care physicians rarely encounter IBC in their practice, and are likely to be misled by the frequency of signs and symptoms suggestive of infection, the young age of the patient, and the pain and swelling rarely seen in cancer (“Breast cancer doesn’t hurt” is a common physician statement to an IBC patient). Primary care physicians, including Ob-Gyn doctors who provide primary care to a large proportion of young women, need to be trained to refer a patient whose breast symptoms do not resolve in two weeks to conservative treatment, including antibiotics, to a breast specialist.

**Table 1:** Diagnostic delay according to epidemiological categories.

Diagnostic Delay	Epi Cat 1	Epi Cat 2	Epi Cat 3	Epi Cat 4	Total Patients
0-30 days	20	16	19	26	81
31-60 days	10	1	8	4	23
61-90 days	2	1	4	4	11
>90 days	7	2	5	1	15

See text for epidemiological categories.

**Table 2:** Patient Delay according to Epidemiological categories.

Patient Delay	Epi Cat 1	Epi Cat 2	Epi Cat 3	Epi Cat 4	Total Patients
0-30 days	12	7	11	15	45
31-60 days	4	2	3	3	12
61-90 days	8	4	3		15
>90 days	6	1	6	5	18

See text for epidemiological categories.

## Conclusion

IBC is an extremely aggressive form of breast cancer requiring neoadjuvant chemotherapy at the outset. Delay in diagnosis is one factor affecting survival and several steps can be taken to improve outcome of patients with his disease. First, since the most florid cases resemble an acute infection, a short term of antibiotics can be attempted but in the absence of an immediate response a surgeon should be consulted. Second, all women and physicians should be better educated as to the importance of early referral to a breast specialist if a breast problem persists.

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