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Exploration of diagnostic methods and novel treatments for inflammatory breast cancer: a review to raise awareness and improve diagnosis and prognosis

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Thesis

EXPLORATION OF DIAGNOSTIC METHODS AND NOVEL TREATMENTS FOR INFLAMMATORY BREAST CANCER: A REVIEW TO RAISE AWARENESS AND IMPROVE DIAGNOSIS AND PROGNOSIS

by

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DEDICATION

To my mother, father, and brother, who consistently provide me with endless love and support to achieve all my goals in life. To my extended family and friends who have been there for me through the ups and downs of life and for all their advice and support in pursuing my dreams. To my amazing coworkers and oncologists at Dana-Farber who have welcomed me with open arms into their team and for supporting me in writing this thesis.

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ABSTRACT

Inflammatory breast cancer (IBC) poses a significant challenge in breast cancer management because of its aggressive nature and propensity for delayed diagnosis. This literature-based thesis investigated the current landscape of diagnostic methods and novel treatments for IBC with the aim of raising awareness and enhancing diagnosis and prognosis. Through an extensive review of existing literature and empirical evidence, this thesis delved into the clinical presentation, diagnostic modalities, prognostic factors, and treatment strategies specific to IBC. Key diagnostic methods, including imaging modalities (e.g., mammography, ultrasound, magnetic resonance imaging) and molecular diagnostics (e.g., biomarkers, gene expression profiling), were examined in detail and highlighted for their utility in early detection and characterization of IBC. Moreover, novel treatment approaches, such as targeted therapies (e.g., HER2 inhibitors, hormone therapy), immunotherapy, and emerging molecularly targeted agents, were explored for their potential to improve outcomes in IBC patients. The resulting discussion encompassed the barriers to early diagnosis and treatment initiation and emphasized the importance of both prompt recognition of IBC symptoms and multidisciplinary management.

Future directions for personalized medicine and precision oncology in IBC are elucidated, underscoring the need for continued research into biomarkers, therapeutic targets, and innovative treatment modalities. By shedding light on the complexities of IBC diagnosis and treatment, this thesis can contribute to ongoing efforts to raise awareness, improve clinical outcomes, and ultimately reduce the burden of IBC on patients and healthcare systems.

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LIST OF ABBREVIATIONS

ADC..........antibody-drug-conjugate

AI..........artificial intelligence

AKT..........protein kinase B

BC..........breast cancer

BMI..........body mass index

BRCA..........breast cancer

BSGI..........breast-specific gamma imaging

CDK4/6..........cyclin-dependent kinases 4 and 6

CEUS..........contrast-enhanced ultrasound

cfDNA..........cell-free DNA

CK..........cytokeratin

CTCs..........circulating tumor cells

ctDNA..........circulating tumor DNA

EMT..........epithelial-mesenchymal transition

ER..........estrogen receptor

FNA..........fine-needle aspiration

HER..........human epidermal growth factor receptor

HR..........hormone receptor

IBC..........inflammatory breast cancer

LABC..........locally advanced breast cancer

MeSH..........Medical Subject Headings

MBI .... molecular breast imaging

MRI .... magnetic resonance imaging

mTOR .... mammalian target of rapamycin

NADJC .... neoadjuvant chemotherapy

PARP .... poly (ADP-ribose) polymerase

PCP .... primary care provider

pCR .... pathologic complete response

PD-1 .... programmed death-1

PD-L1 .... programmed death-ligand 1

PET-CT .... positron emission tomography-computed tomography

PI3K .... phosphatidylinositol 3-kinase

PIK3CA .... phosphatidylinositol-4,5- bisphosphate 3-kinase catalytic subunit alpha

PR .... progesterone receptor

SERM .... selective estrogen receptor modulator

US .... ultrasound

VEGF .... vascular endothelial growth factor

INTRODUCTION

Inflammatory breast cancer (IBC) stands out as a formidable adversary in the realm of oncology. This rare and aggressive form of breast cancer (BC) challenges clinicians at every turn (Curigliano, 2018; Curtin & Szabo, 2013; Dawood et al., 2011). Distinguished by its rapid progression and elusive diagnostic features, IBC poses obstacles to timely intervention and optimal patient outcomes. Statistically, IBC emerges as a tough opponent, wielding diagnostic complexities that far surpass those encountered in noninflammatory breast cancer cases (Anderson et al., 2003). The journey from symptom onset to definitive diagnosis is often fraught with missteps and missed opportunities as physicians and healthcare professionals navigate a landscape with diagnostic pitfalls.

The perplexing nature of IBC often leads to misdiagnoses with conditions such as cellulitis, mastitis, and even other forms of advanced breast cancer masquerading under its guise. Such diagnostic misadventures are exemplified in the narrative of a 44-year-old woman named Jennifer, chronicled on the Susan G. Komen website (Susan G. Komen, 2021). Although her doctor initially dismissed a pink patch on her left breast as a trivial consequence of her bra size, Jennifer’s journey into the depths of IBC's complexity soon unfolded. What began as a seemingly innocuous blemish burgeoned into a distressing tableau of skin thickening, nipple inversion, and debilitating pain.

Jennifer's subsequent journey through the labyrinth of medical consultations and investigative procedures was a microcosm of the diagnostic challenges inherent in IBC (Susan G. Komen, 2021). Despite initial reassurances from a routine mammogram, her escalating symptoms defied conventional explanations. Blood work hinted at inflammation that led to an erroneous diagnosis of arthritis and a futile stint in physical therapy. As the relentless march of pain and debility persisted, a cascade of misdiagnoses followed, culminating in a perplexing diagnosis of mastitis—a bewildering revelation for a patient whose nursing days were long behind her.

Faced with the specter of a protracted diagnostic odyssey, Jennifer relentlessly pursued answers that ultimately led her to the doorstep of IBC awareness (Susan G. Komen, 2021). Armed with newfound knowledge, she confronted her healthcare journey with renewed vigor and advocated for closer scrutiny of her symptoms. The culmination of her persistence was a definitive diagnosis of stage IV IBC—an arduous quest that spanned a harrowing 11 months.

This narrative epitomizes the distressing ordeal faced by countless individuals grappling with the enigmatic specter of IBC. It underscores the imperative for heightened awareness, early recognition, and streamlined diagnostic pathways in the battle against this disease. On a journey through the landscape of IBC, it is critical to unravel its mysteries, confront its diagnostic dilemmas, and pave the way toward improved outcomes for those trapped in its formidable grasp.

Background

Cancer stands as a formidable adversary in the landscape of public health, ranking as the second leading cause of mortality in the United States that trails only behind heart disease (Singletary & Cristofanilli, 2008). Among females, breast cancer (BC) reigns as the most prevalent form of malignancy, and the second leading cause of cancer-related death in women. Although BC can affect both genders, its incidence in women surpasses that in men by a factor of 100. Encouragingly, strides in cancer screening and awareness initiatives since 1989 have heralded a notable decline of almost 42% in BC mortality rates (Abo Al-Shiekh et al., 2021; Albeshan et al., 2020). Concurrently, advancements in treatment modalities have contributed significantly to this downward trend, underscoring the pivotal role of early detection and intervention in mitigating BC-related morbidity and mortality.

Within the spectrum of BC lies a diverse array of subtypes, each possessing unique characteristics and clinical behaviors. Among these, inflammatory breast cancer (IBC) emerges as a rare and particularly aggressive variant, distinguished by its propensity for rapid dissemination and dire prognosis (Khiyali et al., 2017). Frequently diagnosed at advanced stages typically encompassing stage IIIC or stage IV, IBC manifests with an abrupt onset of symptoms and exhibits a remarkable capacity for infiltration into adjacent organ systems (Khiyali et al., 2017; Ning et al., 2019). Despite the widespread awareness surrounding BC, educational initiatives within school health programs and workplace settings often fail to adequately address the nuances of distinct BC subtypes, with IBC remaining absent from the mainstream discourse.

The imperative to delve into the intricacies of IBC diagnosis and treatment cannot be overstated, as heightened awareness and early intervention are paramount in improving patient outcomes and prognosis. This thesis comprehensively explores the multifaceted landscape of inflammatory breast cancer, encompassing its clinical presentation, diagnostic modalities, prognostic indicators, and therapeutic strategies. Moreover, attention is directed toward the barriers impeding the timely diagnosis of IBC and the consequential impact on patient prognosis. By evaluating past endeavors aimed at reducing the incidence of BC and exploring avenues for integrating IBC-related education into existing awareness initiatives, this thesis seeks to catalyze efforts toward enhancing health literacy and fostering a more informed dialogue surrounding breast cancer, particularly its elusive and often overlooked subtype, inflammatory breast cancer.

Through a nuanced examination of IBC knowledge dissemination within various medical specialties and the efficacy of current educational frameworks in promoting workplace awareness among high-risk populations, this thesis endeavors to identify gaps in IBC education and propose actionable steps for their remediation. By illuminating the intricacies of IBC and advocating for its inclusion in broader breast cancer awareness initiatives, this research attempts to empower individuals with the knowledge and resources necessary to navigate the complexities of breast cancer diagnosis, treatment, and survivorship, ultimately striving toward the overarching goal of mitigating the burden of this disease on individuals and communities alike.

Statement of Research Problem

This literature-based thesis addresses critical research inquiries concerning inflammatory breast cancer (IBC) and its societal impact. Specifically, it seeks to elucidate the nature of IBC, including its diagnosis, treatment, and prognosis, with the focus on the significance of early detection. Furthermore, it endeavors to assess the current level of knowledge regarding IBC among primary care physicians and to explore avenues that enhance their understanding, thereby facilitating quicker diagnosis, better prognosis, and improved quality of life for patients. In addition, the thesis aims to investigate the role of existing breast cancer awareness initiatives in reducing incidence rates and to assess the potential for integrating IBC awareness efforts to mitigate the prevalence of this aggressive cancer subtype. Moreover, it seeks to identify strategies for enhancing learning outreach on IBC within educational and workplace settings. Through a comprehensive review of the literature and empirical evidence, this research can provide insight into the multifaceted dimensions of IBC, evaluate the effectiveness of current awareness campaigns, and propose actionable recommendations for bolstering educational initiatives across diverse societal contexts.

Research Objective

This literature-based thesis explores and addresses the following critical research questions:

1. What constitutes inflammatory breast cancer (IBC), and what are the established protocols for its diagnosis and treatment, as well as prognosis, particularly concerning the impact of early detection?

2. What is the existing level of knowledge among primary care physicians regarding inflammatory breast cancer (IBC), and how can this knowledge be augmented to facilitate quicker diagnosis, better treatment and prognosis, and improved quality of life for patients?
3. How have existing breast cancer awareness initiatives contributed to the reduction in breast cancer incidence, and what potential exists for further integration of inflammatory breast cancer awareness efforts to curtail the prevalence of IBC?

Through an exhaustive examination of available literature and empirical evidence, this thesis aims to elucidate the multifaceted dimensions of inflammatory breast cancer, explore the efficacy of existing awareness campaigns in combating breast cancer incidence, and propose actionable recommendations for augmenting educational initiatives surrounding IBC within diverse societal frameworks.

METHODOLOGY

The literature search accessed electronic databases, including PubMed/MEDLINE, Embase, Web of Science, and Google Scholar. The search strategy involved the use of relevant keywords and Medical Subject Headings (MeSH) terms related to inflammatory breast cancer (IBC), primary care providers (PCPs), knowledge, awareness, diagnosis, treatment, prognosis, and educational interventions. Boolean operators (AND, OR) combined search terms for maximum coverage. The search was limited to articles published in English and included studies from 1978 to 2024.

Articles were included if they provided relevant information regarding IBC symptoms, risk factors, epidemiology, diagnostic and treatment approaches, and barriers to early detection strategies for improving education and awareness. Studies conducted in various healthcare settings involving PCPs from different specialties were considered. Letters and editorials were excluded from the analysis.

CHAPTER 1: WHAT IS INFLAMMATORY BREAST CANCER?

Definition and Clinical Features of IBC

Inflammatory breast cancer (IBC) is a unique yet aggressive form of breast cancer (BC). A hallmark feature of IBC is its rapid progression, usually within a period of less than 6 months (Cserni et al., 2018; Dabi et al., 2017; Dushkin et al., 2011; Hance et al., 2005; Hester et al., 2021). In characterizing IBC, there is a rapid onset of erythema ,breast enlargement, peau d'orange (pores of an orange) appearance, , warmth, and edema. High suspicion of IBC is indicated when a patient presents with erythema on at least one-third of the breast. A patient often presents to the primary care physician with skin changes, nipple inversion, and palpable axillary lymphadenopathy. Enlargement of the breast is a direct result of tumor blockage of the lymphatic channels. Although detection of a breast mass is a prevalent symptom in non inflammatory BC cases, it is essential to note that a discrete breast mass does not always accompany IBC (Anderson et al., 2003). The lack of a breast mass contributes to the complicated nature of diagnosing IBC and has led to delays in recognition and treatment initiation (see **Table 1**). IBC is also known for its rapid progression. Patient symptoms typically start progressing within 3–6 months after the appearance of initial symptoms. Because of its fast and aggressive nature, most patients with IBC are diagnosed at advanced stages with locoregional or distant metastasis, stage III or IV (Menta et al., 2018).

Table 1

Common Clinical Presentations of Noninflammatory LABC and IBC

Feature	Noninflammatory Locally Advanced Breast Cancer (LABC)	Inflammatory Breast Cancer (IBC)
Clinical Presentation	Typically presents as palpable breast mass or lump; may have skin changes or nipple retraction.	Presents with rapid onset of diffuse breast swelling, erythema, peau d'orange appearance, and nipple changes.
Lymph Node Involvement	Breast mass, skin dimpling or retraction, nipple discharge or inversion, and axillary lymphadenopathy.	Breast enlargement, warmth, redness, tenderness, skin changes, inverted nipple, and peau d'orange.
Rate of Progression	Usually progresses gradually over time, allowing for detection and intervention.	Progresses rapidly with aggressive behavior, often leading to delayed diagnosis.
Imaging Findings	Possible mass or calcifications in mammogram; ultrasound and MRI used for staging.	Normal or diffuse skin thickening in mammogram; MRI and PET-CT more sensitive for detecting extent of disease.
	Often presents with regional lymph nodes; may have distant metastases.	Frequently presents with axillary lymph nodes and distant metastases.
Treatment Approach	Multimodal treatment including possible neoadjuvant therapy, surgery, radiation, and adjuvant therapy.	Neoadjuvant chemotherapy followed by surgery and adjuvant therapy; immunotheraoy for triple-negative cases and targeted therapy for HER2-positive cases.
Prognosis and Survival	Largely depends on tumor size, tumor grade, lymph node involvement, and response to treatment; overall survival variable.	Poorer prognosis compared with other types of breast cancer; lower survival rate and higher risk of recurrence.

Note. This table compares the common clinical presentations of noninflammatory locally advanced breast cancer (LABC) with inflammatory breast cancer (IBC). HER2 = human epidermal growth factor receptor 2; MRI = magnetic resonance imaging; PET-CT = positron emission tomography-computed tomography. Information from (Anderson et al., 2003)

Epidemiology and Risk Factors Associated With IBC

Although IBC accounts for a small percentage of all breast cancer cases worldwide (approximately 2%–5%), its elusive and aggressive nature poses significant challenges for patients and clinicians alike (Hester et al., 2021; Hirko et al., 2009; Menta et al., 2018; Newman and Lynce 2023). There is a higher incidence of IBC in women of African American descent or from parts of western and northern Africa, including Egypt (Wood et al., 2002). IBC rates are 5%–7% in Morocco and Tunisia and around 11% in Egypt compared with about 2%–4% in the United States (8). The average age for those diagnosed with IBC tends to be lower (40–59 years) than the average age for those diagnosed with LABC (late 50s to early 60s). Patients with a higher body mass index (BMI) are also noted to be at risk of developing IBC (Hester et al., 2021). A genetic mutation or family history is a known risk factor for BC in general. However, no substantial evidence associates inherited genetic mutation and family history of BC with development, in particular for IBC.

Challenges in Early Diagnosis and Impact on Prognosis

IBC often presents with nonspecific symptoms. These symptoms include breast redness and swelling, warmth, skin changes, and potential changes to the nipple. Unlike other types of breast cancer, IBC does not typically present with a distinct, palpable lump, and as a result, possible misdiagnosis and delays in diagnosis often occur. Because most patients being evaluated for BC present with a breast mass, most providers are likely to misinterpret symptoms as being related to IBC and tend to pursue alternative diagnoses.

In addition, IBC is characterized by rapid disease progression in which the cancer cells infiltrate the breast tissue and lymphatic vessels quickly. The rapid growth in cancer cells can lead to advanced-stage disease before symptoms are clinically apparent. This can further complicate early diagnosis, delay treatment initiation, and negatively affect patient prognosis.

Moreover, IBC presents with symptoms that often mimic less severe, benign conditions such as mastitis, cellulitis, dermatitis, breast abscess, or Paget's disease. This situation can lead to misdiagnosis and delayed evaluation by healthcare providers (Devi et al., 2022; Devi et al., 2023; , 33). **Table 2** lists commonly misdiagnosed conditions that present similarly to IBC.

Table 2

Symptoms of IBC and Common Misdiagnoses

Symptoms of Inflammatory Breast Cancer (IBC)	Common Misdiagnoses	Symptoms
Rapid onset of breast swelling or enlargement.	Mastitis	Breast tenderness, redness, and warmth; may have fever and flu-like symptoms.
Persistent breast redness resembling rash or bruise.	Cellulitis	Red, swollen, warm, and tender skin; may have fever and chills.
Thickening or dimpling of breast skin.	Dermatitis	Itchy, red, and swollen skin; may have rash or blisters.
Peau d'orange (orange peel texture) appearance of breast skin.	Breast Abscess	Painful lump, pus-filled pocket, redness, and warmth; may have fever.
Inverted or retracted nipple.	Paget's Disease of the Breast	Crusty, scaly, or oozing skin around nipple; may have itching and burning.

Note. This table shows a comparison of the symptoms of IBC with the symptoms of five other less severe conditions that often lead to misdiagnoses. Information from (Devi et al., 2022; Devi et al., 2023; Hester et al., 2021)

Despite continuing education among medical providers, IBC awareness is usually directed toward oncology teams instead of other specialty providers, the most important being primary care clinicians (Devi et al., 2022; Devi et al., 2023). Because of its rarity and atypical presentation, many providers need more knowledge and experience in recognizing IBC symptoms and differentiating them from other diseases. Imaging studies, such as mammograms, ultrasounds, and magnetic resonance imaging (MRI), may also miss characteristic features of IBC, especially in its early stages. Subtle changes in breast anatomy, including skin thickening and lymphatic involvement, may be slight or difficult for radiologists to visualize in imaging studies, leading to false-negative results, and further delaying diagnosis (Barkana et al., 2022).

Lastly, challenges in early diagnosis of IBC can have a negative psychosocial impact on patients. Diagnostic delays and uncertainty regarding IBC diagnosis can naturally cause anxiety, distress, and feelings of helplessness in patients (Rosenbluth and Overmoyer, 2019). Emotional stressors like these can further exacerbate the challenges of navigating the healthcare system and seeking timely treatment.

CHAPTER 2: DIAGNOSTIC METHODS FOR IBC

Overview of Current Diagnostic Modalities

Routine screening and imaging play a crucial role in disease diagnosis and management. Although imaging techniques have certainly improved through the years and have contributed to a slight increase in IBC recognition, expertise in the field is also necessary to aid in these diagnoses. IBC requires a more comprehensive evaluation compared with LABC (Anderson et al., 2003). Diagnosis includes clinical examination, imaging, and biopsy. IBC is not easily diagnosed with imaging such as a mammogram. As seen in Jennifer's story, a mammogram was done and failed to detect any malignancy upon examination (Susan G. Komen, 2021).

With symptom onset, patients are encouraged at their discretion to see their primary care providers for a physical examination of the affected breast. Providers should be wary of crucial symptoms of IBC, including rapid onset of breast redness, swelling, warmth, and peau d’orange appearance in which the skin resembles an orange peel. Concern for IBC is warranted when redness is present in at least one-third of the breast (Dushkin et al., 2011).

After examination and noted suspicion of IBC, additional imaging studies are used to evaluate the breast and confirm the presence of malignancy. Whereas mammography and ultrasound (US) are standard diagnostic imaging techniques for BC, mammograms only detect 43% of primary lesions for IBC, with the most common finding being skin thickening (Günhan-Bilgen et al., 2002; Guo et al., 2002; Papalouka et al., 2018; Wang 2022; Yang et al., 2008). Mammography can indicate trabecular thickening or architectural distortion without evidence of a definitive mass.

Breast ultrasound can help assess the extent of disease involvement and identify suspicious masses or lymph nodes. A hallmark feature of IBC is skin thickening and edema, which ultrasound is especially useful in detecting (Günhan-Bilgen et al., 2002; Guo et al., 2002). With ultrasound, clinicians can detect dermal lymphatic involvement and evaluate peau d'orange associated with IBC. Because this imaging method uses sound vibrations reflecting off solid masses, US can detect breast masses, lesions, and other architectural distortions (Günhan-Bilgen et al., 2002; Guo et al., 2002). US is particularly useful in guiding biopsy procedures.

MRI is one of the more accurate tests for detecting lesions in breasts with IBC (Dushkin et al., 2011). This technique is extremely sensitive for the detection of any breast abnormality and can assist in determining the extent of the disease, tumor size, and if there is evidence of locoregional or distant metastasis (Yang et al., 2008).

Role of Biopsy in Confirming Diagnosis and Characterizing Tumor

A biopsy is the primary diagnostic procedure utilized to confirm the presence of cancer cells within breast tissue. When clinical suspicion arises regarding inflammatory breast cancer (IBC), breast clinicians often perform a biopsy of the affected breast tissue for pathological review. Various biopsy methods include punch biopsy, fine-needle aspiration (FNA), core needle or surgical biopsy. FNA, a minimally invasive procedure, involves the use of a small needle to collect potential tumor cells from breast tissue. In contrast, core needle biopsy utilizes a larger needle to procure tissue samples. In addition, tissue obtained from surgical procedures such as lumpectomy or mastectomy undergoes pathology assessments to provide further diagnostic information.

Biopsies serve as pivotal tools in categorizing IBC into specific molecular subtypes. This classification is based on the expression (or lack of expression) of hormone receptors (HRs) and human epidermal growth factor receptor 2 (HER2). Immunohistochemical staining of biopsy specimens detects cancer cells' estrogen/progesterone receptor and HER2 receptor of the cancer cells, guiding clinicians toward targeted therapies tailored to tumor cell expression profiles.

Moreover, pathology assessment of tumor grade evaluates the differentiation degree and aggressiveness of the tumor cells. Microscopic examination of cellular morphology and architectural patterns aids in determining tumor grade. Higher-graded tumors, characterized by poorer differentiation and heightened proliferation rates, often denote a more aggressive disease course.

Furthermore, biopsies facilitate the evaluation of biomarkers associated with tumor aggressiveness, treatment response, and prognosis in IBC. Molecular diagnostic assays analyze gene expression, proteins, and genomic alterations to predict responses to chemotherapy, targeted therapy, or immunotherapy. This type of personalized treatment planning enhances therapeutic efficacy and identifies potential therapeutic targets.

Biopsies also play a crucial role in assessing tumor response to neoadjuvant chemotherapy (NADJC). Comparison of pre-and post-chemotherapy specimens aids in evaluating tumor regression, necrosis, and residual cancer cells within the breast tissue. A pathologic complete response (pCR), marked by the absence of invasive cancer in the breast and lymph nodes posttreatment, heralds positive long-term outcomes and guides further treatment decisions.

Lastly, biopsies are instrumental in suspected distant organ progression following recent imaging. Biopsies of distant organs confirm malignancy consistency with primary cancer diagnoses, enabling appropriate treatment adjustments. This practice, common across various cancer types, underscores the indispensable role of biopsies in clinical management.

Advancements in Imaging Techniques and Molecular Diagnostics

Advancements in imaging techniques and molecular diagnostics have improved the early detection and characterization of IBC (see **Table 3**). Imaging techniques such as MRI, positron emission tomography-computed tomography (PET-CT), molecular breast imaging (MBI), and contrast-enhanced ultrasound (CEUS) are used in efforts to diagnose IBC (46).

MRI is a sensitive imaging technique for detecting breast cancer including IBC. Dynamic contrast-enhanced MRI and diffusion-weighted imaging have improved the detection and characterization of IBC lesions. MRI is beneficial for assessing tumor extent, evaluating response to neoadjuvant therapy, and detecting occult metastases (57).

PET-CT combines metabolic information from PET with anatomical detail from CT to provide comprehensive imaging of IBC. PET-CT aids in detecting distant metastases and evaluating treatment response in IBC patients (61). Emerging techniques such as dual-tracer PET-CT and radiomics analysis hold promise for further enhancing the diagnostic accuracy of PET-CT in IBC.

Alongside imaging techniques, molecular diagnostic tests are beneficial in providing valuable prognosis information in IBC or detecting actionable mutations that could be responsive to targeted therapies. Gene expression profiling assays analyze the expression levels of multiple genes associated with tumor aggressiveness and treatment response. Assays like this may help guide personalized treatment decisions for IBC patients.

Liquid biopsy is another molecular diagnostic technique that oncologists may use for additional information regarding a patient's IBC (Gerratana et al., 2021, Maltoni et al., 2020). Liquid biopsy techniques include circulating tumor DNA (ctDNA) analysis and circulating tumor cells (CTCs) enumeration. These tests offer minimally invasive methods for monitoring disease progression and treatment response in IBC. As tumor cells rapidly grow and undergo apoptosis, their contents are released and circulate throughout the blood. The ctDNA is extracted in a simple blood draw and can be sent for further analysis to detect molecular alterations (Gerratana et al., 2021, Maltoni et al., 2020). Because these molecular alterations are detected in real time, may allow for timely adjustments to treatment regimens and early detection of recurrence.

Table 3

Diagnostic Methods Used in Identifying IBC

Diagnostic Method	Description	Role in Diagnosing IBC
Mammography	X-ray imaging of breast tissue used to detect abnormalities.	Detects changes in breast tissue density and calcifications; shows diffuse breast thickening in IBC.
Ultrasound (US)	Sound waves used to create images of breast.	Provides detailed images of breast tissue; identifies masses, fluid collections, or abnormalities in IBC.
Magnetic Resonance Imaging (MRI)	Magnetic fields and radio waves used to generate detailed images of breast.	Provides highly sensitive detection of abnormalities in breast tissue, including IBC lesions and extent of disease spread.
Positron Emission Tomography-Computed Tomography (PET-CT)	Combined PET and CT scans used to produce detailed images of body.	Evaluates metabolic activity and detects areas of increased glucose uptake; helps in staging and detecting metastasis in IBC.
Breast MRI with Diffusion-Weighted Imaging	MRI technique used to assess movement of water molecules in tissues.	Provides functional information about tissue cellularity and tumor aggressiveness; aids in characterizing IBC.
Molecular Breast Imaging (MBI)	Nuclear medicine imaging using radioactive tracer.	Detects breast abnormalities including dense breast tissue; identifies IBC lesions not seen on mammography or ultrasound.
Breast-Specific Gamma Imaging (BSGI)	Breast tissue-specific nuclear medicine imaging using radioactive tracer.	Obtains functional images of breast tissue; detects IBC lesions and treatment response.
Fine-Needle Aspiration (FNA)	Minimally invasive procedure used to collect cells from breast lump or suspicious area.	Provides cellular data for cytological analysis; aids in IBC diagnosis and differentiation from other breast conditions.

Table 3 (con.)

Diagnostic Method	Description	Role in Diagnosing IBC
Core Needle Biopsy	Larger needle used to obtain tissue from breast mass or abnormal mass.	Provides tissue specimens for histological records; assists in confirming presence of cancer cells and determines IBC subtype.
Molecular Profiling Assays	Analysis used to determine gene expression patterns and molecular markers in tumor tissue.	Aids in characterizing biological behavior of IBC; identifies molecular subtypes and guides treatment plans.
Circulating Tumor DNA (ctDNA) Analysis	Analysis used to determine tumor-specific DNA fragments circulating in blood.	Detects genetic mutations and molecular alterations associated with IBC, including mismatch repair status, microsatellite instability, and tumor mutation burden; assists in monitoring disease progression and treatment response.

Note. This table summarizes 11 diagnostic methods that are used in identifying inflammatory breast cancer (IBC). For each method, a description is given together with its role in diagnosing IBC. Information from (Gerratana et al., 2021, Maltoni et al., 2020; Miricescu et al)

CHAPTER 3: NOVEL TREATMENT APPROACHES FOR IBC

Overview of Standard Treatment Modalities

Because of its aggressive nature and the likelihood of recurrence and metastasis, the standard treatment for IBC uses multimodal therapy. Multimodal therapy includes neoadjuvant chemotherapy, surgery, adjuvant radiation, and targeted therapy. Treatment may vary depending on the stage of the cancer, the presence of hormone receptors or HER2 receptors, and individual patient factors such as other comorbidities and patient preference.

Treatment for IBC begins with neoadjuvant chemotherapy. Neoadjuvant chemotherapy (NADJC) is done before surgery to shrink the size of the tumor and to prevent further growth of the cancer (Kridis et al., 2022; Newman and Lynce 2023). With a smaller tumor present, NADJC allows the tumor to be more amenable to surgical resection and reduces the risk of distant metastasis. Anthracycline- and taxane-based chemotherapy are standard regimens used for IBC treatment (Ning et al., 2019).

Following neoadjuvant therapy, surgery is the next step that plays a crucial role in managing IBC. Different types of surgery are offered, and the extent of surgical intervention can vary between patients depending on the response to NADJC and the degree of disease involvement (Kridis et al., 2022). Surgical options include modified radical mastectomy, a procedure involving removal of the entire breast tissues alongside the axillary lymph nodes, or breast-conserving surgery (lumpectomy), followed by radiation therapy.

Radiation therapy is commonly administered following surgery to the affected breast and regional lymph nodes to reduce the risk of local recurrence. In some cases, patients may present with unresectable disease or residual tumor burden following chemotherapy and are therefore offered radiation as a part of their initial treatment.

Targeted Therapies for HER2-Positive IBC

Alongside radiation, targeted therapy may be helpful for patients overexpressing HER2. There are several anti-HER2-targeted drugs used in BC treatment, such as trastuzumab (Herceptin; Genentech, South San Francisco, CA) and pertuzumab (Perjeta; Genentech, South San Francisco, CA). When used in combination with chemotherapy, anti-HER2 drugs have been shown to improve outcomes for those with IBC. Targeted therapies for HER2-positive inflammatory breast cancer (IBC), such as trastuzumab and pertuzumab, have significantly improved treatment outcomes and survival rates for patients with this aggressive subtype of breast cancer (Ueno et al., 2018).

Trastuzumab is a monoclonal antibody that targets the HER2 protein, which is overexpressed in approximately 20%–30% of breast cancers including a subset of IBC cases (35, 55). By binding to the HER2 receptor on cancer cells, trastuzumab inhibits HER2-mediated signaling pathways that lead to growth inhibition, apoptosis (cell death), and immune-mediated destruction of HER2-positive cancer cells (Grace et al., 1985). Trastuzumab is typically administered intravenously and may be used in combination with chemotherapy as part of standard treatment regimens for HER2-positive IBC (Ueno et al., 2018).

Pertuzumab is another monoclonal antibody that targets HER2 but works through a mechanism different from trastuzumab (Grace et al., 1985; Ueno et al., 2018). Pertuzumab binds to a different domain of the HER2 receptor compared with trastuzumab, preventing HER2 from forming heterodimers with other HER family receptors (such as HER3), a step essential for tumor growth and survival. By inhibiting HER2 dimerization, pertuzumab enhances the anti-tumor activity of trastuzumab and chemotherapy. Pertuzumab is often used in combination with trastuzumab and chemotherapy as part of neoadjuvant or adjuvant treatment for HER2-positive IBC.

The combination of trastuzumab, pertuzumab, and chemotherapy has become the standard of care for HER2-positive IBC based on clinical trials such as the CLEOPATRA trial results (55). The CLEOPATRA trial proved that combination therapy for IBC led to a six-month improvement in progression-free survival (55). This dual HER2-targeted therapy regimen has demonstrated superior efficacy compared with trastuzumab alone, leading to improved response rates, progression-free survival, and overall survival in patients with HER2-positive metastatic breast cancer including IBC. The addition of pertuzumab to trastuzumab-based therapy has further optimized treatment outcomes and is now recommended as first-line therapy for HER2-positive IBC.

Although targeted therapies such as trastuzumab and pertuzumab are generally well tolerated, they can cause specific adverse effects including cardiotoxicity (e.g., decreased left ventricular function), infusion reactions, and gastrointestinal symptoms. Close monitoring of cardiac function is essential during treatment with HER2-targeted therapies, and appropriate interventions may be required to manage adverse effects and optimize treatment outcomes (55).

Hormonal Therapies for Hormone Receptor-Positive IBC

Hormonal therapies play a crucial role in managing hormone receptor-positive IBC, which represents a subtype of IBC characterized by the expression of estrogen receptor (ER) and progesterone receptor (PR) in tumor cells. Drugs such as tamoxifen or aromatase inhibitors inhibit the

Tamoxifen is a selective estrogen receptor modulator (SERM) that competitively binds to estrogen receptors, thereby blocking the estrogen-mediated signaling pathways responsible for promoting tumor growth and proliferation in hormone receptor-positive breast cancer including IBC (35). By inhibiting estrogen receptor activation, tamoxifen exerts anti-estrogenic effects and induces apoptosis (cell death) in hormone receptor-positive tumor cells. Tamoxifen is typically administered orally and is considered a cornerstone of hormonal therapy for premenopausal and postmenopausal women with hormone receptor-positive IBC.

Aromatase inhibitors are another class of hormonal therapy agents used in the treatment of hormone receptor-positive breast cancer, particularly in postmenopausal women. Aromatase inhibitors block the activity of the enzyme aromatase, which converts androgens into estrogens in peripheral tissues (Kridis et al., 2022). By reducing circulating estrogen levels, aromatase inhibitors effectively deprive hormone receptor-positive breast cancer cells of estrogen signaling, leading to tumor regression and inhibition of disease progression. Common aromatase inhibitors include anastrozole, letrozole, and exemestane (Kridis et al., 2022).

In some cases, hormonal therapies such as tamoxifen or aromatase inhibitors may be used with other agents to enhance treatment efficacy and overcome resistance mechanisms in hormone receptor-positive IBC (Kridis et al., 2022). For example, combination therapy with a cyclin-dependent kinases 4 and 6 (CDK4/6) inhibitor (e.g., palbociclib, ribociclib, abemaciclib) has shown synergistic effects in preclinical studies and clinical trials. These effects led to improved progression-free survival and overall survival in patients with hormone receptor-positive metastatic breast cancer including IBC. In addition, hormonal therapies may be combined with targeted therapies such as HER2-targeted agents (e.g., trastuzumab, pertuzumab) in patients with hormone receptor-positive/HER2-positive IBC to maximize treatment benefits.

Following primary treatment (e.g., surgery, chemotherapy, radiation therapy), hormonal therapies are commonly used as adjuvant therapy in hormone receptor-positive IBC patients to reduce the risk of disease recurrence and improve long-term outcomes. Adjuvant hormonal therapy aims to suppress residual tumor cells and prevent the development of metastatic disease, thereby prolonging disease-free survival and overall survival in hormone receptor-positive IBC patients.

Hormonal therapies such as tamoxifen and aromatase inhibitors play a critical role in the management of hormone receptor-positive IBC, offering effective and well-tolerated treatment options for patients with this subtype of breast cancer (Kridis et al., 2022). These agents, alone or in combination with other modalities, represent vital components of multidisciplinary treatment approaches aimed at optimizing outcomes in hormone receptor-positive IBC patients.

Immunotherapy and Other Emerging Treatment Strategies

Clinical trials available for BC patients may also allow IBC patients to be enrolled in treatment settings, but clinical trials that target IBC patients specifically are limited overall. These clinical trials can evaluate novel treatment approaches, including new chemotherapy regimens, targeted therapies, immunotherapy, and progressive surgical techniques.

Treatment for IBC is often in a multidisciplinary setting that involves members from several teams, such as medical oncologists, radiation oncologists, surgical oncologists, and other specialists, depending on the extent of the disease (Miricescu et al., 2020). The goal of treatment is to eradicate the disease, emphasizing a complete response to therapy. If the disease, however, is known to be locally or distantly advanced, the goal of treatment is shifted to controlling the disease and improving the patient's quality of life.

Immunotherapy involves harnessing the body's immune system to recognize and eradicate cancer cells. Immune checkpoint inhibitors, which target proteins that inhibit immune responses (e.g., programmed death-1 [PD-1], programmed death-ligand 1 [PD-L1]), have shown efficacy in various cancer types including breast cancer. Clinical trials are evaluating the use of immune checkpoint inhibitors alone or in combination with other therapies in patients with IBC. Preliminary data suggest that immunotherapy may have activity in a subset of IBC patients, particularly those with high tumor mutational burden or immune cell infiltration.

Targeted therapies directed against specific molecular pathways implicated in IBC pathogenesis are under investigation. For example, HER2-targeted therapies, such as trastuzumab and pertuzumab, have demonstrated efficacy in HER2-positive IBC and are commonly used with chemotherapy. Other targeted agents, including phosphatidylinositol 3-kinase (PI3K) inhibitors, protein kinase B (AKT) inhibitors, and mammalian target of rapamycin (mTOR) inhibitors, are being evaluated in clinical trials for their potential to inhibit aberrant signaling pathways in IBC tumors (Miricescu et al., 2020).

Poly (ADP-ribose) polymerase (PARP) inhibitors are drugs that target DNA repair mechanisms in cancer cells (Curtin et al., 2013). PARP inhibitors have shown activity in breast cancer patients with breast cancer (*BRCA*) gene mutations, leading to synthetic lethality and tumor cell death. Clinical trials are investigating the use of PARP inhibitors as monotherapy or in combination with other agents in patients with *BRCA*-mutated IBC or triple-negative breast cancer (Curtin et al., 2013).

Angiogenesis inhibitors target the formation of new blood vessels that supply nutrients to tumors, thereby inhibiting tumor growth and metastasis. Bevacizumab, a monoclonal antibody targeting vascular endothelial growth factor (VEGF), has been studied in combination with chemotherapy in patients with IBC. Other angiogenesis inhibitors, such as tyrosine kinase inhibitors (e.g., sunitinib, sorafenib), are also being evaluated in clinical trials for their potential to disrupt tumor angiogenesis and improve outcomes in IBC patients.

Research is ongoing to identify novel chemotherapeutic agents with improved efficacy and reduced toxicity profiles for treating IBC. Nanoparticle-based drug delivery systems, liposomal formulations, and antibody-drug conjugates (ADCs) are being investigated to enhance the delivery of chemotherapy drugs specifically to tumor cells while sparing normal tissues. These innovative approaches aim to improve treatment outcomes and quality of life for patients with IBC.

Combinatorial approaches involving multiple treatment modalities, such as chemotherapy, targeted therapy, immunotherapy, and radiation therapy, are being explored to enhance treatment efficacy and overcome resistance mechanisms in IBC. By targeting multiple signaling pathways and biological processes implicated in IBC pathogenesis, combination therapies may offer synergistic effects and improve patient outcomes compared with single-agent approaches.

Immunotherapy and other emerging treatment strategies represent promising avenues for improving outcomes in patients with IBC. Clinical trials are underway to evaluate these novel therapies for safety, efficacy, and optimal sequencing in managing IBC. Continued research efforts and collaborative initiatives are essential for advancing the field of IBC treatment and improving survival rates for patients affected by this aggressive form of breast cancer.

Prognosis and Survival Outcomes

Despite advances in treatment regimens, IBC is associated with poor prognosis and inferior survival outcomes compared with LABC subtypes. The five-year survival rate for IBC is notably lower at 25%–50%, emphasizing the crucial need for continued research to improve early detection, treatment efficacy, and long-term outcomes for this patient population (Hirko et al., 2007-2009).

Prognosis and survival outcomes for inflammatory breast cancer are generally worse than other types of breast cancer. IBC is characterized by its aggressive nature, rapid disease progression, and propensity for early metastasis, contributing to its overall poorer prognosis.

The stage of IBC at the time of diagnosis is a critical determinant of prognosis. IBC is typically diagnosed at a more advanced stage compared with other types of breast cancer and has a higher proportion of cases presenting as stage III or IV disease. The advanced-stage disease is associated with a poorer prognosis and shorter overall survival because of the increased likelihood of tumor spread to regional lymph nodes and distant organs.

Lymph node involvement is common in IBC and strongly predicts poor prognosis. IBC often presents with extensive lymphovascular invasion and lymphatic obstruction, leading to early metastasis to regional lymph nodes and distant sites. Lymph node metastases indicate more aggressive disease biology associated with decreased survival rates.

The hormone receptor status of IBC tumors, particularly estrogen receptor (ER) and progesterone receptor (PR) expression, influences prognosis and treatment response. Hormone receptor-positive IBC tumors tend to have a better prognosis and may respond favorably to endocrine therapy, such as tamoxifen or aromatase inhibitors (35). In contrast, hormone receptor-negative IBC tumors are associated with a more aggressive phenotype and poorer survival outcomes.

Amplification or overexpression of the human epidermal growth factor receptor 2 (*HER2*) gene occurs in a subset of IBC cases and is associated with aggressive tumor behavior and worse prognosis. HER2-positive IBC tumors may respond to targeted therapies such as trastuzumab and pertuzumab, which can improve survival outcomes in this subgroup of patients.

Response to treatment, including chemotherapy, targeted therapy, and radiation therapy, influences prognosis in patients with IBC. Neoadjuvant chemotherapy is often used to downstage the tumor and improve surgical outcomes, followed by adjuvant therapy to reduce the risk of recurrence. Patients who achieve a pathologic complete response (pCR) to neoadjuvant therapy have a better prognosis and may experience long-term survival benefits (Ning et al., 2019).

The molecular characteristics of IBC tumors, including molecular subtypes (e.g., basal-like, luminal, HER2-enriched) and genomic alterations, can impact prognosis and treatment response. Basal-like IBC tumors, characterized by high proliferative activity and aggressive behavior, are associated with poorer survival outcomes compared with other subtypes.

Overall, the prognosis and survival outcomes of inflammatory breast cancer are influenced by a combination of clinical, pathological, and molecular factors. Multimodal treatment approaches, including systemic therapy, surgery, and radiation therapy, are typically employed to manage IBC and improve patient outcomes. However, because of its aggressive nature and high risk of recurrence, IBC remains a challenging disease to treat. This fact underscores the importance of early detection, personalized treatment strategies, and ongoing research efforts to improve outcomes for patients affected by this rare and aggressive form of breast cancer.

Ongoing Research and Future Directions

Ongoing research and future directions for inflammatory breast cancer (IBC) encompass a wide range of areas that include improving early detection, optimizing treatment strategies, elucidating the underlying molecular mechanisms, and addressing disparities in healthcare access.

Efforts are underway to identify novel biomarkers associated with IBC aggressiveness, treatment response, and prognosis. Biomarker discovery studies aim to uncover molecular signatures, genetic mutations, and protein expression patterns that can serve as diagnostic, prognostic, and predictive markers in IBC. These biomarkers may help guide treatment decisions, monitor disease progression, and identify patients at high risk of recurrence.

With advances in molecular profiling technologies, there is growing interest in implementing precision medicine approaches for IBC. Precision oncology initiatives aim to tailor treatment regimens to the molecular characteristics of individual tumors, matching patients with targeted therapies based on specific genetic alterations or biomarker profiles (Korde et al., 2021). Clinical trials evaluating targeted therapies, immunotherapies, and combination treatment approaches are underway to assess their efficacy in IBC.

Immunotherapy has emerged as a promising treatment approach for breast cancer including IBC. Clinical trials are investigating the efficacy of immune checkpoint inhibitors, adoptive T-cell therapies, and cancer vaccines in patients with IBC. Immunotherapy may help harness the body's immune system to recognize and eliminate tumor cells, leading to durable responses and improved survival outcomes in patients with advanced or metastatic IBC (Kridis et al., 2022).

Advanced imaging techniques, such as radiomics analysis and molecular imaging, hold promise for improving the early detection and characterization of IBC. Radiomics-based approaches aim to extract quantitative imaging features from medical images and correlate them with clinical outcome, treatment response, and disease progression (Conti et al., 2021). Molecular imaging modalities, such as positron emission tomography and magnetic resonance imaging, are being explored for their ability to detect molecular biomarkers and assess treatment response in IBC.

Addressing disparities in healthcare access and improving outcomes for underserved populations with IBC are critical research priorities. Initiatives focused on community outreach, patient navigation, and health education aim to raise awareness about IBC, promote early detection, and facilitate timely and appropriate care access (Devi et al., 2023). Research efforts also seek to identify barriers to healthcare access, develop interventions to address disparities, and improve healthcare delivery for all patients with IBC.

Collaborative research networks and consortia bring together researchers, clinicians, patient advocates, and industry partners to advance the field of IBC research. These collective efforts facilitate data sharing, promote interdisciplinary collaboration, and accelerate the translation of research findings into clinical practice. By fostering collaboration and innovation, research networks are able to drive progress in IBC research and improve patient outcomes.

Ongoing research and future directions for inflammatory breast cancer span many areas, including biomarker discovery, precision medicine, immunotherapy, imaging technologies, disparities in healthcare access, and collaborative research initiatives. By addressing these research priorities, the scientific community strives to advance the understanding of IBC, develop more effective treatment strategies, and ultimately improve outcomes for patients with this aggressive form of breast cancer.

CHAPTER 4: CHALLENGES AND OPPORTUNITIES IN IBC MANAGEMENT

Barriers to Early Diagnosis and Treatment Initiation

Barriers to early diagnosis and treatment initiation for inflammatory breast cancer (IBC) can significantly impact patient outcomes and pose challenges for healthcare providers. IBC often presents with nonspecific symptoms such as breast erythema, swelling, warmth, and skin changes that can be mistaken for benign conditions such as mastitis or dermatitis. Unlike other types of breast cancer, IBC may not present with a palpable lump or mass, making it difficult to detect through routine breast examinations. The atypical clinical presentation of IBC can lead to delays in diagnosis as patients and healthcare providers may not recognize the significance of these symptoms.

Awareness needs to be heightened among healthcare providers about the clinical features and diagnostic criteria of IBC. Primary care physicians may not be familiar with the characteristic signs of IBC and may fail to consider it as a differential diagnosis when evaluating patients with breast symptoms (Devi et al., 2022; Devi et al., 2023). As a result, IBC may be misdiagnosed or overlooked, leading to delays in referral to specialists and initiation of appropriate diagnostic workup.

Conventional imaging techniques such as mammography and ultrasound may only sometimes detect the diffuse nature of IBC, particularly in the early stages of the disease (Guo et al., 2018). IBC lesions may be missed or underestimated in imaging studies, leading to false-negative results or inconclusive findings. This can delay the diagnosis and initiation of treatment and allow the cancer to progress unchecked.

Specialized care, including breast imaging centers and multidisciplinary cancer clinics, may be limited to specific geographic regions or healthcare systems. Patients in rural or underserved areas may face challenges accessing timely diagnostic evaluations and specialized treatments for IBC. Long wait times for appointments and delays in scheduling diagnostic tests may further exacerbate delays in diagnosis and treatment initiation.

Psychosocial and cultural factors can also influence the timing of diagnosis and treatment initiation for IBC. Fear, stigma, and cultural beliefs about cancer may prevent patients from seeking medical attention or adhering to recommended screening guidelines. In addition, socioeconomic factors such as lack of health insurance, financial constraints, and transportation barriers may impede access to timely healthcare services.

Strategies to Improve Awareness, Education, and Access to Care

Improving awareness, education, and access to care for patients with inflammatory breast cancer requires a multifaceted approach that involves healthcare providers, policymakers, advocacy organizations, and community stakeholders. These strategies are briefly summarized as follows:

1. Public awareness campaigns can be launched to increase recognition of the signs and symptoms of IBC among the general population. These campaigns can utilize various channels, including social media, television, radio, print media, and community events, to disseminate information about IBC and encourage early detection through self-examination and prompt medical evaluation.

2. Targeted education and training programs for healthcare providers can be organized to improve awareness and understanding of IBC. Continuing medical education courses, workshops, and conferences can update clinicians on the latest diagnostic and treatment guidelines for IBC and strategies for effectively communicating with patients about the disease.
3. Evidence-based clinical practice guidelines can be developed for diagnosing, staging, and treating IBC. These guidelines can help standardize care practices, reduce variability in clinical decision-making, and ensure that patients receive appropriate and timely interventions based on the latest scientific evidence.
4. Patient navigation programs can be implemented to assist individuals diagnosed with IBC in interacting with the complex healthcare system and accessing appropriate resources and services. Patient navigators can serve as advocates and guides who provide support, information, and assistance to patients throughout their cancer journey from diagnosis to treatment and survivorship.
5. Multidisciplinary care teams can be established that are comprised of oncologists, surgeons, radiation oncologists, pathologists, radiologists, nurses, social workers, and other healthcare professionals with expertise in treating IBC. Multidisciplinary teams can collaborate to develop individualized treatment plans, coordinate care delivery, and address the comprehensive needs of patients.
6. Community organizations, faith-based groups, schools, and local health departments can be engaged to raise awareness about IBC and promote health literacy. Community outreach programs can involve educational seminars,

support groups, health fairs, and outreach events targeting underserved populations to ensure that all individuals have access to accurate information about IBC and available resources (50).

7. Telemedicine and telehealth services can be expanded to overcome geographical barriers and improve access to specialized care for patients with IBC, particularly those in rural or remote areas. Telemedicine platforms can enable virtual consultations, remote monitoring, and teleconferencing with healthcare providers to facilitate timely access to expert advice and support.
8. Research and innovation can be supported to advance understanding of IBC and develop novel diagnostic tools, treatment modalities, and supportive care interventions. Collaborative research efforts involving academic institutions, industry partners, and patient advocacy groups can accelerate progress in IBC research and translate scientific discoveries into clinical practice.

By implementing these eight strategies, stakeholders can work together to improve awareness, education, and access to care for patients with IBC, and they can ultimately enhance the outcomes and quality of life for individuals affected by this aggressive form of breast cancer.

How Have Delays in Diagnosis Affected Prognosis?

Delays in diagnosis of IBC can have profound implications for prognosis, given the aggressive nature and rapid progression of this disease. Several factors contribute to the impact of delays on prognosis (Brailey et al., 1986; Rosenbluth et al., 2019).

The advanced stage at the time of diagnosis is a common effect of late diagnosis. IBC tends to be diagnosed at more advanced stages than other types of cancer and LABCs. A delay in diagnosis means that the cancer has had more time to grow and progress within the body, resulting in potential increases in tumor size and an increase in the likelihood of local or distant metastasis (Brailey et al., 1986; Rosenbluth et al., 2019). Once cancer has metastasized to distant organs, quality of life and patient outcomes are impacted negatively.

IBC has a high propensity for early metastasis in which the cancer cells spread to nearby or distant organs before evidence of a primary tumor is even apparent. Common sites of metastasis are bones, lungs, liver, and brain (Maltoni et al., 2020). Unfortunately, most patients with distant metastasis succumb to their illness because of deficiencies and failure of these specific organs. For metastatic IBC, the prognosis is significantly worse and can limit the amount of treatment options available (Maltoni et al., 2020).

Delays in diagnosing IBC can also postpone the initiation of treatment and limit the amount of targeted therapy that can be utilized for specific receptor-expressing cancer cells (Rosenbluth et al.,). IBC most likely overexpresses HER2, making it amenable to targeted therapies such as Herceptin, a cancer drug that directly targets HER2 receptors and prevents additional cell growth and division (Kridis et al., 2022). Because treatment is targeted at shrinking the tumor, treatment postponement allows the cancer cells to continue to grow in an unchecked manner. This situation leads to worse patient outcomes and decreased chances of survival or long-term remission.

Delayed diagnosis not only affects patient prognosis but also has a direct impact on psychosocial factors. Patients experience significant amounts of stress, anxiety, and depression when they seek medical attention for IBC at symptom onset and have difficulty getting a definitive diagnosis until months later (48). In addition, because late diagnosis of IBC is often associated with advanced-stage and distant metastasis, patients are likely to experience psychological distress and uncertainty regarding the diagnosis. Psychological distress can influence patients in poor treatment adherence, quality of life, and overall well-being, and these effects can exacerbate the challenges of managing the disease.

Primary care providers (PCPs) are the first point of contact for all patients with any concerning symptoms. Patients with any health-related issues visit their PCPs for a first look (Devi et al., 2023, 20). In the United States, PCPs are the gatekeepers of providers, and they essentially determine when an outside referral to a different specialist is necessary. Since most IBC-related awareness and education tend to be directed toward the oncology specialty, PCPs are at a significant disadvantage in helping screen and diagnose a patient with IBC. The lack of knowledge of IBC in primary care physicians contributes to the patient's late diagnosis and potentially poor prognosis (19, 20). IBC is often misdiagnosed because the symptoms are similar to those of mastitis. However, it is essential to note that a mastitis diagnosis is often odd in the setting of a woman who has not been recently breastfeeding.

DISCUSSION

Recommendations for Implementation of IBC Awareness

Throughout this thesis, IBC symptoms, diagnostic modalities, treatment approaches, and educational awareness were explored to address barriers for diagnosis and research techniques and to help improve diagnosis and prognosis. A review of standard care diagnostic methods, treatments, and provider awareness of IBC was given, emphasizing the challenges posed in diagnosing IBC.

Inflammatory breast cancer represents a rare and aggressive subtype of breast cancer characterized by rapid onset symptoms and poor prognosis. Despite its distinct clinical presentation, IBC remains underrecognized and frequently misdiagnosed, and this situation lead to delays in treatment initiation and worse outcomes for patients. This discussion explores how advancements in diagnostic methods and novel treatments for IBC can contribute to raising awareness, improving diagnosis, and enhancing prognosis.

One of the fundamental challenges in managing IBC is the need for more awareness among healthcare providers and the public. Because of its rarity and atypical presentation, IBC may be mistaken for benign conditions or other forms of breast cancer. By exploring and disseminating information about the clinical features and diagnostic criteria of IBC, healthcare professionals can become better equipped to recognize and promptly refer patients for further evaluation. Educational campaigns targeting healthcare providers and the public can help raise awareness about the signs and symptoms of IBC and can help empower individuals to seek timely medical attention to facilitate early diagnosis.

Advancements in diagnostic methods play a crucial role in improving the accuracy and timeliness of IBC diagnosis. As a result of its diffuse nature, the detection of IBC may be less sensitive to traditional imaging modalities like mammography and ultrasound. However, emerging techniques such as magnetic resonance imaging (MRI), positron emission tomography-computed tomography (PET-CT), and molecular imaging offer greater sensitivity and specificity in detecting IBC lesions and assessing disease extent. In addition, molecular profiling assays and liquid biopsy techniques hold promise for identifying biomarkers associated with IBC and for facilitating early detection and personalized treatment approaches.

Early diagnosis of IBC is paramount for optimizing treatment outcomes and enhancing prognosis. Delayed diagnosis and treatment initiation are associated with higher rates of disease progression, distant metastasis, and mortality in patients with IBC. By exploring novel treatments and therapeutic strategies, such as targeted therapies, immunotherapies, and combination regimens, researchers can improve treatment efficacy and survival outcomes for patients with IBC. Furthermore, identifying prognostic biomarkers and therapeutic targets specific to IBC subtypes can help stratify patients based on their risk profile and tailor treatment interventions accordingly.

Overview of Ongoing Clinical Trials and Research Initiatives for IBC

Ongoing clinical trials and research initiatives for inflammatory breast cancer address various aspects of the disease; for example, improving early detection, optimizing treatment strategies, and elucidating the underlying molecular mechanisms. The following overview provides some key areas of ongoing research in IBC.

Several clinical trials are evaluating novel neoadjuvant and adjuvant treatment regimens for IBC, including chemotherapy, targeted therapy, and immunotherapy. These trials aim to optimize treatment efficacy, minimize treatment-related toxicity, and improve long-term outcomes for patients with IBC.

Targeted therapies directed against specific molecular pathways implicated in IBC pathogenesis are under investigation in clinical trials. These trials include HER2-targeted therapies (e.g., trastuzumab, pertuzumab) for HER2-positive IBC and inhibitors of other signaling pathways such as PI3K, AKT, and mTOR (22). These targeted agents are being evaluated as monotherapy or combined with conventional chemotherapy or other targeted agents.

Immunotherapy has emerged as a promising treatment approach in breast cancer including IBC. Clinical trials are investigating the efficacy of immune checkpoint inhibitors (e.g., anti-PD-1, anti-PD-L1 antibodies) alone or in combination with chemotherapy or targeted therapy in patients with IBC. These trials aim to harness the immune system to recognize and eradicate tumor cells, leading to durable responses and improved survival outcomes.

Research initiatives are focused on identifying novel biomarkers and molecular signatures associated with IBC aggressiveness, treatment response, and prognosis. Biomarker discovery efforts aim to facilitate personalized treatment approaches and identify patients most likely to benefit from specific therapies. Biomarkers such as ctDNA, tumor-infiltrating lymphocytes, and gene expression signatures are evaluated in ongoing clinical trials for their prognostic and predictive value in IBC.

Advanced imaging techniques and radiomics analysis are used to identify imaging biomarkers associated with IBC phenotype, treatment response, and prognosis. These efforts aim to improve the accuracy of imaging-based diagnosis, staging, and monitoring of IBC and guide treatment planning and response assessment. Radiomics-based approaches may help uncover subtle imaging features and patterns that predict treatment outcomes and disease progression.

Initiatives focused on optimizing clinical trial design and promoting collaboration among researchers, clinicians, and patient advocates are underway to accelerate the development of new therapies for IBC. These efforts are focused on overcoming challenges related to patient recruitment, trial enrollment, and data sharing, and the results may ultimately advance the field of IBC research and improve patient care.

Potential Biomarkers and Prognostic Indicators for IBC

Identifying potential biomarkers and prognostic indicators for inflammatory breast cancer improves patient outcomes and guides personalized treatment approaches. Several biomarkers have been investigated for their prognostic significance in IBC, offering insights into tumor biology, treatment response, and disease progression (Ning et al., 2019).

Amplification or overexpression of HER2 is observed in a subset of IBC cases and is associated with aggressive tumor behavior and poor prognosis (Korde et al.,2021). HER2-targeted therapies, such as trastuzumab and pertuzumab, have shown efficacy in HER2-positive IBC and are commonly used with chemotherapy as part of neoadjuvant or adjuvant treatment regimens.

Approximately 40%–50% of IBC cases are hormone receptor-positive, indicating the presence of estrogen receptor (ER) and progesterone receptor (PR) expression (35). Hormone receptor-positive IBC tends to be less aggressive and may respond favorably to endocrine therapy, such as tamoxifen or aromatase inhibitors (35). Conversely, hormone receptor-negative IBC is associated with a more aggressive disease course and poorer prognosis.

The Ki-67 protein is a marker of cellular proliferation and is commonly used to assess tumor aggressiveness in breast cancer (44). High Ki-67 expression is associated with increased tumor proliferation and indicates a more aggressive phenotype in IBC. Ki-67 levels may help stratify patients into risk categories and guide treatment decisions, particularly regarding the use of chemotherapy.

A gene identified as phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*), which encodes the p110α catalytic subunit of phosphatidylinositol 3-kinase (PI3K), is frequently observed in breast cancer including IBC (Miricescu et al., 2020). *PIK3CA* mutations are associated with activation of the PI3K/AKT/mTOR signaling pathway, leading to increased cell proliferation, survival, and metastasis. *PIK3CA* mutations may serve as potential therapeutic targets in IBC and are under investigation in clinical trials evaluating PI3K inhibitors.

Loss of E-cadherin expression, a cell adhesion molecule that maintains epithelial integrity, is associated with epithelial-mesenchymal transition (EMT) and tumor invasiveness in breast cancer (Balamurugan et al., 2023). Reduced E-cadherin expression has been observed in IBC and is correlated with lymph vascular invasion, distant metastasis, and poorer survival outcomes (Balamurugan et al., 2023). E-cadherin expression may serve as a prognostic marker in IBC and a potential target for therapeutic intervention.

Molecular profiling studies have identified distinct molecular subtypes of IBC with unique gene expression profiles and clinical characteristics (Molckovsky et al., 2009). The basal-like subtype, characterized by high basal cytokeratin (CK) expression (CK5/6, CK14, CK17), is associated with a more aggressive phenotype and poorer prognosis than other subtypes. Other molecular subtypes, such as luminal and HER2-enriched, may have distinct biological features and treatment responses.

Future Directions for Personalized Medicine and Precision Oncology in IBC

Future directions for personalized medicine and precision oncology in IBC hold significant promise for improving treatment outcomes and patient care.

Advances in genomic sequencing technologies have enabled comprehensive molecular profiling of IBC tumors that can identify novel biomarkers and molecular alterations associated with disease progression, treatment response, and therapeutic resistance. Future research efforts will continue to explore the genomic landscape of IBC and identify predictive biomarkers that can guide personalized treatment strategies and targeted therapies.

The development of targeted therapies directed against specific molecular targets implicated in IBC pathogenesis, such as HER2, hormone receptors, and other oncogenic pathways, will continue to expand. Future clinical trials will evaluate the efficacy of novel targeted agents alone or in combination with conventional therapies (e.g., chemotherapy, radiation therapy, immunotherapy) to improve treatment responses and overcome resistance mechanisms in IBC patients.

Immunotherapy using immune checkpoint inhibitors (e.g., PD-1, PD-L1 inhibitors) has emerged as a promising treatment modality for various cancer types including breast cancer. Future research in IBC will investigate the role of immunotherapy in harnessing the patient's immune system to recognize and eradicate cancer cells, potentially leading to durable responses and improved survival outcomes in IBC patients.

Liquid biopsies, which involve analyzing circulating tumor cells (CTCs), cell-free DNA (cfDNA), and other biomarkers in the blood, offer noninvasive methods for monitoring disease progression, treatment response, and the emergence of resistance mutations in IBC patients (Gerratana et al., 2021; Menta et al., 2018). Future studies will focus on the clinical utility of liquid biopsies and ctDNA analysis in guiding treatment decisions, detecting minimal residual disease, and identifying actionable targets for precision oncology interventions in IBC.

Advances in artificial intelligence (AI) and machine learning algorithms can revolutionize the field of oncology by analyzing large-scale genomic, proteomic, and clinical datasets to identify patterns, predict treatment responses, and optimize treatment strategies for individual patients with IBC (Sechopoulos et al., 2021). Future research will explore integrating AI-based tools into clinical practice to support personalized treatment decision-making and improve patient outcomes in IBC.

Future directions in IBC research will emphasize the importance of patient-centered care, survivorship support, and quality-of-life interventions to address the physical, emotional, and psychosocial needs of IBC patients and survivors. Multidisciplinary care teams will continue to collaborate to provide comprehensive, holistic care that is tailored to the individual needs and preferences of IBC patients throughout their treatment journey.

CONCLUSION

Inflammatory breast cancer (IBC) is unique and aggressive in its clinical manifestations and poses significant disparities in diagnosing and treating patients. As a consequence, there is poorer prognosis among those affected with IBC. Delays in diagnosing IBC result from a lack of expertise in identifying critical characteristics of IBC, a lack of knowledge and understanding of IBC versus LABC, and a lack of availability of IBC-related research studies for patients. Because primary care physicians are gatekeepers in the medical world, they are often the first set of eyes to see a patient at symptom onset. Their role in identifying IBC can help improve diagnosis and prognosis for affected patients. Understanding the signs and symptoms associated with IBC is crucial for identifying and diagnosing this aggressive BC presentation. Although more research is needed in this field, it is highly likely that IBC will soon be easily recognized and treated through further education.

Recommendations for improvements in IBC diagnosis address the medical field and the general population. Primary care physicians play a potential role in helping recognize IBC at an appropriate time before the disease progresses into a more advanced form of cancer. Emphasis on IBC in continuing education among providers, especially first-line providers like primary practitioners, can significantly reduce the time taken to diagnose IBC and implement a treatment plan. It is essential to note the differences in IBC versus other common diagnoses with similar symptoms, such as mastitis. Emphasis in these areas within continuing education systems would significantly impact the realm of IBC. Educational awareness in school and workplace settings can also help improve health literacy among the general population so they are more likely to recognize the urgency of seeing a medical professional in case their symptoms resemble IBC.

Raising educational awareness among primary care providers and implementing educational initiatives for IBC awareness can assist in earlier diagnosis and intervention for treatment among IBC patients. There is a strong need for increased IBC research to contribute to a higher degree of IBC awareness. Further studies and IBC-specific clinical trials can aid in learning more about IBC and how it manifests within each person's body. Although IBC incidence may increase with these implementations, it serves as a reminder that more knowledge can aid in fighting such a formidable disease.

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CURRICULUM VITAE

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