Aim and Scope

Archives of Breast Cancer (ABC) is an open access, peer-reviewed journal that publishes articles on all aspects of breast cancer research, including the pathophysiology, prevention, early detection, diagnosis, treatment, molecular and cellular biology, genetics, epidemiology, psychological issues, rehabilitation and quality of life. Although the main focus of the journal is breast cancer, some important topics among benign breast diseases and breast health such as breastfeeding will be considered for publication.

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Dear Colleagues,

Happy 2020!

We tried our best to improve the quality and the number of published articles though we think there is a significant potential for improvement. In 2020 we plan to accomplish two essential goals:

1. Empowering our editorial team by inviting the authorities from all around the world involved in breast cancer management to help the journal in policymaking and improving the quality of the peer-review process.
2. Publishing more articles from different centers and countries to improve the international diversity of the published articles.
3. Being indexed in esteemed databases to improve the visibility of the published articles.

We do believe that ABC will have a prosperous time in 2020 by reaching the above-mentioned milestones. We invite all scientists and researchers to use this journal as a platform to share the results of their research with other scientists and researchers.

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Machine learning (ML) is a way of “training” an algorithm so that it can learn how what? The “training” involves feeding huge amounts of data to the algorithm and allowing it to adjust itself and improve. Deep learning is a branch of ML based on learning data representations, as opposed to task-specific algorithms. Bioinformatics, drug design, and medical image analysis are some of the biomedical applications of deep learning. A clear example of deep learning is an artificial neural network, which includes algorithms that mimic the biological structure of the brain. An artificial neural network is an information-processing paradigm inspired by the way the biological nervous system processes information. It is based on the structure of neurons and neuronal interconnections.

What Is Artificial Intelligence?

Artificial intelligence (AI) is an algorithm-based strategy of simulating intelligence programmed in a man-made machine for correction and rationalization of actions. AI encompasses a broad range of concepts, including planning, understanding language, recognizing objects and sounds, learning, and problem-solving. Machine learning (ML) is a way of “training” an algorithm so that it can learn how what? The “training” involves feeding huge amounts of data to the algorithm and allowing it to adjust itself and improve. Deep learning is a branch of ML based on learning data representations, as opposed to task-specific algorithms. Bioinformatics, drug design, and medical image analysis are some of the biomedical applications of deep learning. A clear example of deep learning is an artificial neural network, which includes algorithms that mimic the biological structure of the brain. An artificial neural network is an information-processing paradigm inspired by the way the biological nervous system processes information. It is based on the structure of neurons and neuronal interconnections.

What Are the Applications of AI in Breast Cancer?

Cancer is a collection of diseases, with the unregulated and uncontrolled division of cells being its main hallmark. In breast cancer (BC), this unchecked cell proliferation initially occurs in breast epithelial tissue before forming the actual tumor. Artificial intelligence promises to revolutionize biomedicine and shape cancer medicine in unprecedented speed and precision.

This commentary summarizes a number of advances reported in BC basic investigations, drug resistance, disease modeling, mammography screening, etc.

1. Breast cancer modeling

An AI machine called DeepCode has been used to classify xenograft models of human tumors by identifying tumor subtypes with maximum possible accuracy. The machine is indeed able to monitor molecular events during tumorigenesis in xenograft models and the DeepCode-produced data can be cross-compared with the outcomes of human tumor–based investigations on BC tumor evolution. Several ML algorithms were incorporated into DeepCode and applied to 174 human tumors to examine tens of selective genes for constructing a prediction model. As a result, seven interpretable interactions were detected within the informative genes that were verifiable by previous experimental studies.

2. BC tumorigenicity

This is a fundamental segment of oncology studies and its mechanistic investigations have profound implications for personalized cancer management. The advent of next-generation sequencing made it possible, for the first time, to spatiotemporally map tumor genome, meaning that any segment of the tumor cell genome is sequenced at any time during tumor development. It is now AI’s turn to make the pace of progress even faster: multiregion sequencing data collected from numerous patients were analyzed by an AI-based method called REVOLVER, which identified previously unknown repeated evolutionary trajectories in subgroups of patients. This is the beginning of a big change as it opens avenues for identifying the molecular roots of the whole tumor formation process. In fact, AI technology is able to detect within tumor genome single mutations, tissue-specific gene expression, and expression...
of genes shared between xenograft models and tumors of origin. To elucidate the molecular basis of BC tumorigenesis may require genetic manipulations. AI approaches now facilitate specific cell- and tissue-type targeting. AI-based single-gene delivery can target xenograft model tissues and further expand our capabilities in investigating revolutionary patterns of spatiotemporal gene expression during tumor formation. Such a gene-targeting capacity of AI can be combined with cancer genome–editing ability of the CRISPR/Cas9 system to correct gene mutations and simulate molecular changes within tumor genomes (see subtitle 7: Detection of BC metastasis).

AI-based ML is now developed to measure tumor growth profiles and model validation. The TUGROVIS project is aimed to understand the underlying principles of tumor growth by designing and developing algorithms, methods, and tools. The concept is to integrate multiple approaches towards multidimensional connection of open data sets. These works will allow the creation of more personalized models amenable to specific molecular manipulations with applications in human-mouse matched co-clinical trials that heavily depend on mouse models.

3. Distinguishing tumor cells

Microscopic images of cancer cells are scanned and examined by AI-based convolutional neural network so that animal cells are separated from human counterparts and radio-resistant cells are picked up among a population of cancer cells. The findings by the system were gathered on a two-dimensional plot where the results for each cell type clustered together while being clearly separated from the other cells. The system was then trained to accurately identify cells only using their microscopic images. The accuracy and automation of the system can be used to exactly identify cell types present in a tumor or circulating in a patient’s body. Such knowledge can be important in deciding chemotherapy or radiotherapy applications.

4. Prediction of drug synergism

Using chemical and genomic information as input, an AI-based program called DeepSynergy models drug synergies. The method improved the performance of other methods by 7.2% in predicting novel drug combinations within the space of explored drugs and cell lines. AI technology can be also effective in predicting and redesigning protein–protein interactions for novel drug discovery. As an example, oncology treatment is an AI-based area of investigation by Boston-based biopharma company Berg. It uses an algorithm and probability-based AI to analyze large cohorts of patients’ genotype, phenotype, etc, to find therapies based on cancer biology. Anticancer drug BPM31510 was indeed discovered via AI assistance and is in clinical trial.

5. AI for mammography

False negative and false positive: Mammograms are widely used as a tool to catch BC early on, but they are not accurate. In fact, 20% of them were false negative and 50% false positive in US women tested annually for 10 years. A consortium of AI researchers and health-care professionals in the UK uses Google’s AI technology to improve the reading and assessment of mammograms. It analyzes mammograms and finds signs of cancerous tissue more accurately than current techniques detect. The AI approach DeepMind used in this study develops ML algorithms that, by taking a data set and learning from it, ultimately become capable of predictions.

DeepMind Health is training its AI using data from Optimam, a database of over 80 000 digital images collected via the UK’s National Breast Screening System, to maximally improve the reading of mammograms. Given that over 30 million mammograms are performed each year in the US alone, DeepMind’s ML could save significant time for doctors reading screenings. It could also encompass 3D and other mammography procedures. An AI approach applied by the French startup Therapixel could cut down false-positive rates by 5%, while over 99% accuracy in detecting the signs of BC risk by reading mammograms has been achieved at Houston Methodist Research Institute in Texas, and the method is reported to read those images 30 times faster than humans. Such approaches are also being applied to other cancers such as brain tumors.

6. Changes in breast density

Deep learning algorithms are capable of precisely identifying increases in breast density, a strong risk factor for BC. A deep convolutional neural network–based algorithm has been developed, trained, and tested at Massachusetts General Hospital using over 41000 digital mammograms obtained from over 2700 women. The accuracy of 10763 mammograms determined by the algorithm as either dense or non-dense tissue turned out to be 94%, with a 6% disagreement rate with radiologists. This technology already helps to categorize vast amounts of information into more personalized, more targeted care for BC patients and predict the chance of every
woman to develop cancer in the future.13

7. Detection of BC metastasis

AI innovation has been able to detect the spread of BC to the lymph nodes and it does better than pathologists. A simulation study compared the performance of the system with those of 11 pathologists by analyzing digital scans of tissue slides of sentinel lymph nodes using AI-based computer algorithms.16 Given the complexity of detecting lymph node involvement, the AI-based approach can take huge pressure off pathologists and help them to make the right decisions.

We summarized some of the current applications of AI tools and technologies in BC management. On the horizon lies a glimpse of expanding revolution to storm-wise shake the foundations of traditional views and actions on BC investigations, prevention, diagnosis, and cure.

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A physician’s delivery of physical, psychological, and spiritual care are all influenced when they have to look after their own family members. Patient-physician communication and the quality of care may be especially affected.¹

She was in her 70s, a relatively healthy woman who managed all the house chores by herself. A retired university librarian, she always had a few humorous stories to tell about her interactions with college students to cheer me up when I came back from long night shifts during my medical internship. She rarely complained of anything until one evening when what seemed to be a minor backache was bothering her. “Did you carry something heavy again, Mom?” I asked. “It was only a small shopping bag,” she answered with a guilty smile. Through the next three weeks, her backache turned into radicular pain. An evaluation by a neurologist, who was a former classmate, comforted us that the pain should be stemming from a minor discopathy and prescribed ibuprofen, a muscle relaxant, and adequate rest. However, the pain did not go away.

Coming back home from a long shift one day, at the front door I was confronted by several neighbors surrounding my mother who was lying on the floor. She had a broken leg and was moaning of pain. “You will be fine, Mom!” I repeated several times, though I knew it was not going to be an easy ride.

She was transferred by the ambulance to the hospital where I was working and a thorough evaluation revealed that her backache, the nasty radicular pain, and the broken leg were due to a spinal cord compression syndrome. She underwent an operation and the pathology report revealed breast cancer—very odd presentation for a common type of cancer.

As my mother was undergoing diagnostic assessments and procedures, I spent my evenings reading about how to give bad news to her. The 6 steps of SPIKES protocol for delivering bad news are (1) setting up the interview, (2) reviewing the patient's perception of the illness, (3) getting an invitation from the patient to deliver the news, (4) giving the patient knowledge and information, (5) responding to the patient's emotions, and (6) summarizing the treatment plan and reviewing all that has been communicated.² I wondered if the authors of the SPIKES protocol had performed it for a close relative. It would be very difficult providing information with honesty without destroying the patient's hope.

It is a common practice in Iran for the physician to withhold stress-inducing diagnostic and prognostic information from the patient undergoing treatment.³ The physician is seen as a higher authority who will decide on what needs to be communicated and what does not. What about the patient’s autonomy? Did this so-called paternalistic approach to medical care overruled my mother’s real wishes at that time?⁴

Was she aware of her terminal diagnosis? One day I overheard her conversation with a friend: “I have that BAD disease, and I know this is my last journey.” In avoiding a direct and frank conversation with my mother about her illness, I wonder whose emotions I was protecting, hers or mine? Actually, I was not feeling prepared to manage her emotional reactions and feared to lose her trust in my abilities in the face of an uncontrollable disease.

Years later, I wonder how the end-of-life experience might have been different if I had been upfront with my mother about her diagnosis. Would that have empowered us to share our emotional journey together, make more individualized care decisions for her and reflect on life we had together? Would that have prevented the last chemotherapy she received
The cancer experience deeply affects the whole family. It is common practice in Iran, and is promoted by the medical community, to withhold information from the patient and therefore not include the patient's wishes in care planning. Although this approach is intended to protect the patient and the families from emotional suffering, it has its consequences. Supporting and enabling the family is universally one of the palliative care objectives. According to the World Health Organization, “palliative care is an approach that improves the quality of life of patients and their families facing problems associated with life-threatening illness through early identification and correct assessment and treatment of pain and other problems, whether physical, psychosocial, or spiritual.”

In the common medical practice in Iran, the cancer care provider is set to limit information sharing with patients and sometimes families when it comes to poor prognosis. Involving the patients, as well as the family members, in their care journey and enabling them to gain control of their life decisions is important and an inherent shift the medical community needs to take into consideration. This is especially timely, with the emerging shift in care paradigm from physician-centered care toward patient- and family-centered care. The family, as the physician's partner in the process of care delivery, needs to be taught, supported, and receive care, especially mentally and emotionally. Their concerns should be understood, and their questions should be answered as the family is one of the cancer care pillars.

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5. WHO Definition of Palliative Care [Available from: http://www.who.int/cancer/palliative/definition/en/]
ABSTRACT

Background: Stress is a reaction to physical, psychological, and emotional events. Compared with other chronic diseases, breast cancer (BC) is a dire stressful situation greatly disheartening the patients. Therefore, patients with BC need long-lasting physical and emotional support to cope with stress. The purpose of this study was to systematically review the studies using supportive stress management interventions in patients with BC.

Methods: A literature search was performed in scientific databases including Google Scholar, Scientific Information Database, Magiran, Irandoc, Web of Science, Science Direct, PubMed [including Medline], and Elsevier. The keywords were retrieved from Medical Subject Headings (Mesh). The articles published from 1997 to 2017 were included. Database search returned 440 records. Title and abstract screening identified 152 potentially eligible articles. Finally, 18 articles were included in the synthesis of the review.

Results: All the included studies had an interventional design focusing on stress management approaches and their related covariates in women with BC. The findings were assessed regarding two distinct approaches. First, the studies assessing stress management interventions were scrutinized. Next, the impact of intervention duration, the number of the participants, and the contents of sessions were explored. Of the selected articles, 6 had used a mindfulness-based approach, 2 had utilized relaxation techniques, and 7 had employed stress-related cognitive-behavioral therapy. In addition, one study was related to resilience training and 2 studies investigated problem-based approaches.

Conclusion: Stress management interventions can be helpful in reducing stress in BC patients. Therefore, it is advisable to incorporate stress management strategies along with routine pharmaceutical therapies in these patients.

Introduction
Breast cancer (BC) is among the most common cancers in women around the world. Patients with BC encounter with adverse outcomes affecting their physical, sexual, and psychological health.
Stress is defined as a nonspecific biological response to environmental demands and conditions. Chronic diseases such as BC are important environmental factors leading to stress. BC patients tend to counteract the situation by resorting to nonproductive methods such as excessive sleep, drinking, avoidance, and denial. Studies have shown that 31% to 54% of newly diagnosed BC cases reported sleep problems up to 6 months following the diagnosis. Persistent insomnia (up to 2-6 years following the diagnosis) heralds a serious and urgent problem in cancer patients. In this regards, it has been noted that sleep and stress are interrelated modalities, with stress being a major contributor to sleep problems. On the other hand, stress also contributes to depression, paving the road for emotional, functional, and communicational disturbances as well as reduced life satisfaction. Some of the factors leading to patients' stress and anxiety include advanced disease, time elapsed from the diagnosis, disease recurrence, physical weakness, surgical therapies, and finally the fear of loneliness and death.

The stress inflicts detrimental effects on health and body organs. The response to stress negatively affects emotional, cognitive, behavioral, physical, and social aspects of the patients' health, subsequently leading to problems in personal and interpersonal relationships. A viable option to tackle stress is to implement stress management strategies.

In addition, psychological disorders, i.e., stress, depression, and anxiety, may further complicate the clinical course and treatment of the disease leading to a life-threatening crisis.

Figure 1. Search strategy in the study
Since stress reduction interventions are designed based on a strategic plan, they can assist physicians and psychologists to diagnose mental disorders in patients. However, systematic studies focusing on stress management strategies are limited. Therefore, this study aimed to systematically review the studies that had implemented stress management strategies in patients with BC.

Methods

In the present review, we searched for English- and Persian-language papers published from 1997 to November 2017 according to the following protocol:
1. Developing the research question;
2. Designing the search strategy;
3. Study selection;
4. Presenting the data.

Developing the Research Question

The research question was formulated, using the PICOD framework, as “interventional strategies for managing stress in patients with breast cancer” (population (P): women with BC, intervention (I): stress management strategies, comparison (C): women with BC receiving no intervention for stress management, outcome (O): the severity of stress postintervention, and study design (D): all controlled trials.

Search Strategy in Scientific Databases

The literature search was performed in Google Scholar, Scientific Information Database (SID), Magiran, Irandoc, Barakat Knowledge Network System, Web of Science, Science Direct, Cochrane Library, ProQuest, PubMed [including Medline], Springer, and Elsevier databases using the Medical Subject Heading (MeSH) terms. Keywords included “breast cancer,” “supportive program,” “stress management,” “intervention,” “relaxation,” “meditation,” “problem-solving,” “mental therapy,” and “psychotherapy.” Boolean operators were applied to conduct combined searches as follows: “breast cancer OR breast neoplasm AND supportive program,” “breast cancer AND stress management,” “breast cancer AND stress management AND interventions,” and, finally, “breast cancer AND relaxation.”

Studies Selection

After the primary search, records were screened by title. Out of 440 retrieved records, 32 studies were excluded for being duplicate or irrelevant or lacking the inclusion criteria. In the second screening stage of the remaining 408 articles, an additional 230 articles were omitted after reading abstracts. The reasons were inconsistency with the inclusion criteria, full text unavailability, and publication in languages other than English or Farsi. After that, the full text of the 178 remaining articles was read. Checking the reference lists of these articles, we identified an additional 25 articles and 3 textbooks. After reading full texts, 152 articles were excluded as they did not meet the inclusion criteria. Finally, 54 research items (including the 3 textbooks) were selected. Among these, 18 articles were related to stress management (Figure 1).

Inclusion and Exclusion Criteria.

Articles addressing stress management in women with BC were included. Articles that considered other cancers or other factors such as quality of life, anxiety, depression, or non-stress factors were excluded.

Data Collection

Considering our inclusion and exclusion criteria, the titles, abstracts, and full texts of the articles were evaluated and organized in different subclasses (Table 1).

Results

Descriptive Findings

Of the 18 interventional studies included, 6 studies had used mindfulness approaches, 2 applied relaxation techniques, and 7 had employed stress-related cognitive-behavioral therapy. Stress management using resilience training was evaluated in one report. Another two articles scrutinized the coping and problem-based approaches. The primary outcome in most of the studies was to improve stress in the patients.

The interventional strategies performed in different studies included cognitive-behavioral therapy based on stress management, knowledge of the mind for stress reduction, and stress management by problem-solving, emotion-centered and problem-oriented coping styles. The majority of the studies had been conducted in group-based settings.

The results were classified into primary (stress management interventions) and secondary (impact of the duration as well as the content of the sessions, and the number of participants on stress) outcomes. In all the assessed studies, stress management interventions led to stress reduction in patients.
Mindfulness-Based Stress Reduction

Six studies examined the effectiveness of mindfulness-based stress reduction strategies in patients with BC. The number of sessions varied from 6 to 8.33-36 The interventions were effective in reducing patients' stress. These studies also showed that patients educated about mindfulness were less likely to experience stress and symptoms associated with mental disorders.36 In comparison with patients in intervention groups, the patients in control groups, who did not receive any intervention, were significantly more vulnerable to stress, digestive problems, cardiovascular diseases, behavioral disorders, depression, and irritability.37

Relaxation

Two studies examined the effects of relaxation on stress in patients with BC. Aghabararri et al. and Lechner et al., conducted 9 and 10 relaxation sessions, respectively. The mean postintervention stress levels were significantly reduced compared with the preintervention state in both studies,38 while the mean and percentage of stress significantly increased in the control group.38

Cognitive-Behavioral Stress Management

Cognitive-behavioral stress management (CBSM) method considers both patients' behavior and emotions in stress management procedures. The content of this program includes training anxiety reduction skills, informing about stress resources and stress indicators, learning and replacing negative thoughts, and teaching cognitive and interpersonal stress coping skills. During CBSM sessions, the patients learn how to use these skills to change their perceptions toward stressful conditions and cope with stress.8,9,40-44 Breast cancer has been identified as a major source of stress, anxiety, and difficulties in interpersonal interactions. Therefore, CBSM interventions actually aim to overcome these problems by providing a platform for stress relief. Overall, 7 articles reported that stress was reduced in patients receiving CBSM-based educations and skills.8,42-47 In these studies, the number of sessions varied from 5 to 10, depending on the patients' perception and their conditions. The higher number of sessions led to a more effective education and training skills. These interventions included discussion-based sessions and information exchange that consequently had a positive impact on stress reduction. A common feature of the studies using this style was focusing on stress management through relaxation and change of attitudes.

Stress Management and Resilience Training Program

This strategy is a structured method of reducing stress and enhancing flexibility. Since humans tend to exaggerate their deficiencies, efforts to cope with such deficiencies are associated with stress. In this method, exercises such as relaxation, diaphragmatic breathing exercises, and attention to workouts help to reduce stress by focusing on remote memories. This can increase the patients' flexibility in coping with stress. Studies have shown the effectiveness of this stress management method in alleviating stress in patients with BC. Scheduled meetings included 12 ninety-minute sessions.48

Active and Passive Coping Approach

Kornblith et al. studied the buffering effect of social support against the psychological impacts of stressful life events in women with BC. They showed that emotional support can eliminate stressors, relieving mental stress in patients with BC.49 In fact, seeking emotional support is an essential part of active stress-coping styles. Accordingly, emotional support was a positive predictive factor for improving psychological stress.49

Problem-Centered and Emotion-Centered Approaches

In this stress management style, coping approaches are divided into problem- or emotion-based categories. Problem-based coping styles use methods such as problem-solving, decision-making, conflict resolution, information seeking, counseling, and goal setting to resolve a problem or a stressful situation.

In emotion-based style, emotional responses and stressful events are characterized first. Then, methods such as rehabilitation and cognitive reassessment, emotional expressions, behavioral changes (performing pleasant activities), and reducing physical stress (exercise, relaxation, and deep breathing) are applied to cope with stress.

Problem-solving is a method of analyzing the problem and adopting the best coping strategies. Allen et al. provided BC patients a telephone-based training on the principles of problem-solving stress management style including problem orientation, problem definition and analysis, alternative creation, decision-making and evaluation process, and implementation and validation of the solution. The
<table>
<thead>
<tr>
<th>First Author (Year)</th>
<th>Country/ state/cities</th>
<th>Type of intervention (Group/Individual)</th>
<th>Sample size (case/control)</th>
<th>Duration/ No. of sessions</th>
<th>Outcome</th>
<th>Intervention content</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antoni (2006)</td>
<td>USA</td>
<td>Stress management on behavioral processes in breast cancer patients (Group)</td>
<td>199</td>
<td>10 weeks</td>
<td>Stress management</td>
<td>Relaxation/ anxiety reduction, cognitive reconstruction, and teaching effective interactions and interpersonal skills.</td>
<td>Impact of interventional programs on reducing stress and reducing tumor progression</td>
</tr>
<tr>
<td>Groarke (2013)</td>
<td>Ireland</td>
<td>Cognitive-behavioral stress management (Group)</td>
<td>178/ 177</td>
<td>5 sessions</td>
<td>Stress management</td>
<td>Stress management, fatigue reduction, adaptive coping through relaxation training, guided imagery, and cognitive restructuring.</td>
<td>Effectiveness of CBSM in reducing stress</td>
</tr>
<tr>
<td>Stagl (2015)</td>
<td>Miami (USA)</td>
<td>Cognitive-behavioral stress management (Group)</td>
<td>120/ 120</td>
<td>10 weeks</td>
<td>Stress management</td>
<td>Cognitive reframing, effective coping skills training, assertiveness training, anger management, and relaxation training (e.g. progressive muscle relaxation, guided visual imagery, and diaphragmatic breathing).</td>
<td>CBSM improved physical and emotional well-being</td>
</tr>
<tr>
<td>Khatiban (2014)</td>
<td>Ahvaz (Iran)</td>
<td>Cognitive-behavioral interventional (Group)</td>
<td>12/ 12</td>
<td>10 sessions</td>
<td>Stress management</td>
<td>Explaining the concepts of depression, anxiety, and stress and their effects on breast cancer; expressing the physical and psychological consequences of depression, anxiety and stress for patients with breast cancer; describing negative self-conscious thoughts associated with depression, anxiety, and stress during breast cancer; expressing thoughts of self-efficacy, negative self-esteem, negative self-defense coping strategies, possible responses to these thoughts and how to replace these thoughts with positive ones.</td>
<td>Effect of cognitive group therapy on reducing stress</td>
</tr>
<tr>
<td>Lechner (2014)</td>
<td>Miami (USA)</td>
<td>Community-based stress management intervention (CBSM) (Group)</td>
<td>52/ 56</td>
<td>10 weeks</td>
<td>Stress management</td>
<td>Progressive muscle relaxation, visualization, deep breathing, meditation, providing coping skills training, and building interpersonal skills.</td>
<td>Stress management after stress management intervention</td>
</tr>
<tr>
<td>Antoni (2003)</td>
<td>Miami (USA)</td>
<td>Cognitive behavioral stress management (Group)</td>
<td>63/ 56</td>
<td>10 weeks</td>
<td>Stress management</td>
<td>Didactic explanations, in-session experiential exercises (role-playing) and out-of-session assignments (e.g., practicing in relaxation and completing homework assignments examining responses to stressors encountered during the week), teaching stress reduction techniques such as rational thought replacement with specific modules, improving their coping strategies, interpersonal skills.</td>
<td>Role of interventions on reduction of behavioral disorders</td>
</tr>
<tr>
<td>First Author</td>
<td>Country/State/City</td>
<td>Type of Intervention</td>
<td>Sample Size</td>
<td>Duration/No. of Sessions</td>
<td>Outcome</td>
<td>Intervention Content</td>
<td>Finding</td>
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<tr>
<td>McGregor† (2015)</td>
<td>USA</td>
<td>Cognitive-behavioral stress management (Group)</td>
<td>76/75</td>
<td>10 weeks</td>
<td>Stress management</td>
<td>Awareness of the effects of stress, cognitive reframing, cognitive coping skills training, assertiveness training, anger management, and various relaxation techniques (including progressive muscle relaxation, guided imagery, and mindfulness meditation).</td>
<td>Reduction of psychological distress</td>
</tr>
<tr>
<td>McGregor‡ (2004)</td>
<td>USA</td>
<td>Cognitive-behavioral stress management (Group)</td>
<td>11/18</td>
<td>10 weeks</td>
<td>Stress management, immune function</td>
<td>CBSM techniques (e.g., cognitive restructuring, coping skills training, assertive training and anger management) in a didactic format incorporated with relaxation exercises (e.g., progressive muscle relaxation, guided imagery, meditation, deep breathing), emotional expression and support from group members.</td>
<td>Effect of cognitive behavioral therapy on stress</td>
</tr>
<tr>
<td>Rezaei Ardani et al. (2015)</td>
<td>Mashhad (Iran)</td>
<td>Cognitive-behavioral stress management (Group)</td>
<td>16/16</td>
<td>10 weeks</td>
<td>Quality of life, negative emotions</td>
<td>Stress and responses, stress, musculoskeletal disorders, stress, stress and knowledge, exercise to increase knowledge of physical symptoms of stress, confusion with imaging and diaphragmatic respiratory exercise, the relationship between thoughts and sentiments, thinking exercise, negative thinking and distortion cognitive behavior, negative thoughts and behaviors, recognition of negative thoughts, difference between logical and unreasonable suggestions, steps for the replacement of rational thoughts, practice of replacing rational thoughts, defining coping, efficient coping types, inefficient coping types, discussion in the intervention of coping strategies, anger and knowledge, anger management, expressive teaching, interpersonal styles, behavioral barriers expressive, components of expressive communication, problem solving for conflicts, steps for more expressive behavior, social support, understanding social support, benefits of support social barriers to maintaining social support, stress management techniques for maintaining social support.</td>
<td>The Effect of cognitive behavioral therapy on stress</td>
</tr>
<tr>
<td>Loprinzi* (2011)</td>
<td>Minnesota (USA)</td>
<td>Stress management and resilience training (SMART) program (Group)</td>
<td>12/12</td>
<td>12 weeks</td>
<td>Stress resiliency</td>
<td>Teaching the SMART program, discussed during the first session; relaxation; deep diaphragmatic breathing practice; follow-up session with a physician.</td>
<td>Effect of stress resiliency on stress</td>
</tr>
<tr>
<td>Bisseling* (2017)</td>
<td>Amherst</td>
<td>Mindfulness-based stress reduction (Group)</td>
<td>64/64</td>
<td>8 weeks</td>
<td>Mindfulness-based stress</td>
<td>Sessions consisted of mindfulness practices, didactic teaching on stress, and sharing experience with one another, and psycho-education about grief.</td>
<td>Improvement of psychological symptoms with mindfulness</td>
</tr>
<tr>
<td>First Author</td>
<td>Country/state/cities</td>
<td>Type of intervention (Group/Individual)</td>
<td>Sample size (case/control)</td>
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<td>Intervention content</td>
<td>Finding</td>
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<tr>
<td>Shapiro²⁴ (2003)</td>
<td>Tucson</td>
<td>Mindfulness-based stress reduction (Group)</td>
<td>26/ 28</td>
<td>6 weeks</td>
<td>Mindfulness-based stress</td>
<td>Meditative practices, meditation involving awareness of body sensations, thoughts, and emotions while continually returning the focus of attention to the breath, body scan, Hatha yoga, didactic material was presented on the psychological and physiological effects of stress, and cognitive-behavioral coping tools were introduced as a means to cope with stress.</td>
<td>Improvement of psychological symptoms with mindfulness</td>
</tr>
<tr>
<td>Lengacher²⁵ (2012)</td>
<td>Tampa (Florida/ USA)</td>
<td>Mindfulness-based stress reduction (Group)</td>
<td>41/ 48</td>
<td>6 weeks</td>
<td>Mindfulness-based stress</td>
<td>Educational material related to relaxation, meditation, and the mind-body connection, meditation, group discussion, supportive interaction between group members, the formal meditative training was consisted of four types of techniques (sitting and walking meditation, body scan, and gentle Hatha yoga) that focus attention on breathing, mindfulness in everyday life, and included being aware of pleasant and unpleasant events, routine activities, and everyday events.</td>
<td>Improvement of psychological symptoms with mindfulness</td>
</tr>
<tr>
<td>Huang²⁶ (2016)</td>
<td>Shanghai (China)</td>
<td>Mindfulness-based stress reduction (Group)</td>
<td>429/-</td>
<td>8 weeks</td>
<td>Mindfulness-based stress</td>
<td>Meditations (sitting meditation, body scan, and walking meditation), gentle yoga. The training manual included weekly objectives, exercises, and program content related to the content identified below, daily diary for recording practice activities at home.</td>
<td>Improvement of psychological symptoms with mindfulness</td>
</tr>
<tr>
<td>Sanaei²⁷ (2017)</td>
<td>Tehran (Iran)</td>
<td>Mindfulness-based stress reduction (Group)</td>
<td>20/ 20</td>
<td>8 weeks</td>
<td>Self-efficacy perceived stress life orientation</td>
<td>Nothing was mentioned.</td>
<td>Stress relief in patients with mindfulness intervention</td>
</tr>
<tr>
<td>Speca²⁸ (2000)</td>
<td>Canada</td>
<td>Mindfulness-based stress reduction (Group)</td>
<td>46/ 27</td>
<td>7 weeks</td>
<td>Mindfulness-based stress</td>
<td>Didactic, inductive, and experiential modes, theoretical material related to relaxation, meditation, and the body-mind connection, experiential practice of meditation during the group meetings and home-based practice, group process focused on problem-solving.</td>
<td>Reduction of mood disturbances and stress</td>
</tr>
<tr>
<td>Aghabarari³⁰ (2008)</td>
<td>Tehran (Iran)</td>
<td>Exercise program (Group)</td>
<td>28/ 28</td>
<td>9 weeks</td>
<td>Exercise program stress anxiety depression</td>
<td>Warm-up exercise, stretching exercise, motion movements, sweating movements including relaxing movements and music in each of these stages.</td>
<td>Reducing the stress of patients with exercise programs</td>
</tr>
</tbody>
</table>
results showed that the problem-solving approach was effective in reducing stress in patients with BC.\textsuperscript{51}

**Discussion**

Eighteen studies aiming to manage and reduce stress in patients with BC were evaluated. Three of these studies had been conducted in Iran while 15 were related to other countries. In the present systematic study, we identified 6 groups of stress management interventions, i.e., mindfulness-based stress reduction, relaxation, CBSM, stress management and resilience training program, active and passive stress coping approaches, and problem- and emotion-based approaches. Being diagnosed with BC is a disappointing and stressful experience. In addition, therapeutic interventions (i.e., surgery and chemotherapy) impose further adverse and debilitating complications, influencing the communicative abilities of the patients. Furthermore, long-term negative effects of stress can significantly interfere with patients’ personal and interpersonal relationships.\textsuperscript{52}

The study of Hamzehgardeshi et al. showed that support programs can effectively improve patients' marital life. They implemented a relaxation technique to alleviate patients' stress and to provide them with a stress-free environment. During the study, the researchers continually communicated with the patients by phone calls. These interventions resulted in higher satisfaction with marital status and sex life. The results of this study were consistent with those of Jun et al. and Shariati et al.,\textsuperscript{26-28} although the latter also investigated the effects relaxation skills training on stress.\textsuperscript{26}

On the other hand, individuals' environmental perceptions have been noted as important stress inducers.\textsuperscript{29} In fact, stress may remain undiagnosed in some patients. Understanding the symptoms of stress could help to diagnose and effectively cope with this condition. Therefore, it is a necessity for both psychologists and patients to be aware of stress symptoms. This can help psychologists to recommend various stress management interventions to patients to alleviate stress symptoms. Stress is a physical, mental, and emotional tension which can be triggered by various events. Stress can affect various body organs and reduce the function of the immune system.\textsuperscript{53}

Therefore, methods such as cognitive-behavioral therapy which are based on stress management by providing educational contents aimed at changing patients' thoughts and perceptions are particularly effective in attenuating psychological crises.\textsuperscript{8,9} This has been shown by several studies.\textsuperscript{40, 41, 46, 54} It should be noted that various types of stress management interventions may not directly address the psychological problems (i.e., stress).\textsuperscript{54}

Nevertheless, it seems that considering psychological problems as a spectrum of intertwined disorders, along with giving special attention to the relationships among stress, anxiety, depression, and insomnia, may provide the best stress-coping strategy.

It should be noted that the methods of assessing problems are variable based on their characteristics. The greater the problem is, the more difficult the coping style will be. Therefore, educating patients about the features of coping and adaptation styles can help control stress and improve individuals' responses to the condition. That is why in the emotion- and problem-based stress-coping techniques, the aim is to provide a stress-free setting for the patients. Stress management is a way of enhancing the patients' abilities in fighting stress and also making them more adaptable to stressful situations. Although Behzadipor et al. did not directly assess stress in their study, their patients reportedly had good mental health probably attributable to the implementing of these stress-coping techniques. On the other hand, patients knowledge about the physical symptoms of stress (such as anger) can augment the effectiveness of stress-reducing interventions and accelerate alleviating the problem. The findings of this study were consistent with those of Cruess et al. and Safarzadeh et al.\textsuperscript{40, 41} Our results also showed that stress-based interventions led to the reduction of psychological symptoms, such as stress, in patients. The positive impacts of such interventions on stress not only affected the individuals’ life, but also improved personal and social communications in the patients.

The strengths of this study included a narrative approach to stress-coping interventions. The authors sought to integrate all studies related to stress management. The literature search was conducted in both Farsi and English, including Iranian and overseas studies. However, there were limitations in accessing the full text of some articles. This was a systematic study on the papers focusing on the stress management approaches in BC patients. The purpose of the study was to identify and investigate various stress management interventions in BC patients and to introduce them to health-care providers and patients to be used in clinical practice. According to the abovementioned notations and the
importance of the psychological dimensions of women with BC (as both mothers and spouses), it is recommended that these interventions be considered in parallel with pharmaceutical therapies in these patients. Conducting a systematic review or meta-analysis regarding stress management interventions is also suggested.

Conflict of Interest
The authors have no potential conflict of interest concerning the content of the present article.

Acknowledgments
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Key words: Tamoxifen, adjuvant hormone therapy, breast cancer, abnormal uterine bleeding

ABSTRACT

Background: Selective estrogen receptor modulators (SERMs) have been shown to reduce the risk of developing estrogen-positive breast cancer. Tamoxifen, a potent SERM, has been successfully administered as adjuvant therapy for breast cancer. However, uterine pathologic changes may develop due to the effect of tamoxifen as both an agonist and antagonist of estrogen on the uterus. Here, we discuss a case of breast cancer treated with tamoxifen to clarify one of the most important complications, namely, endometrial hyperplasia.

Case Presentation: A 51-year-old woman presented with left breast mass and axillary lymphadenopathy. Mammography showed a 26-mm spiculated mass consistent with invasive ductal carcinoma in core needle biopsy. Immunohistochemical analysis revealed that the tumor was ER- and PR-positive, HER2-negative. Adjuvant chemotherapy was completed, and the patient was referred to undergo adjuvant radiotherapy (RT). After the completion of RT, treatment with tamoxifen was initiated at the recommended dose of 20 mg/day.

Questions: The questions are when to use tamoxifen as adjuvant therapy for breast cancer, how to follow the patient treated with tamoxifen, and when to discontinue tamoxifen therapy.

Conclusion: Use of tamoxifen for at least 5 years after diagnosis is a reasonable option for the prevention of breast cancer or its recurrence in high-risk patients. For premenopausal women taking tamoxifen, irregular vaginal bleeding should be evaluated by hysteroscopy or uterine ultrasonography, and, if the etiology remains unclear, a biopsy should be done. There are no evidence-based recommendations for uterine malignancy screening in patients who take tamoxifen. Current recommendations are annual gynecologic examination and evaluation of any abnormal vaginal bleeding.

Introduction

Selective estrogen receptor modulators (SERMs) have been shown to reduce the risk of developing estrogen-positive breast cancer. Tamoxifen, a potent SERM, has been successfully administered as adjuvant therapy for breast cancer. However, the
effect of tamoxifen as both an agonist and antagonist of estrogen may cause pathologic changes in the uterus. The agonist effect may stimulate endometrial proliferation leading to endometrial polyps, hyperplasia, and, rarely, endometrial cancers. The use of tamoxifen for more than 5 years does not seem to increase its efficacy. Moreover, the risk of endometrial cancers seems to increase for up to at least 10 years of treatment. These patients must be evaluated carefully; however, the method of choice for screening is controversial. Here, we discuss a case of breast cancer treated with tamoxifen to clarify one of the most important complications, namely, endometrial hyperplasia.

**Case Presentation**

A 51-year-old woman presented with left breast mass and axillary lymphadenopathy. Mammography showed a 26-mm spiculated mass consistent with invasive ductal carcinoma in core needle biopsy. Immunohistochemical analysis revealed that the tumor was ER- and PR-positive, HER2-negative, and P53-negative. Metastatic workup was negative. Due to axillary lymph node involvement (N2), the patient was referred for neoadjuvant therapy.

After 4 cycles of epirubicin and cyclophosphamide (EC), modified radical mastectomy was performed. The pathology report after surgery did not show definite size reduction after chemotherapy (partial response), although none of the 11 dissected lymph nodes were involved. Adjuvant chemotherapy was completed, and the patient was referred to undergo adjuvant radiotherapy (RT). After the completion of RT, treatment with tamoxifen was initiated at the recommended dose of 20 mg/day. This was a case of nonmetastatic, hormone-positive invasive ductal carcinoma, and it has been shown that its recurrence risk can be reduced by adjuvant tamoxifen. In the follow-up, she did not have any sign or symptom of disease recurrence. Her menstrual cycle was stopped after the first chemotherapy course. Uterus and ovarian sonography were performed annually to detect any mass or endometrial hyperplasia. After 3 years of tamoxifen initiation, uterus sonography revealed endometrial cystic hyperplasia (15 mm) with coarse echo pattern. Because the patient had no vaginal bleeding, the multidisciplinary team decided that she did not need further evaluation. However, since endometrial thickness was above 9 mm (15 mm in our patient), tamoxifen was discontinued and replaced by an aromatase inhibitor (AI), letrozole, and a GnRH agonist, triptorelin. Endometrial hyperplasia reversed subsequently and reached 7 mm after 2 years.

**Questions**

The above case was presented in Imam Khomeini Hospital breast multidisciplinary team session. The questions are when to use tamoxifen as adjuvant therapy for breast cancer, how to follow the patient treated with tamoxifen, and when to discontinue tamoxifen therapy.

**Discussion**

Tamoxifen is a selective estrogen receptor modulator (SERM) that blocks the signaling of endogenous estrogen in normal and malignant breast tissue and is a reasonable option for the prevention of breast cancer or its recurrence in high-risk patients including those with atypical breast tissue hyperplasia, history of lobular carcinoma in situ (LCIS), five-year breast cancer risk ≥ 1.7% according to the modified Gail model, and adjuvant therapy in nonmetastatic hormone-positive breast cancer. Tamoxifen possesses estrogen-like effects on the uterus, bone, liver, and coagulation system. Recent studies demonstrated that tamoxifen is associated with an increased risk of both endometrial cancer and uterine sarcoma depending on the duration of its usage. Other risk factors, such as body mass index and prior estrogen replacement therapy for preventing endometrial cancer while using tamoxifen, were also evaluated. The duration of treatment should also be taken into account. Previous studies showed using tamoxifen for more than 5 years increases the risk of endometrial cancers. The ATLAS trial showed a reduced risk of breast cancer recurrence, but an increased risk of endometrial cancer, among patients taking tamoxifen for more than 5 years. The US National Comprehensive Cancer Network (NCCN) guidelines recommend the following for postmenopausal women: (1) an AI as initial adjuvant therapy for 5 years, with consideration of an additional 5 years on AI therapy; (2) an AI for 2 to 3 years followed by tamoxifen to complete 5 years of endocrine therapy; (3) tamoxifen for 2 to 3 years followed by either an AI to complete 5 years of adjuvant endocrine therapy or 5 years of AI therapy; or (4) tamoxifen for 4.5 to 6 years followed by 5 years of an AI, or consideration of tamoxifen for up to 10 years. In postmenopausal breast cancer patients, a tamoxifen-alone treatment regimen is only admissible when the patient refuses to take AI or there is a contraindication to AI use. The NCCN guidelines recommend 5 years of tamoxifen with or without ovarian suppression, or ovarian suppression plus an AI for 5 years in premenopausal women. For the women who become amenorrheic with chemotherapy, periodic assessment of luteinizing hormone, follicle-stimulating hormone, and estradiol is mandatory to be assigned to AI treatment.

Tamoxifen leads to subendometrial gland enlargement and endometrial hyperplasia in the absence of malignancy; therefore, endometrial thickening in the absence of abnormal vaginal bleeding does not indicate further evaluation like a biopsy. According to the American College of Obstetricians and Gynecologists, just taking tamoxifen is not a
reason to perform endometrial sampling or routine ultrasound. In premenopausal women taking tamoxifen who present with abnormal uterine bleeding, transvaginal ultrasound (TVUS) is recommended. If the endometrial thickness is ≤ 4 mm, there is no need for endometrial sampling, and the routine follow-up is recommended. Endometrial biopsy is contingent on the continuation of abnormal uterine bleeding. If endometrial thickening is present in TVUS, then hysteroscopy or saline infusion sonohysterography is recommended. In this group of patients, if endometrial biopsy confirms hyperplasia, it is recommended that tamoxifen be discontinued and cyclic progestin therapy be initiated. In the case of no desire for fertility, hysterectomy may be an option. Some other experts recommend that for premenopausal women, taking tamoxifen, irregular vaginal bleeding should be evaluated by hysteroscopy, uterine ultrasonography and if remains ulcer biopsy should be done. In postmenopausal women treated with tamoxifen, any vaginal bleeding should be pursued with biopsy and close follow-up. Postmenopausal women using tamoxifen with abnormal vaginal bleeding who have endometrial hyperplasia (especially atypical form) are candidates for hysterectomy. Moreover, evidence recommends dividing postmenopausal women into low- and high-risk groups for developing atypical hyperplasia based on the presence of benign endometrial polyps before therapy. In this case, pretreatment screening with TVUS is recommended.  

There are no evidence-based recommendations for uterine malignancy screening for patients on tamoxifen. Current recommendations are annual gynecologic examination and evaluation of any abnormal vaginal bleeding. The value of transvaginal ultrasound in asymptomatic patients on limited tamoxifen treatment (less than 5 years) is unproven. The abnormal endometrial thickness > 9 mm is acceptable in the studies, but further invasive investigations, such as dilation and curettage (D&C), are not recommended in the absence of vaginal bleeding. Some studies recommend using hysteroscopic biopsy because D&C does not seem accurate enough to detect intrauterine pathologies in patients on tamoxifen. New methods of screening are also introduced. Elastosonography, which measures endometrial tissue strain, was recently used to assess the endometrium in patients on tamoxifen. Also, MRI can be used to assess endometrium and myometrium and their related pathologies when the TVUS findings are equivocal and hysterosonography is not possible to perform.  

Other alternatives to tamoxifen, such as anastrozole, were also studied. Trials showed the equivalency of anastrozole to tamoxifen in efficacy and tolerability in postmenopausal women with hormone-positive advanced breast cancer. Moreover, endometrial thickening was not observed

**Multidisciplinary team (MDT) recommendation**

As a conclusion, the use of tamoxifen for at least 5 years after diagnosis is a reasonable option for the prevention of breast cancer or its recurrence in high-risk patients. For premenopausal women taking tamoxifen, irregular vaginal bleeding should be evaluated via hysteroscopy or uterine ultrasonography, and, if the etiology remains unclear, a biopsy should be done. There are no evidence-based recommendations for uterine malignancy screening in patients who take tamoxifen. Current recommendations are annual gynecologic examination and evaluation of any abnormal vaginal bleeding.

**Ethical Consideration**

Medical ethics considerations were fully observed according to the protocol delivered by the ethics committee of the Department of Surgery at Tehran University of Medical Sciences (TUMS).

**Conflict of Interest**

None

**References**


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Results: The anxiety dimension of attachment to God was significantly correlated with the severity of anxiety, but the avoidance dimension had no direct effect on any of the symptoms. Also, the anxiety dimension was found to be positively correlated with depression and stress indirectly via self-compassion. However, in the case of the avoidance dimension, no such relationship was observed. As a result, attachment anxiety causes a decrease in self-compassion in this group of women, and this, in turn, results in more severe psychopathological symptoms like anxiety, stress, and depression.

Background: In many of past studies, the strong role of God as an attachment figure in reducing psychopathological symptoms has been confirmed. In an effort to account for the effectiveness of attachment to God in mitigating psychopathological symptoms in healthy people we came upon self-compassion as a potential mediating variable in this process. Hence, in the current research, we studied this relation in Iranian Muslim women diagnosed with breast cancer.

Methods: A total of 360 Muslim women diagnosed with breast cancer were asked to fill the Attachment to God Inventory, Self-Compassion Scale, and Depression, Anxiety, and Stress Scale. Data were analyzed using path analysis method with AMOS 22.

Results: The anxiety dimension of attachment to God was significantly correlated with the severity of anxiety, but the avoidance dimension had no direct effect on any of the symptoms. Also, the anxiety dimension was found to be positively correlated with depression and stress indirectly via self-compassion. However, in the case of the avoidance dimension, no such relationship was observed. As a result, attachment anxiety causes a decrease in self-compassion in this group of women, and this, in turn, results in more severe psychopathological symptoms like anxiety, stress, and depression.

Conclusion: Considering the results of this study, we conclude that improvements in the mental health of Muslim women diagnosed with breast cancer are not exclusively achieved by attachment to material symbols. Rather, attachment to God as a spiritual symbol can have a great impact on the mental health of these women. In fact, secure attachment to God can help improve mental health through positive effects on self-compassion and should be considered as a treatment in psychological interventions.

Introduction
Cancer is a major public health concern around the world. According to the US cancer statistics in 2016, breast cancer was the most common type of cancer (29%) and the second leading cause of cancer mortality in women living in the US. Breast cancer is also the most common types of cancer in Iranian women. Signs of psychopathology, especially depression, stress, and anxiety, are remarkable and noticeable in these patients. Women with breast cancer are more severely affected by psychopathological disorders compared with healthy people and other cancer patients, which affects their quality of life and coping strategies. Therefore, paying attention to these patients and finding coping strategies for their psychopathological symptoms are very important.
One of the most influential variables in psychopathology is a variety of attachment in people suffering from cancer. Different attachment styles in adults are classified into two categories of anxiety and avoidance. Attachment theory accounts for the different emotional responses that individuals display during illness, especially cancer. According to Bowlby’s attachment theory, finding attachment figures as a safe and accessible haven represents a pattern of self, world, and others in the person’s mind that is named the “internal working model.” If an individual’s experience is positive, representing being accessible and reliable in relation to this source, this pattern is formed positively. That is, the individuals see themselves, others, and the world as a safe and predictable place which makes them securely attached. If the source of the attachment is too intrusive, the pattern formed in the person’s mind becomes negative and insecure. Those who experience secure attachment with the help of reliable internal support resources in times of stress and distress will gain perceptions of self-efficacy and self-regulation that make it possible for them to have effective coping with stress and distress. Although attachment begins in early childhood, it continues until adulthood and later. Then, notice to different types of attachment symbols are developed, and—like the childhood—as attachment security increases, mental health increases. The next important issue to be considered is that without accounting for the role of God in the lives of his believers, we can’t entirely study attachment relationships in this group. Indeed, attention to all aspects of attachment enables us to find a complete picture of the attachment system in individuals.

Attachment to God is very similar to the attachment of a child to his caregiver: as children’s attachment system is activated in stressful situations, making them seek parental care and support, adults find God as a safe and secure haven. A secure attachment to God and creating a secure working model of God in one’s mind increase tolerance for hardships of life. In contrast, if the image of God in someone’s mind is an unkind and insecure one, the impacts on them will be negative.

One of the important questions in this regard is how types of attachment to God influence the symptoms of psychopathology. In response to this question, Homan found self-compassion to be a mediating variable in the association between attachment to God and mental health outcomes, i.e., life satisfaction, in healthy people, suggesting that secure attachment to God in healthy people can increase satisfaction with life and reduce anxiety and depression by increasing self-compassion. Self-compassion means “being kind and understanding toward oneself” and is considered as one of the strategies for emotional regulation. A person with higher self-compassion does not judge and compare himself or herself with ideal criteria; this person does not need an image other than what he or she has to accept. Self-compassion can help patients to enhance their ability to cope with the disease by improving self-regulation, namely, using healthy behavior instead of maladaptive defensive behavior. Cancer is one of the most stressful diseases, and self-compassion can potentially be very effective in reducing psychopathological symptoms and improving quality of life in this population.

According to the attachment theory, the need for attachment and search for a safe haven is greater in life’s difficult moments, such as illness and fear, compared with other times. Also, it is notable that, in some studies, the effects of attachment types on the psychopathological symptoms in some cancer cases have resulted in different outcomes. For instance, Hinnen and colleagues found that avoidant attachment had no relationship with increased psychological suffering of cancer patients, whereas this was not the case for attachment anxiety. However, in Rodin’s study, both attachment anxiety and avoidance were associated with increased depression. Studies on the mediating role of self-compassion have mostly used healthy subjects to investigate the association of the dimensions of attachment (anxiety and avoidance) with psychopathological symptoms; therefore, analyzing the role of self-compassion as an important factor in decreasing anxiety merits more consideration.

Considering the range of psychological problems in breast cancer patients and the importance of strategies to reduce the symptoms of psychopathology in them and given the significance of God as an attachment figure for Muslims, the present study is to investigate the mediating role of self-compassion in the relationship between attachment to God and psychopathological symptom in Muslim women with breast cancer in Iran. The expected conceptual model in this study is shown in Figure 1.
Methods

Participants and Procedures

Based on a 95% confidence level, 80% statistical power, 75 manifest variables and 11 latent variables, and an effect size of 0.5, the required sample size was calculated to be 357. A total of 360 breast cancer patients were recruited via convenience sampling from the Breast Disease Research Center of Shahid Motahari Polyclinic in Shiraz, Iran, from May to July 2017. The participants had completed their treatment. Patients were excluded if they had a chronic illness, suffered from severe psychological trauma (such as accident or death) over the past year, or had a diagnosis of a disease affecting the psychological disorders (like hyperthyroidism). After signing the informed consent form, the patients completed the questionnaires in the clinic. For illiterate patients, the researcher or patient’s attendant read the questions to them and recorded their answers. Data were collected using three questionnaires including attachment to God, DASS-21 short form questionnaire and self-compassion questionnaire.

Depression, Anxiety, and Stress Scale

The Persian version of the DASS-21 questionnaire, originally developed by Lovibond and Lovibond, was used to measure the psychopathological symptoms of the study sample. This questionnaire contains 21 items, and its main application is to measure the severity of the main symptoms of anxiety, depression, and stress. Each scale consists of 7 items rated on a 4-point scale from 0 (Did not apply to me at all) to 3 (Applied to me very much). To complete the questionnaire, the person should specify the status of symptoms within a week. According to the results, the Cronbach’s alpha coefficients for depression, anxiety, and stress were 0.86, 0.77, and 0.86, respectively.

Self-Compassion Scale (SCS-26)

The questionnaire, developed by Kristin Neff, consists of 26 questions rated on a 5-point Likert-type scale (1 = almost never to 5 = almost always) and includes 6 subscales of self-kindness, self-judgment, common humanity, isolation, mindfulness, and over-identification. The higher total score in this questionnaire means more self-compassion. Cronbach’s alpha in this research was 0.83 for self-kindness, 0.74 for self-judgment, 0.71 for common humanity, 0.78 for isolation, 0.69 for mindfulness, 0.67 for over-identification, and 0.92 for the total score. In this research, the validated Persian version was used.

Attachment to God Inventory

The Attachment to God Inventory, derived from the Kirkpatrick model, was developed by Beck and McDonald. The questionnaire has 28 items rated on a 7-point scale (disagree strongly = 1, agree strongly = 7), with items 4, 8, 13, 18, 22, 26, and 28 being reverse scored. The questionnaire has two subscales assessing the two dimensions of attachment, namely, avoidance and anxiety (14 items each). The items are arranged in such a way that even-numbered questions assess the avoidance and odd-numbered items assess the anxiety dimension. Given the inventory developers’ permission to drop items 14 and 16 (these two items of the avoidance dimension correlated strongly with the anxiety dimension), in this study 26 items were used. The alpha coefficient obtained in this research was 0.82 for the anxiety dimension and 0.77 for the avoidance dimension. The alpha coefficient for the whole scale was 0.78, which indicates the desired reliability of the questionnaire in the present study. The questionnaire is valid and reliable in Iran.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Description</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Mean (SD), range, year</td>
<td>47.32 (33.38), [20-83]</td>
<td></td>
</tr>
<tr>
<td>Time from diagnosis</td>
<td>Mean (SD), range, months</td>
<td>38.81 (41.12), [1-288]</td>
<td></td>
</tr>
<tr>
<td>Marital status</td>
<td>Married</td>
<td>306 (85%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Divorced/separated</td>
<td>6 (1.7%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Single/never married</td>
<td>37 (10.3%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Widowed</td>
<td>11 (3.0%)</td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td>High school or less</td>
<td>141 (39.2%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Some college</td>
<td>152 (42.2%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>College</td>
<td>57 (15.8%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Master’s or higher</td>
<td>10 (2.8%)</td>
<td></td>
</tr>
<tr>
<td>Employment</td>
<td>Employed</td>
<td>90 (25%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Housewife</td>
<td>270 (75%)</td>
<td></td>
</tr>
<tr>
<td>Type of treatment</td>
<td>Surgery</td>
<td>17 (4.7%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chemotherapy/surgery</td>
<td>51 (14.2%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Radiotherapy/surgery</td>
<td>4 (1.1%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chemotherapy/radiotherapy/surgery</td>
<td>288 (80%)</td>
<td></td>
</tr>
<tr>
<td>Type of cancer</td>
<td>Metastatic</td>
<td>44 (12.2%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nonmetastatic</td>
<td>316 (87.8%)</td>
<td></td>
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</tbody>
</table>
Results

According to the demographic information in Table 1, the average age of the participants was 47.32 years (SD = 33.38, range: 20-83), and the duration of the first diagnosis was 38.81 months (SD = 41.12, range: 1-288). Eighty-five percent of the participants were married, 10.3% single, 1.7% divorced, and 1% widowed. In terms of education, 39.2% of the participants had a high school diploma or less, 42.2% had some college education, 15.8% had a bachelor’s degree, and 10% had a master’s degree or higher. The majority of the patients had undergone all three treatments (chemotherapy, radiation therapy, and surgery), and a small number had received surgery plus radiation therapy. Only 12.2% of them had metastatic cancer.

Table 1. Descriptive statistics (mean, standard deviation [SD], range) and correlations between variables

<table>
<thead>
<tr>
<th>variable</th>
<th>Mean (SD)</th>
<th>Range</th>
<th>Depression</th>
<th>Anxiety</th>
<th>Stress</th>
<th>Self-compassion</th>
<th>AxGA</th>
<th>AvGA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>11.63 (10.97)</td>
<td>0-21</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>10.85 (9.3)</td>
<td>0-32</td>
<td>0.74**</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stress</td>
<td>18.37 (11.77)</td>
<td>0-21</td>
<td>0.75**</td>
<td>-0.75**</td>
<td>-0.57**</td>
<td>0.72**</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Self-compassion</td>
<td>3.26 (0.79)</td>
<td>1.15-5</td>
<td>-0.75**</td>
<td>-0.65**</td>
<td>-0.79**</td>
<td>-0.72**</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>AxGA</td>
<td>49.9 (17.58)</td>
<td>17-95</td>
<td>0.45**</td>
<td>0.47**</td>
<td>0.47**</td>
<td>-0.57**</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>AvGA</td>
<td>18.4 (8.48)</td>
<td>12-75</td>
<td>-0.33</td>
<td>0.002</td>
<td>-0.2</td>
<td>-0.02</td>
<td>-0.01</td>
<td></td>
</tr>
</tbody>
</table>

Note: AxGA, Anxious God Attachment; AvGA, Avoidant God Attachment
* P < 0.05; ** P < 0.01

The results of the analysis of the model are shown in Table 3. The direct relationship between the anxiety dimension of attachment to God and self-compassion and anxiety was significant. Also, self-compassion had a direct relationship with all the three scales of psychopathological symptoms examined. No other significant direct relationship was observed.

The coefficients for indirect effects (Table 3) were estimated using the bootstrap function in AMOS 22, with a repetition of 5000 and a 95% confidence interval. It is evident that only the anxiety dimension of attachment to God is significantly and positively correlated with and three symptoms of psychopathology, with the strongest relationship being between stress and the anxiety dimension of attachment (B = 0.44, 95% CI = 0.37-0.45).

It can be concluded that there is both direct and indirect relationship between the anxiety and dimension of attachment to God. In the case of the other two psychopathological variables, stress and depression, this relationship is only indirect, mediated by self-compassion. The avoidance dimension of attachment to God does affect symptoms of psychopathology directly or through self-compassion.

We used fitness indicators to evaluate the model. These indices can determine the suitability of the model for the data. For our model, root mean square error of approximation (RMSEA) was 0.001, Comparative Fit Index (CFI) 0.99, and incremental fit index (IFI) 0.99. Since the first criterion is close to zero and the other two criteria are close to one, the model can be said to fit well.35

Because of the effects of education and employment status on dependent variables, the model was retested after controlling for demographic variables. The results indicated that the model had a good fit, and differences were only related to the direct effects: the direct effects of attachment anxiety in women with high school education or less was not significant for any of the psychopathological variables, whereas the relationship with the three variables was significant for employed subjects. For

Statistical Analysis

Descriptive statistics (mean, standard deviation [SD], range) and correlations between variables were calculated using SPSS version 19. AMOS version 22 was used to perform path analysis to test the research hypotheses. Also, we used the bootstrap method to determine the significance of the indirect paths.
Self-compassion is the cause of many good attributes, such as optimism, and the ability to deal with harsh situations in life and helps individuals to see all the different aspects of the same issue, and improve their quality of life. Through their proper internalization of receptive and accessible attachment figures, people with safe attachment develop the capacity to create a sensation of self-efficacy which improves their self-regulation. In fact, self-compassion can be defined as positive self-esteem toward oneself.

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Self-compassion is one of the self-regulation methods in people that is linked with sense of relief and satisfaction. In people with attachment anxiety, this relation is not a secure haven. As a result, self-efficacy that was meant to work as a heart some fact as God’s aid does not have any impact but reduces their self-compassion. Self-Compassion is not just a single attribute, rather is a variable that affects other positive attributes to change and has a vast effect on different characteristic variables. Compassion plays a role as a protector against anxiety, stress, and depression symptoms on patients with cancer and enhances patients’ satisfaction with life. Women with breast cancer can make a better vision of themselves by concentrating on compassion, and it can drastically decrease their mental pain and suffering.

This model for anxious attachment to God is comparable to that of a model on healthy people, but this was not the case for the avoidance dimension of attachment to God: the avoidance dimension also correlates with psychopathological symptoms in healthy individuals too, but in our study, there was no significant correlation.

It seems that avoidant attachment in individuals with cancer has no relationship with psychopathological symptoms. The reason for this can be seen in the coping strategies of individuals with avoidant attachment. They are unable to express their need for an attachment source because of the use of reciprocal strategies.

women with university education, the direct effect was significant for anxiety and stress. The model for women with some college education and housewives were similar to the crude model.

**Discussion**

Our model showed that the relationship of anxiety dimension of attachment to God with psychopathological symptoms was mediated via self-compassion, although attachment anxiety had a direct effect on increasing the anxiety level in women with breast cancer. Secure attachment to God can help improve anxiety and other psychopathological symptoms in a direct manner, by affecting the nervous system, as well as an indirect manner, by increasing self-esteem. Self-compassion can be defined as positive self-esteem toward oneself.

**Table 3. Direct and indirect effects for the mediation model**

<table>
<thead>
<tr>
<th>Table 3. Direct and indirect effects for the mediation model</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Criterion variable</strong></td>
</tr>
<tr>
<td>------------------------</td>
</tr>
<tr>
<td>Depression R² = 0.83</td>
</tr>
<tr>
<td>Anxiety R² = 0.78</td>
</tr>
<tr>
<td>Stress R² = 0.92</td>
</tr>
<tr>
<td>self-comp R² = 0.33</td>
</tr>
</tbody>
</table>

**AxGA:** Anxious God Attachment; **AvGA:** Avoidant God Attachment; **self-comp:** self-compassion

* P < 0.05
coping methods, which makes them even refuse to demonstrate and confess to their psychological problems. In fact, in difficult times when psychological suffering is greater than their endurance, these individuals tend to deny and suppress perceived psychological suffering despite the increased need for close proximity to attachment figures. Therefore, it can be said that the symptoms of the psychopathology expressed in this group are not necessarily the true suffering perceived in them. Of course, this relationship varies in different studies, and some studies have actually found a significant relationship. Perhaps the type of cancer and the severity of the disease also contributes to this.

The current model has a good consistency even after controlling for demographic variables, and there were only some differences in direct effects of attachment anxiety on psychopathological symptoms. These differences can be accounted for by similarities of psychopathologic symptoms with each other and their similar origin, which can make it difficult to distinguish between them.

The mediating effect of self-compassion in the relationship between attachment anxiety and depression and stress has been demonstrated in previous research. As a result, those who perceive God as being almighty, always present, kind, and gracious, can also be compassionate to themselves, and this alleviates their psychopathic symptoms greatly.

Based on the results of this study, we can recommend clinicians and psychological health professionals to consider using attachment to spiritual and religious figures such as God to help their patients, especially those in terminal stages of the disease. Safe attachment to God can even affect threat structure in the brain, which can reduce the huge costs of psychiatric interventions in these individuals.

Also, according to the results of this study, reducing the anxiety dimension of attachment to God can increase self-compassion in these individuals. Moreover, self-compassion can strengthen other positive personality traits, such as optimism and acceptance of life events, and helps the patient to see different aspects of an event, resulting in improved quality of life.

Given the fact that cancer patients require a safe haven, attachment to God as an omnipotent and omnipresent entity can play a safe supporting role for these patients; and since this can affect other psychological functions of the individuals to reduce their psychopathological symptoms, it would be helpful to include encouraging attachment to God in psychological and clinical interventions for these patients.

Acknowledgment
We thank all the people who collaborated with the authors of this study in this project, especially the staff and nurses of the Breast Disease Research Center of Shahid Motahari Clinic in Shiraz and Clinical Research Center of Namazi Hospital for assisting us with statistical analysis and all patients with breast cancer who kindly participated in our study in spite of their difficult and suffering conditions.

Conflict of Interest
None.

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The study findings indicated a significant, negative correlation between mental well-being, existential well-being, and religious well-being and death anxiety in patients with breast cancer (α = 0.05).

Methods: In this descriptive, correlational study, the statistical population included all women with breast cancer referred to Shahid Rahimi Hospital in 2017. A sample of 100 patients was selected through convenience sampling and data were collected using Templer’s Death Anxiety Scale, the Warwick-Edinburgh Mental Well-being Scale, and the Spiritual Well-being Scale. For the purpose of data analysis, mean, standard deviation, Pearson’s correlation coefficient and multiple regression were applied using SPSS 22.

Results: The study findings indicated a significant, negative correlation between mental well-being, existential well-being, and religious well-being and death anxiety in patients with breast cancer (α = 0.05).

Conclusion: According to the results of this study, mental, existential, and religious well-being are important contributors to mental health and quality of life of patients with breast cancer. Therefore, enhancing these components in cancer patients can be introduced as a complementary treatment along with medical treatments in order to improve psychological problems in clinical settings.
two components of psychological action and affection from two distinct perspectives: a pleasure view and virtuosity view. Positive and negative emotions can affect the health and illness of people suffering from cancer by influencing the immune system. Various studies suggest that patients with cancer have low mental well-being. Mental well-being has a close but complex association with values, and the criteria based on which people evaluate their perception of happiness are different. In fact, achieving well-being and satisfaction is the ultimate goal of life, and feelings of sadness and dissatisfaction are often regarded as constraints to performing the tasks.

Another common psychological experience in cancer patients is death anxiety. Death anxiety involves the thoughts, fears, and emotions associated with the end of life. As a matter of fact, it is defined as an abnormal fear of death or apprehension when thinking about the process of dying and issues that occur after death. Death is one of the most important ontological concerns. Proponents of terror management theory maintain that the most important function of religion is to help cope with the awareness of death. Human beings always struggle with this awareness that they will die eventually. Religion reduces this anxiety because it claims that life does not end with death. Religion thus provides a kind of psychological security and hope for eternity and increases the level of the individual’s well-being.

Spiritual well-being is one of the basic yet important concepts regarding how to deal with the problems and tensions caused by cancer. It has two dimensions, namely, existential and religious well-being. Religious well-being refers to the satisfaction of having a relationship with a superior power, while existential well-being refers to an attempt to understand meaning and purpose in life. When spiritual well-being is seriously compromised, a person may experience mental disorders such as loneliness, anxiety, and loss of meaning of life. Patients whose spiritual well-being is reinforced can effectively adapt to their illness and perhaps spend the last stages of their illness better. Therefore, support from mental or religious sources and a relationship with a superior power can help improve the quality of life, mitigate mental disorders, provide interpersonal support, reduce the severity of disease symptoms, and affect positive medical outcomes. In fact, a significant number of studies on the relationship between spirituality and mental health and patient recovery have confirmed a significant, positive effect of spirituality on mental health. The findings of a study aimed to determine the relationship between spiritual health and anxiety and depression in cancer patients at end-of-life stages in the UK suggest a significant relationship between spiritual well-being and anxiety in these patients.

Hall and colleagues found that God’s remembrance developed positive feelings about life, friends, family, and relatives in a group of breast cancer patients. This suggests that the medical team may be able to increase happiness and enthusiasm in the affected women by means of prayers, worship, and remembrance of God. Moreover, McMahon’s study suggested a significant relationship between spiritual well-being and anxiety in patients with cancer. The objective and historical experience of mankind is indicative of the fact that no human being is eternal in this world, and sooner or later all human beings will experience death. Whether young, old, weak, or full of existence, we all confront this fate. Life is essentially a means to die, and so death may even be viewed as being more important than life. If an individual lives a life full of fun and enthusiasm, merely following ordinary superficial rational rules, then he or she can be expected to fear death, because that would be interpreted as the end of their happiness. Likewise, people living a helpless and lonely life would be expected to feel happy upon their death, because it would signal the end of their misery. However, this is not what usually happens with this population. Interestingly, it has been shown that those who live in vain are more afraid of dying than others are.

Those who express great love towards life are less afraid of death in comparison with those who live a superficial life. Those who have a meaningless life cannot give meaning and value to death. In fact, individuals who have passed through different stages of life with satisfaction experience a mental feeling of well-being as well as satisfaction and accept death as a reality. Since denial is the simplest and most inappropriate way of dealing with any unfortunate event, such as death, the first step of coping is to recognize this painful fact. Moreover, acceptance of the ultimate reality of death can demonstrate the peak of an individual’s emotional maturity. Such psychological factors affect other important parameters including patients’ quality of life, immune system, the course of illness, treatment efficacy, duration of hospital stay, and even survival. In addition, studies have reported conflicting findings regarding the relationship between spiritual well-being, mental health, and death anxiety in cancer patients. Therefore, the present study aimed to investigate the relationship between mental well-being, existential well-being, and religious well-being and death anxiety in women with breast cancer.

**Methods**

In this descriptive-correlational study, predictor variables included mental, existential, and religious well-being and the dependent variable was death anxiety. The statistical population of the study consisted of patients with breast cancer referred to Shahid Rahimi Hospital in Khorramabad, Iran, in 2017. The sample size was determined to be 100 according to Morgan’s sampling table, and the
participants were recruited through convenience sampling. Selection criteria included being 20 years old or older, having a definite diagnosis of breast cancer, being aware of the medical diagnosis, lacking mental illness, and being willing to participate in the study.

**Research Instruments**

**Templer’s Death Anxiety Scale (DAS)**

Templer’s Death Anxiety Scale contains 15 questions that assess the subject’s attitudes towards death. The subject answer to each question with a “yes” or “no,” where “yes” indicates anxiety in that area. Total score ranges from 0 to 15, with a higher score corresponding to a higher level of anxiety. Templer obtained a test-retest reliability coefficient of 0.83 for the scale. In Rajabi and Bohrani’s study, the split-half reliability of the DAS was calculated to be 0.62 using the Spearman-Brown prediction formula.

**Warwick-Edinburgh Mental Well-being Scale (WEMWBS)**

This 14-item scale, developed by Tenant et al., is rated on a 5-point Likert scale (1 = never to 5 = always). The minimum and maximum scores on this scale vary from 14 to 70, with a higher score indicating a higher level of psychological well-being. Cronbach’s alpha coefficient for this scale was 0.89 for a sample of students and 0.91 for the community. Cronbach’s alpha coefficient for the scale estimated by Clarke et al. was 0.87. The test-retest reliability of the scale was relatively high (r = 0.66), and the scale showed good correlation with other scales such as the Psychological Well-being Scales (r = 0.59), the short form of the Mental Health Continuum (r = 0.65), and the well-being index of the World Health Organization (r = 0.57). The Persian version of the questionnaire had a Cronbach’s alpha coefficient of 0.78 for the entire scale.

**Spiritual Well-Being Scale**

This instrument was developed by Palutzin and Ellison in 1982, containing 20 items and two subscales. Odd-numbered questions are related to religious well-being and measure the individual’s experience of a satisfactory relationship with God, and even-numbered questions are related to existential well-being and measure the feeling of purposefulness. The items are scored on a 6-point Likert scale ranging from totally agree to totally disagree. In one study, Palutzin and Ellison reported Cronbach’s alphas of 0.91, 0.91, and 0.93, for religious, existential, and cognitive well-being, respectively. In another study, alpha coefficients for the whole scale, religious dimension, and existential dimension were reported to be 0.90, 0.82, and 0.87, respectively, in a sample of male and female students. Moreover, the whole scale and its religious and existential dimensions were found to have good test-retest reliability (0.85, 0.78, and 0.81, respectively). The data were analyzed using SPSS 22. Means, standard deviations, Pearson correlation coefficients, and multiple regression were utilized for the purpose of data analysis. The significance level was considered to be 0.05 in all tests.

**Results**

In this study, the mean age of participants was 49.06 years. In terms of education, 54 had finished middle school, 18 had a high school diploma, 13 had received an associate degree, and 15 held a bachelor’s degree or higher. Additionally, 69 of the participants were married, and 31 were single. Seventy-two of participants lived in the city, 28 in the village. Fifty-nine people were employed, while 41 were not employed. As shown in Table 1, the highest and lowest mean belonged to mental well-being and death anxiety, respectively. Moreover, the highest and lowest standard deviation belonged to existential and religious well-being.

According to Table 2, there was a significant negative relationship between spiritual, existential, and religious well-being and death anxiety (R = 0.505). In other words, the higher the mental, existential, and religious well-being of the patients, the lower the level of their death anxiety.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>Standard deviations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mental well-being</td>
<td>3.74</td>
<td>0.73</td>
</tr>
<tr>
<td>Existential well-being</td>
<td>3.27</td>
<td>0.75</td>
</tr>
<tr>
<td>Religious well-being</td>
<td>3.73</td>
<td>0.58</td>
</tr>
<tr>
<td>Death anxiety</td>
<td>1.67</td>
<td>0.65</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mental Well-being</th>
<th>Existential Well-being</th>
<th>Existential Well-being</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death anxiety</td>
<td>-0.220 0.028</td>
<td>-0.282 0.004</td>
<td>-0.502 &lt;0.001</td>
</tr>
</tbody>
</table>
As shown in Table 3, the obtained value of F for the predictor variables (mental, existential, religious) was 10.954, which, on the basis of the significance level, reveals that the variables could be used to predict death anxiety in the sample (P < 0.001).

Based on the results of multiple regression, there was a significant relationship between mental, existential, and religious well-being and death anxiety (α = 0.05). The analysis of the regression model showed that the variables of mental, existential, and religious well-being can predict 51% of the variance in patients’ death anxiety.

### Table 3. The Results of Prediction of Death Anxiety Variance by Predictors (Mental, Existential, Religious Well-being)

<table>
<thead>
<tr>
<th>Sum of Squares</th>
<th>Degree of Freedom</th>
<th>Mean Square</th>
<th>F</th>
<th>Sig</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regression</td>
<td>1171.389</td>
<td>3</td>
<td>390.463</td>
<td>10.954</td>
</tr>
<tr>
<td>Residual</td>
<td>3421.851</td>
<td>96</td>
<td>35.644</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>4593.240</td>
<td>99</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 4. Estimation of Regression of Death Anxiety by Predictive Variables (Mental, Existential, and Religious Well-being)

<table>
<thead>
<tr>
<th>Dependent Variable</th>
<th>Independent Variables</th>
<th>Nonstandardized Coefficients</th>
<th>Standardized Coefficients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant value</td>
<td>13.974</td>
<td>5.802</td>
<td>2.408</td>
</tr>
<tr>
<td>Mental well-being</td>
<td>-0.329</td>
<td>0.105</td>
<td>-0.329</td>
</tr>
<tr>
<td>Existential well-being</td>
<td>-0.153</td>
<td>0.170</td>
<td>-0.273</td>
</tr>
<tr>
<td>Religious well-being</td>
<td>-0.703</td>
<td>0.151</td>
<td>-0.536</td>
</tr>
</tbody>
</table>

### Discussion

The results of this study indicated that there was a significant, negative relationship between mental, existential, and religious well-being and death anxiety in patients with breast cancer. In other words, with an increase in mental, existential, or religious well-being, the level of death anxiety decreases. In fact, the study findings are in line with the findings of previous research.13,18 Regarding the interpretation of these findings, it can be concluded that breast cancer is a frightening and an anxiety-provoking event for many women, so feelings of grief, fear of death, confusion, and anger are considered as natural responses in the process of diagnosis and treatment of this medical condition.

Unfortunately, in addition to the difficulties and hassles associated with the medical complications of breast cancer, there exist social stereotypes and taboos for cancer patients. For example, cancer is viewed by most people as equating to imminent death, hence the actions and reactions of patients are often coordinated with these social stereotypes, more than with the real risks of death from cancer. Owing to scientific advances, cancer patients can be treated almost completely. Cancer presents itself with fragility, instability, unpredictability, as well as physical and mental damage to the patients, such that it makes it necessary for the patients to rethink and redefine the meaning of life in order to regain their mental well-being. Mental well-being is the greatest wish and the most important goal of human life, which affects people’s mental health more than any other factor.
apparent loss of health, religion helps the patient not to concentrate upon deficiencies and problems, but rather be in search of meaning. In other words, reliance on religious beliefs would make the world meaningful for people, drawing attention to the duties they have towards life and awakening a sense of responsibility to accomplish those duties. Meaningfulness, purposefulness, and hope in life are components which consolidate mental health. As a result, if life is purposeful and meaningful, it is natural that any incident, even though overwhelming, such as intense stress or terminal illnesses, is redirected in a meaningful manner.

In addition to exerting positive effects on death anxiety, religious interventions also improve psychosocial adaptation and well-being among cancer patients. In this sense, individuals with religious orientation will have a greater sense of control and domination over their living conditions through ultra-social attitudes, reliance on God, and mental resources during illness and death and, as a result, will experience better social adaptation. It is recommended that the findings from this study be used by counselors and other mental health professionals for providing more effective treatment plans for women with breast cancer.

Conflict of Interest

None.

Acknowledgments

We sincerely appreciate the management team and personnel at Shahid Rahimi Hospital in Khorramabad, Iran, as well as all the patients who cooperated with us in carrying out this research project.

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16. McMahon RL. The Impact of Spirituality, Social Support, and Defensive/adaptive Coping on Death Anxiety at End of Life: Catholic University of America; 2004.
Conclusion: This psychological approach can be used as a non-pharmacological treatment to improve mental health and quality of life of women with breast cancer.

Background: The goal of this research was to determine the effects of intensive short-term dynamic psychotherapy (ISTDP) on emotional facilitation of emotional expressiveness and defense mechanisms of women with breast cancer.

Results: ISTDP led to facilitation of emotional expressiveness (expression of latent feelings), reinforcement of mature mechanism, and adjustment of neurological and immature mechanisms in patients with breast cancer.

Methods: This was a quasi-experimental study. The statistical population of the study included women with breast cancer who had completed the course of chemotherapy and were referred to Raj psychodynamic center to receive psychological services. Six eligible patients were selected to enter the psychodynamic therapy program based on the Davanloo treatment approach. The participants were selected through purposive sampling and volunteered to be part of the study. Measurement instruments included the Emotional Expressiveness Questionnaire (EEQ) and Defense Style Questionnaire-40. Pre-post data were analyzed using a t-test, Bonferroni correction, and one-variable covariance analysis.

Results: ISTDP led to facilitation of emotional expressiveness (expression of latent feelings), reinforcement of mature mechanism, and adjustment of neurological and immature mechanisms in patients with breast cancer.

Conclusion: This psychological approach can be used as a non-pharmacological treatment to improve mental health and quality of life of women with breast cancer.

Introduction
Breast cancer is the most common cancer among Iranian women and accounts for 25% of all cancers in this population, according to the Iranian Cancer Institute.1,2 The incidence of breast cancer is often a very stressful event. In addition to a high death rate, breast cancer has significant negative effects on emotional and mental health of women and affects different aspects of their lives.3,4 Many breast cancer patients end up losing one or both breasts, causing a feeling of being an amputee in some women. The partial or complete removal of the breast as an important body part is likely associated with a drastic change in body image, decrease in feminine emotions, decrease in sexual attractiveness, anxiety, depression, lack of motivation, embarrassment, rejection, and thoughts of death.5,7 After being diagnosed with breast cancer, many women show a high level of inability and disappointment in adaptation to cancer in their personal and family life.5 These patients need help in adapting to their condition and meeting their disturbed needs to return to their normal lives.5 Cancer patients often use spiritual methods, cognitive reconstruction, hope, and social support to adapt to and accept their illness.8,9 Given the severe psychological stresses in female patients with breast cancer, coping

Key words: Intensive short-term dynamic psychotherapy, emotional expressiveness, defense mechanisms, breast cancer.

ABSTRACT
Background: The goal of this research was to determine the effects of intensive short-term dynamic psychotherapy (ISTDP) on emotional facilitation of emotional expressiveness and defense mechanisms of women with breast cancer.

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Results: ISTDP led to facilitation of emotional expressiveness (expression of latent feelings), reinforcement of mature mechanism, and adjustment of neurological and immature mechanisms in patients with breast cancer.

Conclusion: This psychological approach can be used as a non-pharmacological treatment to improve mental health and quality of life of women with breast cancer.

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mechanisms are necessary for adaptation to the disease. The use of various coping mechanisms in these patients requires their adaptation to the disease, while many women have problems in this regard and are not able to adapt to the conditions of their illness and thus suffer from more problems.  

One of the psychological variables important for cancer patients is emotional expressiveness. Kring and colleagues defined emotional expressiveness as external expressions of emotion regardless of its value (positive or negative) or method (verbal or physical).  

Some people express their emotions more freely and without much fearing the consequences; others tend to be conservative in expressing their emotional states.  

Some people do not express their emotions, yet feel comfortable about it. There are also people in whom the suppression of emotions will increase the risk of psychological distress and physical health problems. Emotions have four main functions: balancing the arousal, developing self-understanding, improving coping skills, and enhancing interpersonal relationships.  

Furthermore, sharing negative emotional experiences is one way to restore emotional balance and protect the health of individuals.  

Being familiar with Freud’s classical psychoanalysis and the defense mechanism, Habib Davanloo developed a series of emotion-focused interventions to mobilize emotions and challenge defense mechanisms to achieve balanced levels after a stressful emotional experience.  

Research indicates that long-term emotional disclosure improves anxiety, insomnia, depression, negative mood, and inhibition, psychological health, physical problems, social abilities, and self-esteem.  

Among psychological variables that should be considered in patients with cancer is the utilization of defense mechanisms. Davanloo has paid special attention to these mechanisms in his dynamic approach. The system of operationalized psychodynamic diagnosis considers defense mechanisms as one of the important factors in relation to the vulnerability of individuals to psychological problems. The *Diagnostic and Statistical Manual of Mental Illness* (DSM) also discusses them as an axis that can be considered in the future. For this reason, the role of defense mechanisms in pathologies, diagnostic processes, therapeutic interventions, and therapeutic outcomes has been identified as one of the reconciliation.  

Defense mechanisms is considered one of the sides of the conflict triangle. They are subconsciously active as internal processes and are initiated in response to intense internal (impulses) or external factors (intermediate situations or real dangers). In addition, distortion of reality modifies the level of anxiety resulted from the conflict between different parts of the character; this anxiety can create psychological distress so great and intense that self-awareness or consciousness would be unable to withstand. Reality distortion is the price a person pays for her feeling of coherence.  

Vaillant classifies defense mechanisms hierarchically based on the maturity, from the most mature defenses at the higher to the most immature defense mechanisms at the lowest levels. This hierarchical model provides the basis of the works of Band and Vaillant. Additionally, the mechanisms mentioned in the DSM-7 are distinguished by Andrews in three styles: mature, neurotic, and immature. Mental health is correlated with mature and adaptive defense styles, and immature and neurotic defensive styles are associated with pathology and disturbance indices. Despite the importance of the role of psychological variables in cancer patients, especially emotional expression and defense mechanisms, not enough attention has been paid to this issue. The provision of any psychological services to promote adaptation to and acceptance of the disease requires the identification of emotions and having a working knowledge of the disease and the ways to deal with it. Also, as cancer brings about a series of changes to the path of one’s life (long-term physical admission, frequent visits to the doctor, various treatments, and high financial costs) and causes countless social, physical, psychological, economic, and family problems, it is crucial to study the psychological factors in order to be able to provide more effective psychotherapy services for these patients. Gates believes that providing counseling to cancer patients will reduce their psychological stress; therefore professional consultation is well received by the patients’ support system and can be very effective in helping patients adjust to the range of emotions they experience.  

In a study on a group of cancer patients, the patients believed that counseling and psychotherapy could be the key to admitting the reality of the disease and to coping more effectively with the psychological problems associated with the illness. In some research interviews, about 29% to 50% of patients find counseling and psychotherapy to be beneficial. In addition to increasing the range of relationships among patients, psychotherapy increases awareness, engagement, and effective decision-making, eases worries, and increases self-esteem.  

Intensive short-term dynamic psychotherapy (ISTDP) is rooted in Freud’s psychoanalytic theory and evolved through the studies of Malan, Mann, Sifneos, Strap, Binder, Davanloo, Polack, Horner, and Diyang. The prominent features of this therapeutic approach are the deep emotional experience during the treatment session, the level of therapist activity, the encouragement of the patient to cooperate, and the active attention to time constraints, as well as the focus of treatment and special selection criteria. ISTDP has yielded positive results in reducing symptoms and reducing disturbances in interpersonal and social/occupational domains. Given the fact that ISTDP has proven its usefulness in
the treatment of psychological disorders and some chronic physical conditions, it might be reasonable to hypothesize that it can also reduce the psychological symptoms of patients with breast cancer. Therefore, the present study aims to investigate the effect of ISTDP on emotional expressiveness and defense mechanisms employed by women with breast cancer.

**Methods**

This was a quasi-experimental study, with the statistical population of women with breast cancer who had completed the course of chemotherapy and were referred to Raj psychodynamic center to receive psychological services. Six eligible individuals were chosen to enter the psychodynamic therapy program based on Davanloo’s approach. The participants were analyzed for emotional expressiveness and the use of defense mechanisms at baseline and after the intervention. The pretest and posttest values were compared using a t test, Bonferroni test, and single-variable analysis of covariance, in addition to Wilks’ Lambda test.

**Measurements**

*Emotional Expressivity Questionnaire (EEQ)*

The questionnaire was developed by King and Emmons to examine the emotional expressivity in three components of positive emotional expression, intimacy, and negative emotional expression. It consists of 16 items rated on a 5-point scale, with the overall score varying between 16 and 80. The correlation between the scores of the EEQ and the Minnesota Multiphasic Personality Inventory and the Bradburn Positive Affect Scale scores are positive. The Persian version of the scale had a Cronbach’s alpha coefficient of 0.68, and alpha coefficients for subscales of positive emotional expressivity, expressive intimacy, and negative emotional expressivity were, 0.65, 0.59, and 0.68, respectively. Reliability of the scale in our study was 0.83, which is accepted as statistically significant.

*Defense Style Questionnaire (DSQ)*

This questionnaire is based on the defense hierarchy model by Andrews et al. and consists of 40 questions rated on a 9-point Likert scale (I totally agree = 1 to I totally disagree = 5). This scale evaluates 20 defense mechanisms in three categories of “mature,” “neurotic,” and “immature” styles. Reliability and validity of the scale were evaluated and determined by Heidarinasab et al. Cronbach’s alpha coefficients for the scale were 0.71 and 0.78 in precollege and college students, respectively. The correlation coefficient obtained from the split-half method was 0.54. Reliability of the scale in our study was 0.76, which is acceptable.

**Intervention**

The participants received 15 two-hour sessions of therapy, twice a week, based on Davanloo’s intensive short-term dynamic psychotherapy (ISTDP-D) method in the following seven steps (Table 1).

**Results**

According to Table 2, the age of the participants was between 36 to 51 years, and four of them had used psychotherapy and/or psychiatric medications during their survivorship. Four of the patients had a university education, while two had a high school diploma. Moreover, two of the subjects were housewives, one was a teacher, one a student, one worked as a salesperson, and one was an accountant.

<table>
<thead>
<tr>
<th>Table 1. The intervention protocol used in the study</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Asking about the patient’s problem: Searching for symptoms of a disorder; emphasis on objective and specific responses; focus on feelings.</td>
</tr>
<tr>
<td>2. Pressure: Asking for a more detailed and objective explanation; focusing on defenses; awakening transitional feelings; regulating anxiety; stimulating commitment therapy, etc.</td>
</tr>
<tr>
<td>3. Challenge: Identifying and clarifying defenses; stimulating the patient against his own defenses.</td>
</tr>
<tr>
<td>4. Transitional resistance: Challenging with transitional resistance; direct involvement with transitional resistance; targeted commitment therapy against resistance; emphasizing the refusal of the patient from emotional proximity to the therapist, emphasis on the patient’s need for self-defeating in the treatment process to withstand resistance, etc.</td>
</tr>
<tr>
<td>5. Direct access to the unconscious: Direct experience of transitional feelings and the first breakthrough; experience of feeling in cognitive/physiological and motor dimensions; creating a relationship between transitional feelings and the patient’s far and near past.</td>
</tr>
<tr>
<td>6. Transition analysis: Association and analysis of similarities and differences between the patient’s communication patterns in the individual’s relationships in their current/past life and transition; creating a relationship between the triangle of conflict (defenses, anxiety, feelings) and the triangle of personality (transition, current relationships, past).</td>
</tr>
<tr>
<td>7. Dynamic examination of the unconscious: Systematic and deeper exploration of the sides of the conflict triangle and the personality triangle; exploring the family life of the patient; consolidating the insight</td>
</tr>
</tbody>
</table>
There was a significant decrease in the overall score of defense mechanism from baseline to postintervention (215 vs 98.33). Except for the mature defenses, the decrease was observed in the immature and neurotic defensive styles. In other words, ISTDP enhanced the expression of the emotions and strengthened the mature defense styles on the one hand, and, on the other hand, reduced the immature and neurotic defense styles in patients with breast cancer (Table 3). Before using the parametric test, an analysis of variance with repeated measurement was performed using Mauchly’s test of sphericity and Greenhouse-Geisser test to check for violation of assumptions of the technique.

Based on the findings presented in Table 4, the Multivariate Lambda Wilks statistics are statistically significant at 95% confidence level. Therefore, the null hypothesis is rejected and it is determined that the dependent variables are in fact influenced by the independent variable. More precisely, the results of this experiment show that ISTDP was effective in improving the participants’ emotional expressivity and defense styles. Effect sizes for defense styles and emotional expressivity were 0.912 and 0.992, respectively.

The results of the within-subjects test in Table 5 show that ISTDP had a significant impact on emotional expressivity and defense styles. Therefore, it can be said that this treatment approach facilitated the expression of emotions of the participants and developed more mature defense mechanisms. Effect sizes for defense styles and emotional expressivity were 0.912 and 0.992, respectively.

<table>
<thead>
<tr>
<th>Table 2. Descriptive characteristics of the participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
</tr>
<tr>
<td>Age, year</td>
</tr>
<tr>
<td>Morbidity duration, year</td>
</tr>
<tr>
<td>History of psychotherapy</td>
</tr>
<tr>
<td>History of using psychiatric drugs</td>
</tr>
<tr>
<td>Education</td>
</tr>
<tr>
<td>Job</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 3. Pre-post comparison of emotional expressivity and defense styles and their components</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variables</td>
</tr>
<tr>
<td>------------</td>
</tr>
<tr>
<td>Emotional Expressivity</td>
</tr>
<tr>
<td>Positive emotion</td>
</tr>
<tr>
<td>Intimacy expressive</td>
</tr>
<tr>
<td>Negative emotion</td>
</tr>
<tr>
<td>Defense Styles</td>
</tr>
<tr>
<td>Mature defenses</td>
</tr>
<tr>
<td>Neurotic defenses</td>
</tr>
<tr>
<td>Immature defenses</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 4. The results of Wilks' Lambda test for emotional expressivity and defense styles in women with breast cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variables</td>
</tr>
<tr>
<td>-----------</td>
</tr>
<tr>
<td>Defense Styles</td>
</tr>
<tr>
<td>Emotional expressivity</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 5. The results of Within-Subjects tests of difference associated with emotional expressivity and defense styles in women with breast cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variables</td>
</tr>
<tr>
<td>-----------</td>
</tr>
<tr>
<td>Emotional expressiveness</td>
</tr>
<tr>
<td>Defense styles</td>
</tr>
</tbody>
</table>
The findings in Table 6 show that the total postintervention scores for emotional expressiveness and defense styles are respectively higher and lower compared with baseline. This means that the intervention was effective in the participants.

**Discussion**

The goal of this study was to determine the effectiveness of ISTDP in improving emotional expressiveness and defense styles of women with breast cancer. The findings of this study showed that ISTDP treatment was effective in facilitating the expression of emotions, the development of mature defense styles, and the modification of immature and neurological defense styles. ISTDP also appears to help patients with their conflicts or emotions. Conflicts and emotional fluctuations are often a result of the losses and psychological damage that occur to people with breast cancer. These results are congruent with the findings of other studies regarding the effectiveness of this therapeutic approach. Kramer and colleagues showed that the clarifying of defense mechanisms and psychological symptoms improves the immune function, reduces sadness, increases adaptability, reduces resistance and defensiveness, and also reduces the phenomenon of resubmission of the disease in individuals. Johansson et al. showed that ISTDP can have a positive effect by improving emotional factors at a subconscious level. The findings of Angeletti et al. indicated that ISTDP had a significant decreasing effect on the levels of depression, anxiety, and suicidal thoughts, while its effect on the feeling of disappointment was relatively small. Hilsenroth et al. showed that ISTDP significantly improved depression and some interpersonal problems. The research by Mahdavi et al. found that ISTDP lowered mortality rates, feeling of loneliness, depression, and anxiety in women with breast cancer, consequently improving their quality of life. Beutel et al. also showed that ISTDP is widely used to treat depression and improve the quality of life in women with cancer. Leutritz et al. suggested that short-term psychosocial therapy has a significant effect on quality of life and physical and emotional functioning.

In explaining the findings of this study, it can be said that the activation of some rigid, extreme, and resistant beliefs in cancer patients causes rumination, often followed by symptoms of mood and anxiety disorders, eventually affecting the person’s attitudes and thoughts. Because of the diagnosis of cancer, these patients experience conflicting feelings about the doctor, family, and people around them. In a way, these women may think of them as the causes of their illness and thus try to punish them by social isolation and noncompliance with the treatment process. Therefore, instead of accepting the illness and receiving comprehensive help, they may try to distort the reality of their condition by using defense mechanisms in order to reduce their anxiety. They mostly use mechanisms that are very basic and immature. Since the use of these mechanisms is unconscious, they cannot see how these psychological mechanisms harm them. Patients with cancer using neurotic and immature defense styles cannot easily perceive and experience feelings of anger, guilt, and self-consciousness. Therefore, they are possibly unable to readily express emotions. On the other hand, when the mood and anxiety problems of cancer patients reach their highest levels, the patient may lose the ability to show appropriate emotional response and can get irritated more easily. This will lead to ambivalence in expressing emotions, and subsequently, metacognitive beliefs of the patient will also be affected. One of the main goals of dynamic psychotherapy is to increase the awareness and tolerance of patients about the highly mixed and conflicting feelings in their lives. The goal of ISTDP is to make patients able to accept, dominate, and integrate a wide range of human emotions. This approach uses techniques of unlocking unconscious and illustrating feelings mildly and empathically to help patients confront conflicts caused by cancer, past relationships, and relationship with the therapist. By acquiring insight into their emotions and the ways of inhibiting them, patients will be able to reconcile their emotional conflicts. Given that people with breast cancer suppress their emotions and avoid community involvement to prevent rejection, expressing emotions in a safe environment, without feeling uncomfortable in front of the therapist, can improve their social functioning. This process makes it possible for patients to abandon maladaptive styles that they use to communicate with themselves and others and adopt more developed and mature styles instead.

**Conflict of Interest**

The authors have none to declare.

**Acknowledgment**

Authors sincerely thank all the patients who participated in this study and those who patiently helped us during this study.
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30. Trief PM, Donohue-Smith M. Counseling needs...


Parotid Gland: An Unusual Site for Breast Cancer Metastasis: A Case Report and Review of Literature

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Abstract

**Background:** Breast cancer, which is the most common site-specific cancer in women, usually metastasizes to lung, liver, bone, and brain, although other sites can be involved less frequently. Parotid gland invasion by breast cancer, first reported in 1950, is extremely rare with very few reports worldwide.

**Case presentation:** A 54-year-old woman with stage IIIA breast cancer presented with a right parotid mass and signs of facial nerve palsy 3 months after treatment completion, which was finally diagnosed as metastatic involvement of parotid gland.

**Conclusion:** Breast cancer metastasis to parotid gland is extremely rare but can happen metachronously or synchronously even years after the primary disease. Therefore, this diagnosis should be kept in mind in any patient with a history of breast cancer presenting with a periauricular mass. Despite proposed treatments, including surgery, radiation, and chemotherapy, patients have a poor prognosis with a reported 5-year survival rate of 10%. However, palliative management should be recommended to all patients with parotid metastasis.

Introduction

Breast cancer is the most common site-specific cancer in women. It is the first and second leading cause of cancer-related death in developing and developed countries, respectively. Breast cancer is also the most frequently diagnosed cancer among Iranian women, accounting for 24.6% of all cancers, and it is reported the fifth leading cause of cancer death in Iranian females. Nowadays, owing to comprehensive screening programs and remarkable improvements in treatment modalities, an increasing number of patients are diagnosed at earlier stages of the disease and few distant metastasis; as 5-year survival for stage I, II, III, and IV breast cancer patients are 100% and 93%, 72%, and 22% respectively. However, patients at any stage of the disease can develop distant metastasis in her lifetime. The most prevalent sites of breast cancer metastasis are bone, lung, liver, and brain. Breast cancer metastasis to the parotid gland, first reported in 1950, is extremely rare, with only 21 cases reported between 1982 and 2017.

Here we report the case of a 54-year-old woman with stage IIIA breast cancer who presented with right parotid mass and signs of facial nerve palsy 3 months after treatment completion, which was finally diagnosed as metastatic involvement of parotid gland.

Case presentation

A 54-year-old woman with a family history of breast cancer (aunt with breast cancer diagnosed at age 41) presented with a lump on the right breast at the 6 o’clock position. Diagnostic workup indicated invasive ductal carcinoma of the right breast with axillary lymph node involvement. IHC examination revealed an ER+/PR+/HER2− tumor with an average Ki-67 labeling index of 25%. She underwent breast-
conserving surgery and axillary lymph node dissection. Pathologic examination reported invasive and in situ ductal carcinoma, grade 1. Maximum tumor size was 3.5 cm and lymphovascular invasion was present. All surgical margins were tumor-free. Of 20 excised lymph nodes, 7 were involved. In systemic workup, a 4-mm subpleural nodule in the posterior segment of the right lower lobe was reported, and follow-up CT was recommended. Abdominopelvic CT scan revealed no pathologic lesion. In the obtained bone scan, increased uptake in T7 vertebral body—which was highly suspicious for solitary osteometastasis—was observed. Magnetic resonance imaging of the spine showed small abnormalities in bone marrow signal of T7 vertebral body, which could be an atypical hemangioma. The patient received 8 sessions of adjuvant chemotherapy and 30 sessions of adjuvant radiotherapy. About 3 months after treatment completion and 11 months from the first diagnosis, she presented with a right periauricular mass, incomplete right eye closure, and mouth deviation, indicating right peripheral facial nerve palsy. In ultrasound examination, a 16 × 12-mm round lesion in the tail of the right parotid gland was detected. A fine-needle aspiration (FNA) biopsy of the mass was done, and pathologic examination reported a lesion which was highly suspicious for malignancy (Figure 1). For more evaluation, cervical CT scan was requested, which revealed a right masticator space mass measuring 23 × 17 × 21 mm, suggestive of minor salivary gland tumor or trigeminal schwannoma. In PET-CT scan, hypermetabolic tumoral lesion in the right masticator space (periauricular region), hypermetabolic bone metastasis in T7, T8, and left sacral area, and suspicious metabolically inactive pulmonary nodules were reported (Figures 2 and 3). Core needle biopsy of the parotid lesion confirmed invasive ductal carcinoma metastasis (Figure 4). IHC examination was positive for ER, PR, and HER2 and negative for CK5/6 and P63. The case was presented to the ear, nose, and throat tumor board and breast cancer multidisciplinary team, and palliative chemoradiation with Herceptin administration was recommended.

Figure 1. Fine needle aspirate of the right parotid mass with papanicolaou staining(a). Tumoral cells are depicted at the right and salivary gland cells at the left central part of the picture(b).

Figure 2. PET-CT scan reveals accumulation of SUV 9.36 in the right masticatory space in periauricular region

Figure 3. PET-CT scan reveals accumulation of SUV 6.79 in the left sacral ala.
The most common sites for breast cancer metastases are bone, lung, liver, and brain. Breast cancer metastasis to the parotid gland is extremely rare, with the first one reported in 1950 by Abrams et al. in a review of autopsy studies of 167 cases of breast cancer, in which only 1 case of metastasis to the parotid gland was detected. From 1982 to 2017, only 21 cases were reported worldwide. Metastasis to other salivary glands, i.e., submandibular gland, is even rarer, with very few reports in the literature.

Metastatic involvement of the parotid gland in breast cancer patients has been reported at different ages (36 to 74 years) and various disease stages (II, III, IV), and may occur synchronously or metachronously, and alone or along with metastases to other sites—although the sole involvement of the parotid is less common. Metachronous involvement of the parotid gland has been reported to happen from 11 months to 21 years after the primary disease.

Discussion

The most common sites for breast cancer metastases are bone, lung, liver, and brain. Breast cancer metastasis to the parotid gland is extremely rare, with the first one reported in 1950 by Abrams et al. in a review of autopsy studies of 167 cases of breast cancer, in which only 1 case of metastasis to the parotid gland was detected. From 1982 to 2017, only 21 cases were reported worldwide. Metastasis to other salivary glands, i.e., submandibular gland, is even rarer, with very few reports in the literature.

About 9% to 14% of parotid lesions are primary or metastatic malignant lesions. Head and neck malignancies (mostly squamous cell carcinomas) comprise most cases of metastatic lesions. Infraclavicular origins of metastatic involvement of parotid glands, including breast, kidney, lung, GI tract, and prostate, are rare (0.16%-0.4%). In one report by Franzen et al. on 644 consecutive parotidectomies between 1980 and 2012, 89 patients (14%) had malignant tumors, of which 39 were metastatic (6% of total); in 5 cases, the primary tumor was located below the clavicle (0.77% of total), only one of them being a breast carcinoma. Infraclavicular metastases of the parotid gland are thought to reach the parotids through the thoracic duct or Batson’s paraspinal venous plexus. Different studies have proposed that breast cancer metastasizes to the parotid gland via a hematologic route, as the involvement of the right and left parotid has been reported in patients with carcinoma of right and left breast.

Metastatic involvement of the parotid gland in breast cancer patients has been reported at different ages (36 to 74 years) and various disease stages (II, III, IV), and may occur synchronously or metachronously, and alone or along with metastases to other sites—although the sole involvement of the parotid is less common. Metachronous involvement of the parotid gland has been reported to happen from 11 months to 21 years after the primary disease.

Breast cancer, including invasive ductal carcinoma, invasive lobular carcinoma, and even malignant phyllodes tumor, has been reported, although the most frequent type has been invasive ductal carcinoma.

Patients usually present with a periauricular mass, sometimes with signs of peripheral facial nerve palsy, which is seen in 30% to 40% of malignant parotid lesions. Imaging alone cannot differentiate between a primary malignant tumor of the parotid gland and a metastatic one; therefore, when a patient with a history of breast cancer presents with a periauricular mass, an FNA is usually done after proper imaging. FNA is considered to be an appropriate and accurate primary diagnostic intervention, with a diagnostic accuracy of 85% in distinguishing malignant from benign lesions and primary neoplasms of the parotid from metastatic ones. Rarely, FNA results may be misleading, as in a case of parotid metastasis from hepatocellular carcinoma reported by Yu et al., where FNA did not show any specific cytopathologic features to allow an appropriate diagnosis.

It is of note that metastatic involvement of parotid gland can be mistaken for primary salivary duct carcinoma of the parotid gland, and the similarities between these two entities, including immunoprofiles, makes the differentiation difficult. Despite similarities, there are some characteristics that can be valuable in making an accurate diagnosis. In metastatic ductal carcinoma, residual normal parotid acini can be seen between the neoplastic glands, while salivary duct carcinoma of the parotid gland is expansile, leaving no or very rare normal parotid gland elements between its neoplastic cells. In addition, metastasis from breast cancer lacks the pattern of intraductal cribriform carcinoma that is characteristic of primitive salivary duct carcinoma of the parotid gland. Some studies have reported IHC staining to have limitations in distinguishing between primary salivary duct carcinoma of the parotid gland and metastatic ductal carcinoma from breast cancer as
salivary duct carcinomas are positive for CK 7, GCDFP-15 (87%), AR (72%), HER2/neu (40%) and, rarely, positive for ER (1%) and PR (5%). However, others claim that IHC staining can provide valuable information—the absence of expression of estrogen and progesterone receptors favors the diagnosis of a primary ductal tumor of the parotid gland. In addition, salivary duct carcinoma has been reported to almost invariably express androgen receptors. Comparing the hormone receptors profile of both the parotid tumor and the primary breast tumor can be helpful, although discrepancies in hormone receptor expression between primary breast tumor and metastatic ones have been described in up to 25% of cases.

Treatment for parotid metastatic disease includes a combination of surgical removal of solitary tumors, chemotherapy, radiotherapy, endocrine therapy, and targeted therapy (as needed). For single parotid metastasis, some advocate parotidectomy (total or superficial) with negative margins (preferably with preservation of facial nerve) and postoperative radiotherapy to obtain local tumor control and to exclude a primary parotid tumor. Some authors have postulated that parotidectomy with complete excision of the tumor can be a curative measure or an essential part of symptom control and should be considered in all but the most moribund patients. Yet, others have suggested ipsilateral neck dissection; however, as this entity is extremely rare, only limited data about the benefit of such procedures exist. Shi et al. advocate the use of an ipsilateral neck dissection when the parotid metastasis is from head and neck primaries as spread occurred predominantly via the lymphatic system, whereas, in the case of hematogenous spread from distant sites, neck dissection is thought to be unnecessary. Adjuvant radiotherapy for the parotid gland and neck is recommended by most authors for patients without nodal involvement; however, others favor the use of adjuvant chemotherapy, reserving the use of irradiation for cases where local control could not be achieved by surgery alone.

In the case of multiple-site metastases, chemotherapy alone or in combination with radiation therapy has been administered. For HER2+ tumors, targeted therapy with Herceptin following adjuvant chemotherapy is reported to be associated with increase disease-free survival, although the effectiveness of adjuvant chemotherapy in stage IV breast cancer patients remains disputed. Despite the proposed treatments, patients with metastatic involvement of the parotid gland have poor prognosis, with the 5-year survival rate reported to be 10%. Although metachronous solitary parotid metastases with longer disease-free survival are considered as good prognostic factors, many authors believe that parotid surgery does not improve life expectancy and that the management of a parotid metastasis is palliative regardless of the therapeutic modality used as the prognosis of such patients is poor. However, palliative management should be recommended to all patients with parotid metastasis.

In conclusion, breast cancer metastasis to parotid gland is extremely rare. It has been reported to happen synchronously or metachronously, even years after the primary disease regardless of the stage of primary cancer and appropriate primary treatment. Therefore, this diagnosis should be kept in mind in any patient with a history of breast cancer presenting with a periauricular mass. Proposed treatments are parotidectomy and radiation therapy for local control and palliation of solitary lesions and chemotherapy, hormone therapy, and targeted therapy, if indicated. Despite these treatments, however, patients with metastatic involvement of parotid have a poor prognosis, with reported 5-year survival rate being 10%. Many authors consider that parotid surgery does not improve survival and that the management of a parotid metastasis is palliative regardless of the therapeutic modality used, as the prognosis of such patients is dismal. However, palliative management should be recommended to all patients with parotid metastasis.

**Ethical Consideration**
The patient declared her consent for reporting her disease for this case report.

**Conflict of Interest**
None

**References**
With enthusiasm, we have read the article titled “Delivering bad news: when my patient was my own mother” by Doctor Tahmasebi published in the latest issue of Archives of Breast Cancer. We congratulate the author for this valued article on such an important theme, and at the same time would like to make some comments regarding the issues presented in that paper.

The author shared her experience as the first degree family member of a breast cancer patient, her mother, as well as the responsibilities she shouldered as her doctor to guarantee the best care. She beautifully described her exigent feelings in performing these two demanding tasks well as withholding the “cancer” diagnosis from her mother: “In avoiding a direct and frank conversation with my mother about her illness, I wonder whose emotions I was protecting, hers or mine?”

When the patient is an immediate family member of a physician, the personal feelings may unduly influence his/her professional judgment and practice. The American Medical Association (AMA) recommends that physicians do not treat their immediate family members due to several challenges such as compromising professional objectivity, patient autonomy, and informed consent. Thus, except for emergencies, minor acute conditions or isolated settings where no other qualified physician is available, AMA discourages doctors from being the physician in charge for their close relatives. The UK General Medical Council's Good Medical Practice also advises the doctors to generally avoid providing medical care to those with whom they have close personal relationships. Medical boards in Australia, New Zealand and Canada also advise against treating family members.

Another aspect of this paper was withholding the cancer diagnosis from the patient. Based on the paper, we understand that the patient did not have any problems with that as her daughter, a competent doctor, was in charge. Although this was done with obviously good intentions (i.e. protecting the mother’s emotions and maintaining hope) and was accompanied with provision of the optimal care, is not considered a recommended approach. While the author considers this as a common practice in Iran, patients are increasingly more willing to know about their diagnosis and participate in decision-making. In a study conducted in 11 cancer centers in Iran, 72.7% of cancer patients were aware of their disease at the time of interview and 85.2% were willing to be informed about their disease. Patients’ awareness was significantly associated with some underlying variables including age under 50, female gender, and having breast, skin or head and neck cancer. According to another survey performed in Tehran, 88% of cancer patients who were not aware of their diagnosis, said that they preferred to be more informed about their diagnosis. In addition, physicians and nurses are also more willing compared to the past to share information regarding diagnosis with cancer patients.

As the author of that paper, a skillful practitioner, decided to be responsible for the diagnosis and care of her mother, a breast cancer patient, it would be not easy to appraise withholding the bad news which simultaneously occurred in that case. As the author said, “I wonder how the end-of-life experience might have been different if I had been upfront with my mother about her diagnosis… Would that have prevented the last chemotherapy she received a week before dying?”

As it seems very exhausting for a physician to tackle with both of these issues, it reflects the underlying reasons that the physicians are advised not to practice medicine for their loved ones.

Conflict of Interest
None

References
1. Tahmasebi M. Delivering Bad News: When My


In medical practice, delivering bad news to patients is a complicated issue. Clinicians sometimes are faced with the dilemma of delivering bad news to a patient: to tell or not to tell the truth. In this context, the religion of patients is an important factor. Some people, such as Muslims, believe in life after death and Judgment Day. Accordingly, avoiding disclosure of the pertinent information to such patients is a clear violation of patients' rights because it denies them the opportunity to do penance and seek God's forgiveness for their sins. This situation is an instance of "the kiss of death."

I read with interest the Invited Commentary by Tahmasebi1, entitled “Delivering Bad News: Deal With Collusion for Love,” which was recently published in this journal. I would like to draw attention to the issue of breaking bad news to patients from a religious perspective.

Today, generally, avoiding the disclosure of the pertinent information to a patient is not ethically acceptable,2,3 On the other hand, in medical practice, giving bad news to patients is a complicated issue and a difficult task.4,5 Clinicians are sometimes faced with the dilemma of delivering bad news to a patient, i.e., to tell or not to tell the truth. In this way, the patient's family may ask the doctor not to reveal such information as cancer diagnosis to their patient for one reason or another. Furthermore, patients' religion is one of the concepts that exert an influence on their care process and consideration of bad news.6 Some people, such as Muslims, believe in life after death and Judgment Day as well as the existence of Hell and Heaven. They believe that after death, sinners will go to Hell and good people will go to Heaven, and that God will accept the sinners' repentance and, with true penitence, they will go to Heaven. Now imagine that a patient with such a religion and beliefs has terminal cancer, and the clinician does not provide information about prognosis to the patient per her family's request or for some other reason. This would be a clear violation of the patient's rights because it denies her the opportunity to do penance and pray for God's forgiveness. This situation is an instance of "the kiss of death." Hence, patients' religion is an important factor in breaking bad news. Therefore, doctors must tell the truth and disclose pertinent facts to such patients (of course, in supportive ways) and allow them to make changes to the remnants of their lives and eventually to their destiny.

Conflict of Interest
None.

References
Minor Changes
We believe the changes introduced into the latest edition of the ACR Atlas can be classified into minor changes, completing changes, and major challenging changes.

Minor Changes can be further categorized into three groups: (1) lexical changes, such as using rim calcification instead of eggshell and lucent-centered calcification, asymmetry instead of simple asymmetry, which is mostly to make reporting easier; (2) changes in classifications, i.e., moving global asymmetry from the “special cases” category to the “asymmetries” category or taking intermammary lymph nodes out of the “special cases” category and making it an independent category; and (3) addition of new items such as simple cyst and fat necrosis to the “special cases” category. These changes are easily substituted.

Adding and Completing Data
Some new useful parts were added to the latest edition of BI-RADS, including a background on parenchymal enhancement in MRI (minimal, mild, moderate, or marked) and a new subsection on prosthesis assessment. The previously deficient parts of the BI-RADS atlas have now been completed.

Major Changes
Major changes are those that had a great impact on daily clinical practice and are as follows: (1) density description; (2) omitting the “intermediate concern” group from calcifications categories, and BI-RADS 4a; and (3) BI-RADS 3, 4, and 5 should only be used after a full imaging workup and not for mammography screening.

Density
The 2003 edition of BI-RADS used breast composition categories (ACR category 1–4) based on the overall density (%) of fibro glandular tissue as a breast cancer risk indicator. However, the ACR Committee on BI-RADS concluded that the association of breast density with the sensitivity of mammography is clinically more important than the percentage of breast density as an indicator for breast cancer risk (Figure 1). Therefore, in the 2013 edition, new breast composition categories (assigned alphabetically a–d to avoid possible confusion with the numbered BI-RADS assessment categories), have been introduced.

There is intra- and inter-observer variation in visually estimating breast density between any two adjacent density categories in both types of categorization. In a study performed in our center, substantial inter-observer agreement was seen using both the fourth and fifth editions, and the intra-observer agreement was high for both editions. The percentage of women who were classified as having dense breasts was also not statistically significant using both methods.

BI-RADS 3
Since the release of the ACR BI-RADS fifth...
When a patient attends our center for screening or a benign-appearing lesion, such as when an oval circumscribed mass is found, we classify it as BI-RADS 0 in the report and perform a full evaluation including targeted sonography. The authors of the BI-RADS 2013 believed that some of these patients would not need short-term follow-up mammography after a full evaluation. For example, the mass may be identified as a cyst on the targeted sonogram (Figure 2). On rare occasions, the described mass can be a solid circumscribed one on sonography with a high flow in a simultaneous color Doppler, which suggests a high-grade malignancy. Some of these lesions may have a solid oval circumference and appear to have a homogenous texture on sonography; these will obtain a classification of BI-RADS 3. In this case, the patient will be recommended to have a short-term follow-up via sonography. In palpable lesions with a BI-RADS 3 appearance on imaging, different clinicians have different approaches because of nonrobust evidence in the literature, with some preferring to order a biopsy. As mentioned in the BI-RADS edition 5, and based on our experience, persistent focal asymmetry after full evaluation and a group of punctate microcalcifications are the most prevalent mammographic BI-RADS 3 classifications that need short-term follow-up with mammography.

**BI-RADS 4 and 5**

In the previous BI-RADS edition, categories 4 and 5 could not be reported during a screening mammography. Both categories required additional images before they could be classified. However, in some imaging departments, such as our center in Iran, the screening and diagnostic wards are not separate, and the same radiologists often perform both tasks on the same day. In addition, for insurance and legal reasons, the radiologists are not supposed to take any additional images without the request of a clinician. Thus, if we encounter a suspicious or highly suspicious finding, we will assign it to BI-RADS 4 or 5 category based on the descriptors in the screening mammography. For example, if we detect a spiculated mass containing suspicious microcalcifications during a screening mammography, we assign a classification of BI-RADS 5 instead of BI-RADS 0 in the same session (Figure 3).

**Calcifications**

We believe that the most challenging changes in the BI-RADS 2013 as compared to the 2003 edition are reporting microcalcifications. The changes are as
In the 2013 edition, “lucent-centered” and “eggshell” calcifications in the “typically benign” category have been replaced by the new term “rim” for ease and simplicity.

One major change in microcalcification classifications in the 2013 edition is the omitting of the “intermediate concern” category. The three calcification types (amorphous, coarse heterogeneous, and fine pleomorphic) are grouped as “suspicious morphology,” and since their probability of malignancy is 10% to 50%, they are assigned BI-RADS 4b. Fine linear or fine linear branching calcifications are placed in category 4c or 5 depending on their distribution.

- Solitary group of punctate microcalcifications, which is probably a benign assessment with a short-term follow-up requirement, has been placed in BI-RADS 3 category. If a similar group of calcifications is new, increasing, or adjacent to a known cancer, it warrants a biopsy.

- One major change in microcalcification classifications in the 2013 edition is the omitting of the “intermediate concern” category. The three calcification types (amorphous, coarse heterogeneous, and fine pleomorphic) are grouped as “suspicious morphology,” and since their probability of malignancy is 10% to 50%, they are assigned BI-RADS 4b. Fine linear or fine linear branching calcifications are placed in category 4c or 5 depending on their distribution.

However, problems still remain in the ACR BI-RADS 2013 regarding the reporting of microcalcifications:
- The number of microcalcifications in each group is not identified, but we know that when their number increases, the probability of malignancy will increase.
- Although some types of microcalcifications encountered in daily clinical practice are not mentioned, such as punctate microcalcifications with regional distribution and regionally distributed microcalcifications with some degree of pleomorphism. This may be because there is little robust data in the literature.
- Heterogeneity in the density and size of microcalcifications were also not focused. For example, it is not clear which BI-RADS score should be assigned to a group of punctate microcalcifications varying in size and density (Figure 4).

In summary, the BI-RADS system has greatly improved breast imaging reporting by standardizing the reports and has made data collection for research purposes much easier, but some other important details may be considered in the future editions.

Conflict of Interest
None.
References


Oral contraceptives are contraindicated in women with current or previous breast cancer. Among women at high risk for breast cancer, those with preceding chest wall irradiation should not use pills, while these are allowed in cases with BRCA mutations or with a positive family history of breast cancer. Oral contraceptives may be beneficial for benign breast diseases. For low-risk woman, pills either pose no risk or may induce a very mild risk for breast cancer.

**Methods:** We first reviewed international clinical guidelines about the subject. Then, a comprehensive search of the literature was carried out using appropriate keywords. Clinical trials, population-based or cohort studies, nested case-control studies, and narrative/systematic reviews were reviewed and relevant data were extracted.

**Results:** Oral contraceptives are contraindicated in women with current or previous breast cancer. Among women at high risk for breast cancer, those with preceding chest wall irradiation should not use pills, while these are allowed in cases with BRCA mutations or with a positive family history of breast cancer. Oral contraceptives may be beneficial for benign breast diseases. For low-risk woman, pills either pose no risk or may induce a very mild risk for breast cancer.

**Conclusion:** Oral contraceptives are generally safe regarding breast diseases except in breast cancer patients or high-risk women, especially those with a history of chest wall irradiation.
classified as carcinogenic to humans (Group 1), 82 probably carcinogenic to humans (Group 2A), and 311 possibly carcinogenic to humans (Group 2B). Oral contraceptives containing both estrogens and progesterone are classified as Group 1, with a notice that evidence also shows protective effects for endometrial and ovarian cancer, and those comprising only progesterone are classified as Group 2B.

All these details lead to uncertainty and worry when prescribing hormonal medications. This article reviews the concerns physicians confront while prescribing OCPs to women undergoing BC treatment, BC survivors, groups at high risk for BC, women with benign breast disorders (BBDs), and healthy women.

**Methods**

The objective of our search was to find the most valid scientific material as well as reviewing the latest findings, recommendations, and suggestions about the subject. First, we investigated international clinical guidelines and references, including the guidelines of the Society of Family Planning, WHO’s Medical Eligibility Criteria for Contraceptive Use (MEC), the US Selected Practice Recommendations for Contraceptive Use, and the US Medical Eligibility Criteria for Contraceptive Use by the Centers for Disease Control and Prevention (CDC), the Canadian Contraception Consensus, the IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, the Clinical Management Guidelines for Obstetrician-Gynecologists by the American College of Obstetricians and Gynecologists (ACOG), UpToDate (from January 2019), and the Clinical Practice Guidelines in Oncology, 4th edition, by the National Comprehensive Cancer Network (NCCN). All the relevant topics and points were extracted from these references. Then, we performed a comprehensive search of the literature for all relevant publications using the following keywords: contracept*, breast cancer, breast neoplasia, risk factor, benign breast, fibroadenoma, breast fibrocystic, steroid hormone, family history, high risk, BRCA, chest wall radiation, and screening. Search phrases were synthesized using various combinations of 2, 3, or 4 of these keywords. We carried out our first screening by reading titles and abstracts to detect review articles, systematic reviews, clinical trials, population-based and cohort studies, and nested case-control works. Thereafter, we sorted out selected works based on journal impact factors and citations of papers and excluded the last quartile of the resulting list from the investigation. In our second screening, we studied methods, results, and conclusions of articles and selected papers that contained pertinent scientific material. Finally, eligible articles were carefully read to extract any point and fact that was related to our subject.

**Results and Discussion**

*Types of Oral Contraceptive Pills*

OCPs have been used for many years now and have always been a very common and quite effective method of birth control. They have also been used for therapeutic purposes in disorders such as menstrual irregularities, premenstrual syndrome, endometriosis, uterine lesions, and even acne. OCPs are made of synthetic sex steroid hormones, namely, estrogens and progesterone compounds. The formulation of the drugs, specifically type and dosage of components, has been modified through time to increase safety. More than 30 types of OCP are in use today, which can be classified into two groups in terms of hormonal constituents: combined OCP (cOCP), which contain both estrogens and progestins and are used more frequently, and progesterone-only pills (POPs), which contain only progestins. Older forms of OCPs that were marketed before 1975 contained higher doses of estrogen, whereas newer preparations contain lower doses, mostly 20 or 30 μg of ethinyl estradiol per tablet.

Also, the progestin component of OCP varies widely across products. There are four generations of progestins in the market, with varying levels of androgenic activity; therefore, various kinds of OCP harbor diverse desired or adverse defects. Some forms of OCPs increase progestin exposure up to fourfold normal serum level.

One of the most common side effects of most kinds of OCP is breast tenderness, which makes users worry about their breast health and seek medical care. However, OCP-induced breast tenderness can be viewed as a welcomed excuse for performing breast examination or BC screening and is not accompanied by breast disease. Like most adverse effects of OCPs, the symptom is usually mild and resolves with time or by consuming another kind of OCP.

Emergency or postcoital contraception is used after unprotected intercourse and consists of several methods, taking POPs and cOCPs being one of them. While the latter is used less frequently nowadays, the former is gaining popularity.

1. **OCP in Newly Diagnosed BC**

Soon after a diagnosis of BC, therapeutic modalities with varying sequences are instituted. Cytotoxic drugs of chemotherapy may induce anovulation and temporary or permanent infertility. Failure of ovarian function occurs at a rate of 14% to 100% depending on age and the type of agent used. Also, hormone therapy may contribute to contraception to some degree. However, ovulation might take place under any therapeutic regimen, and pregnancy can occur. Therefore, to prevent potential harms to the fetus as well as interference
with medical plans, contraception adherence is imperative during all stages of treatment, including surgery, chemotherapy, radiotherapy, endocrine therapy, and targeted therapy. Patients should be instructed about the necessity of contraception and counseled on appropriate methods; nonetheless, these do not occur every so often. In a recent study, women of reproductive age who had undergone breast cancer treatment within the previous 5 years were interviewed about what they knew and how they had been informed about correct methods of contraception during their treatments. There was a serious lack of accurate knowledge on the topic. Moreover, because of deficient instructions from physicians, patients recognized their peers as a decent source of information. Also, in a survey carried out among women diagnosed with BC before the age of 40, results showed that most of the patients had neither been notified about nor used contraception while under chemotherapy or endocrine therapy. This malpractice may be due to the bulk of information that BC patients should receive in a short time, which makes medical staff overlook the subject. But unfamiliarity with the best applicable contraceptive approach during BC management also plays a significant role.

No study has been designed to investigate the use of OCP during BC treatment, because these drugs may significantly contribute to tumor progression. According to international guidelines, when a new breast mass is detected in a woman on OCP, she can remain on it till the diagnosis of breast cancer is made, and a substitute effective contraception is initiated. However, cOCP and POP are contraindicated in newly diagnosed breast cancer patients and those under treatment. The best contraceptive methods in these patients are nonhormonal modes, which will be discussed in relevant parts of these series of articles.

The risk of using emergency OCP in patients under treatment for BC has not been studied. When postcoital contraception is needed, one-time use of emergency pills should not cause any harm, but effects of repeated consumption are questionable. Then again, a non-OCP method would be superior, which has been discussed elsewhere.

2. Oral Contraceptive Pills in Breast Cancer Survivors

Studies assessing the safety of pregnancy following BC treatment and the safe time interval between diagnosis and conception have found that a minimum interval of 2 years, depending on the type and stage of BC, would yield favorable results. Nonetheless, pregnancy should be prevented at any other time when the patient does not wish to have a baby. It has been shown that, as in patients under treatment, BC survivors of reproductive age undergo contraception in comparison with their control counterparts.

A large portion of the literature about OCPs and BC risk is centered on women with average risk, and research about the consequences of OCP consumption in breast cancer survivors is heterogeneous and limited while prospective studies are lacking. Decisions and recommendations regarding the limitation of hormonal contraceptive methods in breast cancer survivors are actually an extrapolation of the data obtained from the former, and also reflects general fear of administering hormonal products in these high-risk women.

For the time being, both cOCP and POP are contraindicated in BC survivors as well as those under treatment. However, emergency hormonal contraception is allowed in these patients, although the frequency of use should probably be limited. In these women, non-OCP emergency contraception is preferred.

3. Oral Contraceptive Pills in Groups at High Risk for Breast Cancer

Because prospective trials are difficult to design about this challenging subject, there is insufficient consistent literature about the use of OCP in high-risk groups. Still, numerous works have been carried out in order to answer the question of safety of OCPs in women with a positive family history or genetic predisposition to BC.

3.1. Family History of Breast Cancer

Women with a family history of BC, especially when several young first and second degree relatives are affected, are at greater risk for BC. Whether the risk increases further with consumption of OCP has been considered in a number of studies.

In an evaluation of nearly 3500 cases of BC and 4500 controls, simultaneous positive family history and OCP consumption had cumulative positive effects on BC risk, and investigation of around 1500 cases and controls showed an increment in the risk of BC in women with a history of the disease in their first-degree relatives. Likewise, in a cohort of more than 3 000 women in 426 family lineages of BC patients, significantly higher risk of BC was found in women who had used OCP and who also had a first-degree relative with BC. One important point is that this positive association was mainly related to high-dose estrogen pills which were used before 1975. Thus the question remained open for more inquiry about recent low-estrogen formulations.

However, null results were more often obtained in earlier studies. In a case-control study enrolling about 1000 cases and 900 controls, women who used OCP and who had sisters with BC had only a nonsignificant additional risk. Also, in the evaluation of nearly 1000 cases and 10000 controls from a cohort of nurses, OCP use caused no increase in BC risk in women with a BC family history.
publications have yielded contrasting results over this topic. Some studies have shown no additional increased BC risk for OCP use in women carrying defective BRCA genes, while others have shown a positive association.

A study of 83 BC patients with mutated BRCA1 or BRCA2 genes found no increased risk of BC for OCP users in comparison with controls. In another research, involving nearly 1500 BC cases under the age of 50, of whom 94 carried mutated BRCA genes, and 450 healthy matched controls, OCP use had no effect on the risk of BC. Also, in an assessment of more than 2500 high-risk women attending a family cancer center, cOCP had no effect on the risk of BC in genetically-positive women. However, publications favoring some unfavorable effects of OCP consumption on risk of BC in BRCA carriers are not scarce. In a sample of 50 Ashkenazi Jewish women with BC, 14 of whom were positive for BRCA1 or BRCA2 mutations, consuming OCP for more than 4 years in advance of the first pregnancy was recognized as a probable risk factor for BC. In partial agreement with this finding, a large case-control study encompassing 52 centers in 11 countries and comprising 1311 pairs of BRCA1 or BRCA2 mutation carriers found no association between OCP use and risk of BC in carriers of BRCA2 mutation, while women with mutated BRCA1 who consumed OCPs manufactured before 1975, who used OCPs for more than 5 years, or who had begun using them before age 30 were more likely to develop BC at an early age. However, a study involving around 500 carriers of BRCA1 and 300 carriers of BRCA2 mutations found BC risk increments with long-term (>5 years) but not with short-term (<1 year), OCP use. Also, in a retrospective cohort of more than 1500 women with mutations in BRCA1/2 (the International BRCA1/2 Carrier Cohort Study [IBCCS]), a positive association between risk of BC and OCP intake, intensified with consumption for more than 4 years before first full-term pregnancy, was detected. Age of the patient at the time of beginning OCPs or recent versus previous use did not affect the risk. One more investigation among 888 Jewish Israeli women with mutated BRCA1 or BRCA2 genes revealed a positive association between OCP use and risk of BC, especially early-onset BC. Additionally, a case-control study assessing around 2500 matched pairs of BRCA1-positive women showed an increased risk of early-onset BC with OCP use before age 20 or 25, enhanced with the length of consumption. One study on 200 BRCA-positive women also showed that OCP users tended to develop BC at younger ages than non-users.

The contrast seen in these various works is reflected in the results of review papers and meta-analyses investigating the subject, which also involved different inclusion criteria for entering studies in their evaluations. A work which analyzed
studies performed before December 2009 found heterogeneous and inconsistent results. However, two independent works reviewing studies carried out till March 2010 and from 2000 to 2012 found null results. Likewise, the meta-analysis of case-control studies performed before September 2013 could not find any relationship, while a positive association was detected from the combination of hazard ratios of cohorts carried out till that date, where the duration of use of the pills had no effect. Finally, in a very recent work recruiting participants of several cohorts, past data and new information (via questionnaires) about OCP consumption and other issues were gathered from around 10000 BRCA1 or BRCA2 positive women and were analyzed both retrospectively and prospectively. Although a positive association between consumption of OCP and risk of BC was not proved, results were inconsistent, and authors conclude that safety of OCP for BRCA carriers is unclear in the long term and should only be used for contraceptive purposes, and that as the second-line option.

3.3. History of Chest Wall Radiation

Specific studies have not been performed, but considering the increased likelihood of BC in women who have received radiotherapy of the chest wall (mantle field radiation) in childhood, OCP is generally contraindicated in these cases.

3.4. General Recommendations on High-Risk Women

As inferred from above studies, and according to international societies and clinical guidelines, the OCP and POP can be used in women with a family history of BC and are not contraindicated in those with BRCA mutations, albeit as a second-line choice. Because of lack of sufficient consistent data, these should not be used in women with a history of chest wall radiation.

4. Oral Contraceptive Pills in the General Population

The question of possible carcinogenetic effects of OCPs in the breast has been considered since many years ago and is still an area of active investigation. In 1977, the cohort study of the Royal College of General Practitioners, which enrolled around 50000 women using OCP and followed them to age 44 years, revealed an increased risk of BC in current as well as recent users. Several years later, the Collaborative Group on Hormonal Factors in Breast Cancer reviewed and analyzed nearly all epidemiological evidence of that time about hormones and breast cancer. Results showed an increased risk of BC with current or recent (within the preceding 10 years) use of OCP, especially in those who had started pill consumption before the age of 20, but not with earlier use. BCs in OCP users were less advanced, particularly with high-dose formulations. They discuss that these findings might be due to earlier detection of the disease because of tighter screening and should be investigated further.

Results of the Norwegian-Swedish Women's Lifestyle and Health Cohort Study, with more than 100000 participants, aiming at understanding any association between OCP and BC were published 6 years later. Long-term, higher-dose users, as well as current/recent users of OCP, were shown to be at a higher risk of BC. In a recent case-control study involving 1031 cases of BC and 919 controls, all younger than 55 years, a relative risk of 1.1 was shown for ever use of OCP. In a very recently published prospective cohort study, which raised many arguments and debates, a 20% to 30% increase in risk of BC was observed for current and recent users of OCP, and the risk was correlated with the duration of consumption. These figures, although apparently high, mean only one extra case of BC in a year for every 7690 women consuming OCP.

Opposite results, favoring the safety of OCP in relation to BC, have been reported in several works, including very large cohort studies with prolonged follow-up. In 1976, among 17000 women recruited for the Oxford Family Planning Association Contraceptive Study, a decreased hospital referral for BC was revealed in women who had used OCP. The Nurses' Health Study, using data from about 3400 BC patients with a follow-up of 1.6 million person-years, showed null results even for long-term intake of OCP. Similar results came out of the interview of more than 9200 BC cases and controls, where even adjustments for estrogen dose or current versus past use did not alter the results.

Findings were null also in an updated analysis of the data from the large cohort study of the Royal College Of General Practitioners, comprising around 740000 and 340000 woman-year of observation for never users and ever users of OCP, respectively. Thereafter, the last update of the Oxford Family Planning Association Contraceptive Study was released, where the previous results (no association) were confirmed. A very recent report of the NIH-AARP Diet and Health Study, which covered more than 100000 women with more than 11000 cases of BC, found no association of the disease with OCP use.

The above large-scale studies had taken place in Western countries, but studies have also been conducted in other countries. A case-control study on 225 women with and without BC in Iran has demonstrated a rise in BC with OCP use for more than 16 years. Also, a systematic review in Iran analyzed the data on 46260 patients from 26 studies carried out in the country between 2000 to 2015 and concluded that using OCP increased the risk of BC up to 1.52 times in Iranian women.

In a case-control study in Thailand among 514
Thai premenopausal women, OCP use was found to increase the risk of breast cancer threefold, and the risk was higher in those with a longer duration of consumption. A recent study in Korea has shown that the consumption of OCP could lead to a rise of 3.4 cases of breast cancer per 10,000 women. The risk was not higher in women older than 45 years in comparison with younger women.

Besides studies considering invasive cancers or all types of BC, a study investigated nearly 900 cases of DCIS and 1000 controls and found no association with OCP consumption, length of use, dose of estrogen, or timing of the last usage. Few studies have focused on the effects of POPs on BC risk. The association of POP (except for mini pills) use after the age of 40 and before menopause with BC was studied in women enrolled in the French E3N Cohort Study. No increased risk of BC with POP use was detected, except for long-term (>4.5 years) current use.

A systematic review published in 2016 concentrated on the relationship between BC and using progesterone compounds, including oral and injectable contraceptives as well as implantable forms or intrauterine devices, and revealed no association for progestin contraceptives. Of 6 studies included in the study, only 2 (both published in 2002) were about POPs. One of these 2 studies involved more than 9000 cases and controls and included more than 7000 women who had ever used OCPs. Nonetheless, a very small fraction (32 and 39 cases and controls, respectively) had ever used POPs. In this small sample, no increased BC risk was detected. The second was the Women's Lifestyle and Health Study, with more than 100,000 participants. Although the risk of BC was shown to increase with cOCP use or consumption of both cOCP and POP, ever use of POP alone did not affect BC risk.

Another study carried out shortly after the above review tried to investigate POP effects in near 5000 BC cases, 135 of whom consuming POPs. Although the sample size was too small to allow a definite conclusion, the group using POP had a lower breast cancer mortality.

In contrast to previous publications, the Norwegian Women and Cancer Study (NOWAC) including near 75000 women with 1245 BC cases documented an increased risk of BC by consumption of POP.

As pointed above, the subject is still being considered, but it can be deduced overall that OCP may cause only a very small, if any, increase in BC risk in women without predisposing factors.

4.1. Oral Contraceptive Pills and Risk of Breast Cancer by Hormone Receptor Status

Because of the diversity of hormonal profile of breast malignancies and the dissimilar clinical behavior of subtypes, a number of researchers have investigated the effects of OCP on BC by estrogen receptor (ER), progesterone receptor (PR), and HER2 status.

Several studies suggest that OCP intake may contribute to ER-, PR-, and HER2-negative (triple-negative tumors) tumors. In one study, immunohistochemical assessment of near 900 tumors showed that OCP use for one or more years increased the risk of triple-negative BC 2.5-fold, especially with longer and more recent use. For women 40 years of age or younger, OCP intake for 1 or more years was associated with a 4.2-fold increased risk for triple-negative BC.

The risk for other subtypes was not affected by OCP use. Also, in a cohort study conducted among African American women, the use of OCP was positively associated with hormone receptor-negative BC, and this relation was stronger with longer duration and more recent use. Besides, in a study on more than 3200 women, a 2.9-fold increase in triple-negative BC risk was detected among those between 45 to 64 years of age who had begun using OCP before the age of 18.

But then again, some studies have reported contradictory findings. In the evaluation of more than 155,000 participants of the Women's Health Initiative, OCP use was not found to be associated with any subtype of BC.

In addition, in a population-based case-control study of more than 1800 women under age 45, the difference in risk of ER-negative and triple-negative BC with OCP use was not significant between those using for ≥15 years and current users for 5 years. A nested case-control study with 1105 BC survivors found a nonsignificant propensity for ER+ tumors with consumption of high-estrogen OCPs.

Two systematic reviews about the relationship between OCPs and BC subtypes revealed that OCP use had a possible negative association with luminal A subtype and a significant positive or possible association with triple-negative BC.

Given the different effects for estrogen and progestin components of OCPs, the relationship between cOCP or POP and BC subtypes was investigated in the NOWAC study as well. The researchers used data on 74862 premenopausal women and the 1245 BC events. They demonstrated an increase in risk of ER-positive BCs in women who had used POP for ≥5 years and an increase in risk of ER-negative BCs with cOCP consumption.

4.2. Screening for Breast Cancer Before Initiating Oral Contraceptive Pills

BC is not common in women of reproductive age. As a consequence, despite the contraindication for OCP use in current BC and survivors, the WHO's
Medical Eligibility Criteria for Contraceptive Use (MEC), the US Selected Practice Recommendations for Contraceptive Use, and the US Medical Eligibility Criteria for Contraceptive Use have mentioned that no screening for breast cancer is necessary before initiating OCPs in women who have no symptom of the disease.\textsuperscript{14,20,27} According to WHO-MEC, even in those who have a mass in the breast that has not yet been assessed, OCP can be initiated while the assessment of the mass is being undertaken.\textsuperscript{24}

### 5. Oral Contraceptive Pills in Benign Breast Disorders

BBDs are very common lesions with heterogeneous clinical and pathological pictures. Some conditions such as fibrocystic changes (FCC) impose no risk on the patient; certain lesions such as fibroadenomas (FA) may slightly increase the risk for BC; some particular disorders, including papillomas, might count as risk factors for BC; and others such as atypical ductal hyperplasia may even be a precancerous lesion. FCC is the most common BBD, and FA is the most frequent benign tumor of the breast. FAs respond to endogenous sex hormones, as normal breast tissue does. Normal breast tissue and FA have similar ER levels; however, FAs have higher protein levels of PR-A and PR-B, suggesting that sex hormones and PR may play a role in FA development.\textsuperscript{89}

Most works inspecting the relationship of BBD and OCP have been performed in far past times, and, because large cohorts were involved, multiple reports have been released through time. Results encompass mainly favorable effects of OCP on BBD. Nevertheless, medical staff has not been acquainted with this subject, as a survey of patients and physicians showed that the latter believed OCP should not be used in BBD, and advised the former as such.\textsuperscript{99}

In a comparison between women under age 40 harboring benign breast masses and controls who were hospitalized for non-breast lesions, use of OCP for more than 2 years was recognized as a protective factor against BBD and decreased the risk of undergoing a biopsy up to 4-fold.\textsuperscript{100}

In another study involving 640 women with either pathologically confirmed BBD or normal breasts, there was no association between OCP use and BBD,\textsuperscript{101} while another study performed in the same period showed that hospitalization for FCC and FA decreased with use of OCP for more than one year, and this negative association strengthened with longer duration of use.\textsuperscript{102} Similarly, in the Oxford Family Planning Association Contraceptive Study, referral to hospital for BBDs was less frequent in OCP users.\textsuperscript{76} In the large-scale, prospective Royal College of General Practitioners' Oral Contraception Study, OCPs containing higher doses of progestins had a higher impact on BBD risk reduction.\textsuperscript{72} The subsequent report of the Oxford Family Planning Association Contraceptive Study, with a 5-year interval from the previous one, again announced that OCPs were negatively associated with FA and FCC. Current pill users, especially those with prolonged use, had the lowest risk, and progestin dose seemed to mediate the reduction in FCC risk.\textsuperscript{103} In contrast with previous works, a study in women hospitalized for BBD showed an increased risk of FCC with OCP use in postmenopausal but not in premenopausal women.\textsuperscript{104} However, the update of the Royal College of General Practitioners' Study and another large cohort, the Canadian National Breast Screening Study, again emphasized that OCP use had a protective effect on BBD.\textsuperscript{105,106} Similar results were found for FA in a large cohort in China.\textsuperscript{107} The succeeding report of the Oxford Family Planning Association Study confirmed a reduced rate of hospitalization for FA and FCC with longer consumption of cOCP, especially in recent users.\textsuperscript{108} However, in a study comparing the effects of cOCP associated with estriol or placebo on FA, it was demonstrated that estriol hampered the effectiveness of cOCPs in decreasing FA size.\textsuperscript{109} Also, in a study carried out on 50 cases of FA under the age of 45 and 100 controls, lower age at first OCP consumption was found to be a risk factor for the development of breast FA.\textsuperscript{110}

Atypical lesions have also been considered in regard to OCP consumption. The Canadian National Breast Screening Study, enrolling about 55,000 women aged 40-59 years, of whom 2000 had BBDs, found that OCP consumption was inversely associated with BBD risk, especially with longer duration of use, but longer use of OCP (> 7 years) was associated with increased risk of atypical lesions.\textsuperscript{106} A study investigating the possible role of exogenous estrogen and/or progesterone consumption in atypical hyperplasia of the breast also showed a positive association between them; however, type of hormone and whether OCP was investigated is not clear in that publication.\textsuperscript{111}

According to the US Medical Eligibility Criteria for Contraceptive Use and the US Selected Practice Recommendations for Contraceptive Use, there is no limitation for consuming OCP in BBD.\textsuperscript{20,27} All studies on the subject are old, and none (except one) has assessed the effect of OCP on FA size. It appears that OCP can be prescribed in patients with FA if the diagnosis is made according to the histologic review of biopsy specimens. When the diagnosis is based on typical clinical and imaging findings, prescription of OCP with close observation and short-time follow-up of the mass is probably safe. FCC was previously known as fibrocystic disease and was named with various terminologies. The recent term shows that this is not a disease and may even not be a disorder, but just a “change.” Considering the present
knowledge, OCP consumption need not be limited in FCC.

Table 1 summarizes OCP limitation in various conditions of the breast according to the current knowledge.

Despite the bulk of research, questions regarding the association of OCP with different breast conditions still exist and need to be answered by further investigations.

Conflict of Interest
The authors have none to declare.

References


ARTICLE INFO

Background: As cancers, especially breast cancer, have become the most lethal and concerning subject, new methods to promote therapies and achieve better results are strongly essential. Nanotechnology has offered a new approach to advocate the strategies being used and to vanquish their impediments. This article provides a review of the nanomaterials used most recently, mainly in breast cancer, for more effective and specific treatment.

Methods: Documents were found in PubMed and Google Scholar using “nanomaterials” and “breast cancer” as the main keywords. Additionally, each individual nanomaterial with “liposomes”, “polymeric NPs”, “dendrimers”, “quantum dots”, “virus like nanoparticles” and “magnetic NPs” keywords were searched and selected after assessing publishers, journals impact and their relativities to the subject of the review.

Conclusion: Extensive research in nanotechnology in medicine, especially in cancer, suggests that nanotechnology could be the dawn of a new era in cancer treatment and imaging.

Results: Six frequently used nanoparticles in breast cancer treatment including liposomes, polymeric NPs, dendrimers, VLPs, quantum dots, and magnetic NPs were selected to be discussed in this review. They all showed correlative results such as promoting drug maintenance, hydrophilicity, and accumulation in the tumor site by their specific cell targeting system and high cellular uptake. Each of these NPs has unique properties and disadvantages and therefore many in vitro and in vivo experiments have been carried out.

Key words: Breast Cancer, cancer nanotechnology, nanomedicine
odds of developing a tumor are 10-12.8% throughout a woman’s lifespan. Unfortunately, these values have had an increasing trend since 1990 which had 1.5% increase rate of breast cancer development per year. Characteristics such as mutated genes (BRCA1, BRCA2 and p53), an abnormal endocrine system, metabolism and environmental agents; exhibit cancers specially breast cancer a unique life-threatening system. Different receptors are expressed on breast cancer cells that distinguish them from one another, such as the progesterone receptor (PR), estrogen receptor (ER) and human epidermal growth factor receptor 2, also known as HER-2/neu receptor. In test results, triple negative breast cancer (TNBC) indicates a deficient amount of the above three receptors on breast cells.

Despite the fact that breast cancer is a heterogeneous disease, the therapeutic modalities are almost the same in many patients. Surgery is Principle treatment and could be used along with other therapeutic modalities. It includes mastectomy, defined as the removal of the whole breast, and lumpectomy in which part of the breast is removed.

Radiotherapy with the use of intense radiation, chemotherapy by exploiting highly toxic drugs, endocrine therapy, also recognized as hormone therapy, to alter the cell cycle or immune system, immunotherapy, and finally combination therapy are listed as the most common therapeutic strategies implemented for breast cancer treatment.

Although different technologies have been developed and several investigations have been carried out to help better comprehend cancer etiology and desirable treatment outcome, their limitations could not be overlooked. All the above methods, collectively known as conventional therapy, have their specific limitations that make them less efficient. The highly hydrophobic nature and lack of solubility make chemical drugs unstable with inadequate bioavailability. Furthermore, their toxicity causes serious side effects such as hair loss, vomiting, nausea and diarrhea. On top of all the major drawbacks of these methods is that they could not differentiate between normal and cancerous cells, resulting in nonspecific delivery of drugs. Therefore, there is a need for an appropriate therapeutic strategy to overcome these issues.

Nanotechnology is a field of science that uses material within the size of 1 to around 100 nm, providing new and unprecedented properties for materials not available in their bulk form. Nanoparticles could be used in many therapeutic methods not only to facilitate and improve these techniques, but also to overcome their limitations such as imaging and defense against cancer. By combining nanotechnology and medicine, a redemptive science called “nanomedicine” was born. Nanotechnology could be employed as a new technology and indeed a new versatile instrument to vanquish the problematic drugs used for treatment of cancers such as breast cancer and other malignancies threatening the precious human lives. They could be applicable by enhancing the solubility and stability, reducing drug toxicity and more importantly, bringing targeted drug delivery strategies for better accumulation of drugs nanotechnology.

The main goal of this study was to review the most contemporary drugs provided by nanomedicine used for breast cancer treatment (Figure 1), their process, and results.

**Methods**

The main portals used for this particular review were PubMed and Google Scholar. “Nanomaterials” and “breast cancer” were the main two keywords of the review article search within the last 5 years and it presented 90 results. After initial screening of titles and abstracts, 42 papers were selected. Due to references and journal eligibility investigation, it was limited to 20 papers. As this review focused on different nanomaterials, each particular nanomaterial was searched individually including “Breast cancer”, “liposomes”, “polymeric NPs”, “dendrimers”, “quantum dots”, “virus like nanoparticles” and “magnetic NPs” main keywords and with the same evaluation methods, and finally 41 articles were reviewed.

**Results**

**Liposomes**

With their globular lipid bilayer made of a variety of phospholipids and cholesterol, they can encapsulate a large number of molecules such as drugs and biological agents. Liposomes have several features such as enzyme degradation immunity, high circulation time, weak immunogenicity, and high biocompatibility due to PEGylation both in vivo and in vitro. They could be delivered to the tumor site either by taking advantage of enhanced permeability and retention (EPR effect) or by coating ligands on their surface to target overexpressed receptors by abnormal cells.

Etoposide was encapsulated in liposomal NPs with 99.1± 2.8% efficiency to investigate its cytotoxic effects on MCF-7 and T-47D cells. Both non-encapsulated drug and liposome encapsulated Etoposide showed cytotoxicity in a concentration dependent manner. However, MTT assay showed that the drug loaded into liposomes have displayed higher cytotoxic efficiency than the free drug itself in vitro (Figure 2a).

A study of the effect of pH-responsive liposomes encapsulated with Cisplatin on MDA-MB-231 and MDA-MB-468 metastatic breast cancer cell lines was carried out and the results were compared with non-
sensitive liposomal Cisplatin and also free Cisplatin in different pH ranges. By altering pH from a normal range of 7.4 to 6.5 and 6, although the retention rate of pH sensitive liposomes in both cell lines reduced and the drug release ratio increased, a weak cellular uptake was observed. However, pH appeared to be insignificantly effective for non-pH-responsive liposomes and its releasing efficiency. An exclusive increase in the incubation time (24 hours of incubation) resulted in stimulation of the releasing rate in non-pH-responsive liposomes. Free Cisplatin also showed no dependency on pH (Figure 2b). The use of liposomes as carriers for immunological agents has its own advantages. In this particular research, DOX (Doxorubicin) was loaded into different NPs coated with CD44, αIL-6R Ab-PE (PE conjugated antibody) and αIL-6R Ab-PE-CD44. Referring to the sensitivity of liposomes to pH, releasing potency of encapsulated drugs and agents were increased by reducing pH levels. Active targeted delivery of liposomal Dox and anti-IL6R Ab-PE with CD44 was applied to mice with 4T1 triple negative metastatic breast cancer cells and showed more than 6-fold anti-IL6R and 4-fold Dox cellular accumulation than a non-targeted liposome that was used as a control. The use of discussed nanoparticles in MMTV-PyMT mice by targeting strategy of anti-IL6R Ab-PE showed enhanced accumulation in the tumor site that was about 11 times larger than the control cell line; therefore, the accumulation of liposomal drug in unnecessary organs such as the liver, lungs, spleen, kidneys, and intestines reduced significantly. In addition, this method was also used with CD44 and showed more promising results than free drugs. Furthermore, all experiments carried out in this study showed significant antitumor results in vivo.

As liposomes are very modifiable, they have been moderated by PEGylation using hyaluronic acid (HA) for delivering GGCT (γ-glutamylcyclotrasferase) SiRNA to drug resistance MCF7 breast cancer cell lines. In vitro studies have demonstrated cellular uptake enhancement by assessing with Cy5-labeled siRNA. Moreover, gene silencing effect was detected by western blotting assay which gives strong evidence of desirable cellular uptake and internalization of synthetized liposomes (G-PEG-HA-NP). MTT assay approved the cytotoxic effect of G-PEG-HA-NP with increasing the siRNA concentration to 100 or 200 nM in vitro by decreasing cell viability. Also, FITC-Annexin V/PI showed an increased ratio of apoptosis and necrosis of G-PEG-HA in comparison to control formation. The western blotting technique revealed downregulation of GGCT in tumors treated with G-PEG-HA-NP compared to other control structures in vivo.

Another study investigated the use of liposomes as a multidrug targeted delivery system. The liposomes were synthetized at a size of 140-160 nm. However, coating mAbs and loading drugs may cause size increase. According to measurements, Doxorubicin (DOX) and Bevacizumab (Avastin) were encapsulated to liposomes with 80% and 37% encapsulation efficiencies respectively. Although the release rate was high in the first 24 hours, it has achieved a steady release rate through the next 48 hours. In vitro cellular uptake analysis of immunoliposomal DOX in BT474/MDR showed targeted delivery and internalization, while free DOX used as control was not able to pass the cell drug resistance barriers. Moreover, in vivo studies started when the tumor size was 100 mm3 and the effects of different forms of encapsulated drug (Free DOX, liposomal DOX, immunoliposomal DOX, liposomal bevacizumab and immunoliposomal DOX+ liposomal bevacizumab)
were investigated during 60 days in BT474/multidrug resistance bearing nude mice in which a combination of immunoliposomal DOX and liposomal bevacizumab had the highest tumor growth inhibitory strength. In one study, liposomes with a mean size of 101.50±0.44 nm were synthesized and Epirubicin and Quinine were loaded onto them with 95.0±1.3% and 94.5±1.3% of encapsulation efficiency and 1.12±0.16% and 1.51±0.19% of releasing flux, respectively. Free drugs at different dosages were supplemented to MCF-7 cells which were sensitive to Epirubicin and the results were compared to their liposomal forms, indicating a lower survival rate of cancerous cells. As for the MCF-7/ADR cells, free Epirubicin presented no sensitivity while a combination of free Epirubicin and quinine showed cytotoxic effects. However, liposomal drugs had less cytotoxic effects on normal cells. Further details are shown in Figure 2c. Confocal laser scanning microscopy approved accumulation of functional Epirubicin liposomes, specifically in the mitochondria, to induce apoptosis, slow release, and internalization of the drug into the cells. Confocal laser scanning microscopy approved accumulation of functional Epirubicin liposomes, specifically in the mitochondria, to induce apoptosis, slow release, and internalization of the drug into the cells. In vivo imaging findings in MCF-7/ADR cells in nude mice also explained localization of functional liposomes at the tumor site and promoted drug retention time as it was observed. In table 1, the most ultimate drugs loaded to liposomal NPs for breast cancer therapy has been indicated.

**Figure 2.** Calculated IC50 and LD50 of liposomal NPs in different cell lines and pH ranges. A) IC50 (µg/mL) of etoposide liposomal NPs was compared with that of free etoposide in T-47D, MCF-7 and MCF-10A cells. B) LD50 (mg/mL) values were compared within free cisplatin, non-pH-releasing and pH-releasing liposomes in pH 6.0, 6.5 and 7.4. C) Different forms of Epirubicin, quinine and their resistance index IC50 were assessed in MCF-7/ADR and MCF-7 cells.
ISL-loaded hybrid NPs composed of a polymeric PLGA core coated by a layer of lipids and PEG were prepared, and iRGD peptides were modified on the surface of NPs. ISL-iRGD NPs with an average size of 137.2±2.6 nm and zeta potential of -34.21±1.23 mV were used to deliver loaded Isoliquiritigenin (ISL) to breast cancer cells. The nano formed drug showed more anticancer effects on MCF-7, MDA-MB231 and 4T1 cells than its unstrained form. In addition, drug loaded NPs presented 40% higher apoptotic effects in vitro. Better internalization of drug loaded NPs due to their smaller size (137.2 nm) and both passive and active targeting systems was confirmed in MDA-MB-231. In vivo discoveries in bearing nude-mouse 4T1 cells exhibited tumor shrinkage (474 mm3), augmented mitotic body, decreased effective dosage and eventually no toxicity in none targeted organs such as the lungs, liver, and kidneys.

Polymeric-based nano structures

ISL-loaded hybrid NPs composed of a polymeric PLGA core coated by a layer of lipids and PEG were prepared, and iRGD peptides were modified on the surface of NPs. ISL-iRGD NPs with an average size of 137.2±2.6 nm and zeta potential of -34.21±1.23 mV were used to deliver loaded Isoliquiritigenin (ISL) to breast cancer cells. The nano formed drug showed more anticancer effects on MCF-7, MDA-MB231 and 4T1 cells than its unstrained form. In addition, drug loaded NPs presented 40% higher apoptotic effects in vitro. Better internalization of drug loaded NPs due to their smaller size (137.2 nm) and both passive and active targeting systems was confirmed in MDA-MB-231. In vivo discoveries in bearing nude-mouse 4T1 cells exhibited tumor shrinkage (474 mm3), augmented mitotic body, decreased effective dosage and eventually no toxicity in none targeted organs such as the lungs, liver, and kidneys.

PLGA as a core, lectin as a shell, and polyethylene glycol (PEG) as a modifier were used to manufacture hybrid NPs to deliver Salinomycin (Sali) to breast cancer cells with 55% and >8% encapsulation and loading efficiency, respectively. Flow cytometry results showed that CFPE-Sali-NPs-HER2 had the highest accumulation in MDA-MB-361 ADH+, ADH-, and BT-474 cells. It also showed more drug release (80%) than the free drug and NPs without HER2 targeting system. CCK-8 assay confirmed that Salinomycin loaded to NPs and coated with HER2 had the highest anti proliferative efficiency among other forms of the drug (Figure 3). Tumorsphere studies revealed that Sali-NP-HER2 caused a significant decrease in MDA-MB-361 and BT-474 tumorsphere quantities. Furthermore, in vivo investigations demonstrated a 79% decrease in the tumor volume, lessen in tumor mass and therefore reduction in breast cancer stem cells.

DOX (D) and redox sensitive indocyanine green (ICG or I) with strengths of 98.54±0.2% and 96.54±0.03% were loaded onto polycaprolactone (PCL)-polyethylene glycol (PEG) NPs with folate (FA) on the surface (159.93±8.08 nm). Enhanced thermal responses at 43°C and drug release of I-NPs and FA-DINPs were confirmed by infrared thermal imaging camera and TEM. Glutathione and laser irradiation were used to reach 82.2% release in 24h. Moreover, NPs were taken by cells with receptor-mediated endocytosis (RME) and promoted uptake of FA-DINPs was observed by laser irradiation. Interestingly, FA-DINPs neutralized 75.86% of EMT-6 cells at a concentration of 20µg/ml in comparison to non-toxic black NPs. NIR imaging confirmed the highest accumulation and intercellular retention of FA-DINPs. Furthermore, drug accrual in unassociated organs such as the kidneys, lungs, spleen and liver was scarcely observed in vivo.

Table 2 presents the most recent strategies being carried out for breast cancer therapy using polymeric Nps.
**VLPs (Virus like Particles)**

Nanoparticles were derived from Nicotiana glutinosa plants, identified as PVX NPs. Herceptin (HER) was coated on NPs as an active targeting agent and receptor blocker, approved by western blot and ELISA sandwich technique. In cytotoxicity studies of NPs on SK-OV-3 and SK-BR-3 cell lines, Herceptin linked NPs showed more promising outcomes than the free form of Herceptin (Figure 4).

In constitution of VLPs, potato virus X (PVX) from N. benthamiana plants was used and DOX was selected as the cargo for delivery in breast cancer cases. Neutralizing activity studies in MDA-MB-231 cells showed elevated IC50 values for DOX-PVX (0.94µM) compared to free DOX (0.13µM).

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**Figure 3.** Polymeric nanoparticles in different forms such as free Salinomycin, Salinomycin loaded NPs-HER2 receptor and none targeted Sali-NPs IC50 (µg/mL) in MDA-MB-361 and BT-474 with negative and positive ADH.

**Figure 4.** Effects of VLPs conjugated with Herceptin (HER) and free HER at concentrations of 10 and 20 µg on SKOV-3 and SKBR-3 cell lines A) apoptotic values in SK-OV-3 cell line in 10 µg and 20 µg of free Herceptin and virus coated Herceptin and B) the same experiment in SK-BR-3 cell line.
Nps showed better biocompatibility, enhanced distribution and interestingly 1.2 times higher tumor shrinkage contrasted to free DOX.

Another investigation carried out with PVX-As equally consequential, fluorescence microscopy findings explained higher values of nuclei HER and free HER by ELISA, western blot. As PVX has gained enormous attention in breast cancer treatment, it was conjugated with HER to investigate its cytotoxicity influences on various cell lines. SKBR3, SKOV3, MCF-7, MDA-MB-231 and MCF-12A were treated with 10 and 20 µg of PVX-HER and free HER.

After 24 hours, no significant toxicity was seen in MCF-7, MDA-MB231 and MCF-12A but cell viability reduced when SKBR3 and SKOV3 were treated with PVX-HER and Free-HER at both 10 and 20 µg dosages.

As equally consequential, fluorescence microscopy findings explained higher values of nuclei accumulation in cells treated by PVX-HER compared to free-HER.

Although the DOX-PVX showed less toxicity, it resulted in more therapeutic activity and drug retention than free DOX. Thus, the NPs were PEGylated and evaluated in vivo. PEGylated NPs showed better biocompatibility, enhanced distribution and interestingly 1.2 times higher tumor shrinkage contrasted to free DOX.

Another investigation carried out with PVX-HER and free HER by ELISA, western blot and RT-PCR resulted no pathogenicity of fabricated NPs.

As PVX has gained enormous attention in breast cancer treatment, it was conjugated with HER to investigate its cytotoxicity influences on various cell lines. SKBR3, SKOV3, MCF-7, MDA-MB-231 and MCF-12A were treated with 10 and 20 µg of PVX-HER and free HER.

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As equally consequential, fluorescence microscopy findings explained higher values of nuclei accumulation in cells treated by PVX-HER compared to free-HER.

**Dendrimers**

As for delivering DOX and [(Cyclo) (D-Tyr-Arg-Arg-L-3-(2-naphthyl) alanine-Gly (FC13)] as CXCR4 antagonist to breast cancer cells, dendrimers (D) were used to convey the agents. Linear FC131-DOX-D4 (LFC131-DOX-D4) and DOX-D4 also presented 97.25%±0.04% and 92.37%±1.03% encapsulation efficiency and the agents were loaded with a strength of 57.96% on average. Furthermore, drug release measurements resulted in higher tax at a pH 5.5 in comparison with a normal pH range in vitro. BT-549 and T47D cells were selected for this study. Fluorescent microscopy confirmed that LFC131-DOX-D4 (4th grade dendrimers) were taken by cells with a greater internalization in comparison to the none antagonist supplemented drug (Figure 5).

Toxicity assessments on both cell lines explained that LFC131-DOX-D4 have a greater killing efficiency comparing to DOX-D4, LFC131-D4, D4 and free DOX itself. LFC131-DOX-D4 presented IC50 of 25.2 and 124.4 µg/ml in both BT-549 and T47D cells after 120h in respect. LFC131-D4 showed the highest value of the migration inhibition index at 0.5mg/ml in both cell lines.

Polyamidoamine (PAMAM) with unparalleled molecular uniformity was used to form dendrimers.
Maleimide PEG NHS (NHS-PEG-MAL) was conjugated to dendrimers for stability and biocompatibility improvement. In addition, Trastuzumab (TZ), also known as Herceptin, was grafted to the structure for better active targeting of 216.4±2.79 µg/ml loaded Docetaxel (DTX). Eventually, 71.84% and 93.5% drug release rate in 24 and 48 hours confirmed continuous release of drug. Hemolysis activity was assessed and resulted in 1.5% of TZ-D hemolytic cytotoxicity in comparison with dendrimer alone. Toxicity estimations showed 36.2% and 60.9% cell viability in TZ-D-DTX treated MDA-MB-453 and MDA-MB-231 cells, respectively. Figure 6 presents IC50 values of D-DTX and TZ-D-DTX.

Cellular uptake inspection by FITC demonstrated more TZ-D-DTX (23.5%) cellular uptake than DTX-D (11.4%) after 1h. As the time passed, it increased to 57.9% and 34.2% in MDA-MB-453 cells, respectively. There was no consequential distinction between D-DTX and TZ-D-DTX in MDA-MB-231 cells. Competition assay disclosed more efficient uptake of TZ-D-DTX in MDA-MB453 cells. In apoptotic efficacy evaluation with acridine orange and ethidium bromide, the lowest cell viability was seen in MDA-MB-453 cells treated by TZ-D-DTX. In addition, Annexin V FTIC/PI assay in an similar cell line showed 54.35% cell viability, which was the lowest rate among control and other forms.

In another case of using PAMAM dendrimers (D) for drug delivery, Pluronic F68 (PF68) was conjugated to the fabricated structure to reduce the hemolytic effect of the dendrimer. Moreover, cytotoxicity reports elucidated that DOX loaded to D-PF68 diminished the tumor spheroid volume, its protein content and cell viability in HEK293 and MCF-7/ADR cells. DOX was encapsulated to PAMAM-n2 PF68 (second-degree conjugation) with an efficiency of 60.6% DOX per macromolecule. In addition, drug release was sensitive to pH and the highest releasing rate was observed at pH 5.5. Furthermore, Annexin V-FITC/PI and Hoechst 33342 stain confirmed DOX loaded grafted PAMAM, especially the second grade, had the highest apoptotic and necrotic activity (31.0±13.5%). In vivo studies of the distribution using ICG revealed that drug loaded grafted dendrimers were accumulated desirably in the tumor site with markedly reduced cardio cytotoxicity. In vivo tumor inhibition test by histological and TUNEL assay showed tumor volume and density shrinkage of MCF-7/adr after treating with DOX-D-PF68.

Quantum Dots

Hybrid NPs were assembled by combining quantum dots with liposomes to produce quantum dots liposomes (QLs). Subsequently, the structure was loaded with siRNA and anti-EFGR (Cetuximab). Two times of PEGylation (for QDs and receptor binding) were coated on the surface, resulting in a size of 175.5±9.0 nm and potential of -1.9±0.7 mV. The mean fluorescent intensity showed that Cetuximab coated QLS (called immuno QLS) had a promising targeting efficacy in MDA-MB-453 and MDA-MB-231 cells. Furthermore, confocal microscopy revealed the great strength of immuno-QLs in QD delivery in the same cell lines. Clathrin assistance, receptor mediated endocytosis, and endosomal escape of siRNA were confirmed as cellular uptake activities during 7 hours of observation. Inhibition of protein kinase C (PKC), cell migration, tumor growth, and induction of cell apoptosis and autophagy were observed when siRNA was delivered.

In spite of valuable in vitro findings, encouraging in vivo results are still needed. Hence, MDA-MB-231 xenograft mice were selected. Subsequently, upon intravenous (IV) injection of immuno QLS, even though a large accumulation of NPs was seen at the tumor site, NPs were still observed in the liver and lungs; however, as the time passed, the density of NPs in non-targeted organs began to decrease. Anti-tumor assessments of immuno-QLs showed 44.89±2.87% apoptotic cells. In addition, pathological and histological investigations revealed no specific toxicity and non-targeting accumulation in other organs.

Graphene, rhodamine, β-Cylodextrin (β-CD) as a...
Celecoxib (CXB) and Hydroxynorketamine (HNK) loaded, Lactoferrin (LF) coated Nanocapsules (NCs) were congregated with cadmium telluride (CdTe) derived mercaptopropionic acid (MPAs) modified QDs to form a theranostic system. Promoted cytotoxicity in MCF-7 and MDA-MB-231 and reduced IC50 levels (20.04 and 28.16 µg/mL respectively) were also detected in comparison to free drug, blank NPs, CS-NCs and LF-CS-NCs. Moreover, more extravagant cellular uptake compared to free QDs was observed in the MCF-7 cell line after 24h. Interestingly, size shrinkage and protein corona were observed as in vitro findings. In vivo studies confirmed desirable cellular uptake and internalization of DOX loaded GQDs in BT474 cells. Finally, apoptosis assessments in vitro showed that DOX loaded GQDs could decrease cell viability to no more than 30% compared to unexposed GQDs.

Chitosan as a modification for super paramagnetic Magnetic nanoparticles
Magnetic nanoparticles have shed light on LF-QDs-CS-NCs cyclooxygenase-2 (COX-2) inhibitory activity, antiangiogenic and apoptotic inducer activity, and protein kinase B (p-AKT) reduction. Moreover, no immunogenicity material has fabricated magnetic nanoparticle (MNP) with special characteristic such as mesoporous structure. As a drug delivery system, DOX was loaded onto chitosan coated mesoporous magnetic nanoparticles (CMMNs) with about 19% strength and more than 90% entrapment effect. The final size of the DOX-CMMN was about 120nm using SEM imaging. In vitro studies confirmed pH sensitivity of CMMNs. In addition, enhanced rate of drug release were observed (~55%) at 5.5 pH in 24h and after 48h nearly 100% of the drug were released. By contrast, in a normal pH range, only about 35% and 60% release was reported after 24 and 48h, respectively. Furthermore, the results of MFC-7 cells treated with NPs showed that CMMNs loaded with DOX had the lowest cell viability at 1.25 µg/mL in comparison with free DOX. The cell death rates increased markedly from 40% to 90% when applied alternating current magnetic field (ACMF) was implemented.

In one study, super paramagnetic iron oxide NPs, also known as SPIONs, were characterized and modified with a 12.5 nm layer of PEG for biocompatibility achievement. Paclitaxel (PTX) was loaded to SPIONs as a therapeutic agent. Assessments on MCF-7 cells has indicated that SPIONs loaded with PTX with hyperthermia ability cause a viability downgrade in both wild type (WT) and Taxol-resistant (TR) cells. Moreover, PTX loaded to SPIONs with a hyperthermia ability reduced the viability of both cell types (WT and TR) about 10% at 25nM of concentration. Elevated amounts of apoptotic and micro-nucleated cell were observed when WT and RT MCF-7 cells were treated with PTX-SPIONs-HT, which explains its apoptotic efficacy.

In one study, 200 ng magnetic NPs and Lipofectamine as a lipid-based transfection agent were selected to induce CD95 (Fas), c-FLIP and procaspase-8 expression in MCF-7 breast cancer cells. Presence of Fas in transfected cells were confirmed.
with fluorescence microscopy due to simultaneous expression of Fas and green fluorescence protein (GFP). Meanwhile, apoptosis assessments demonstrated that NPs loaded with gene and grafted with FasL (Fas ligand) could cause apoptosis to more than 50% of cells within 24h.

Discussion

In this review, we explored the most recent and most commonly used nanomaterials in breast cancer treatment. It was found that nanomaterials used in medicine, especially in breast cancer, could enhance therapeutic drugs efficacies, promote circulation time in the body, enhance the drug retention time, enhance their solubility and hydrophilicity, reduce the product price, and most importantly, prevent toxicity in healthy cells by their active and passive targeting systems. Therefore, it can be concluded that breast cancer cells treated with drug loaded NPs have less cell viability, decreased tumor size, and increased drug accumulation in the tumor site compared to treatment with free drugs.

According to different studies, liposomes with their specific structure could be loaded by various numbers of drugs; however, hybrid nanoparticles such as quantum dots liposomes, magnetic polymeric NPs, and PLGA-Lectin NPs have a higher circulation time. Averagely in MCF-7 cells treatment, liposomes presented 9.855 µg/ml of IC50 while with polymeric NPs an 8 nM of IC50 could be observed. It could be comprehended that in this particular study loading drugs to polymeric NPs causes more influence on MCF-7 cells than liposomes.

In the assessment for MDA-MB-231 cells drug loaded to dendrimers dispensed significantly lower IC50 value than VLPs and quantum dots. Therefore, it explains drug loaded dendrimers more excessive therapeutic action. Nevertheless, this information is limited to this particular review and results of further investigations could be slightly different. Despite all advantages, there are some limitations for this new method. Cationic liposomes could show toxicity and induce mononuclear phagocyte system (MNP), deterioration in polymeric NPs, toxicity of quantum dots and more importantly, establishment of a bimolecular layer on NPs recognized as protein corona that could alter NPs properties and interrupts drug delivery system.

For instance, studies on mesoporous silica NPs (MSN) and gold NPs presented seve protein absorption intensity which leads to protein corona development on the surface of the NPs. Furthermore, some NPs such as TiO2, Au, Ag and SiO2 induce endothelial leakiness in the tumor site. As nanotechnology is a new field of science being combined with medicine, further research is firmly required. However, there are many drug loaded nanomaterials in the process of earning approval from drug associations and it is likely to expect more development from nanomedicine science.

Conflict of Interest

None.

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Methods: Data were derived from Cancer Research Center database from 38 pure DCIS cases who had received intraoperative radiation therapy between 2012–2017. Intraoperative electron radiotherapy (IOERT) was performed according to Iran’s intraoperative radiation therapy consensus.

Conclusion: There is not a lot of data on the effectiveness of IOERT in DCIS management. Although there are not large number of cases in our study, the local recurrence (13.1%) was only event in our study with 31 months median follow up with no contralateral metastasis, distant metastasis, or death.

Results: The median age of the patients was 55 years and median histological lesion size was 1.8 centimeters. Number of extracted lymph nodes had a median of 1 and all extracted nodes were negative. Hormonal therapy was performed in 42.1% of patients. IOERT was done as radical full exposure for 86.9% of cases and as boost dose for 13.1% of cases, who needed to complete radiotherapy by external beam. One case in the group received boost dose and 4 cases in the group received full dose had recurrence. The median follow-up of patients was 31 months. Pathology of recurrence was reported as DCIS in 3 cases and invasive breast cancer in 2 of them.

Background: Ductal Carcinoma In Situ (DCIS) which has recently been renamed into Ductal Intraepithelial Neoplasia (DIN), is a malignant cell proliferation without invasion to basement membrane of ducts or lobules of breast. DCIS consists 20-30% of newly diagnosed breast cancers in some Western countries due to higher diagnosis resulting from screening by mammography. Relative Risk (RR) of invasive ductal carcinoma is 8-10 times in DCIS, although high grading lesions and positive or close surgical margins are two important predictive factors in DCIS recurrences. The adjuvant radiotherapy has decreased the rate of ipsilateral local recurrence about 60%. In this article, we evaluated the recurrence rate as DCIS as well as invasive breast cancer in patients with DCIS undergoing breast conserving surgery (BCS) and intraoperative electron radiotherapy (IOERT).

Methods: Data were derived from Cancer Research Center database from 38 pure DCIS cases who had received intraoperative radiation therapy between 2012–2017. Intraoperative electron radiotherapy (IOERT) was performed according to Iran's intraoperative radiation therapy consensus.

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Introduction

Ductal Carcinoma In Situ (DCIS), which has recently been renamed to Ductal Intraepithelial Neoplasia (DIN), refers to proliferating malignant cells within their normal site in ductal and lobular sections with no invasion through he basement membrane with an higher risk for subsequent
development of invasive ductal carcinoma. In this study, we use the term DCIS instead of DIN.

Consideration of DCIS as a specific disease, gradually happened in the first half of the twentieth century. Due to a lack of invasion through the basement membrane in DCIS, it is classified as a nonlethal type of cancer and a precursor to invasive breast cancer.

Previously, DCIS consisted of only about 1-2% of newly diagnosed breast cancers. But considering the aging of the population, increases in screening and diagnostic mammography, DCIS consists 20-30% of newer cases of breast cancer in some Western countries nowadays.

The main goal of DCIS treatment is prevention of local recurrence, and choosing the method with minimum side effects due to the noninvasive nature of it.

Relative Risk (RR) of invasive ductal carcinoma for intraductal hyperplasia without atypia is 1.5-2%, and with atypia is 4-5%. The RR of invasive ductal carcinoma for DCIS is 8-10%, but the main problem is the lack of distinction between the three grades of DCIS (low, intermediate and high) with regards to the relative risk.

According to a contemporary cohort study conducted by the Mayo Clinic, the 12 year follow-up RR for Atypical Ductal Hyperplasia (ADH) in developing breast cancer is about 20.4% and after 25 years this RR increases up to 29%.

Previously, mastectomy was the standard choice for DCIS in all patients. Nowadays it has changed from radical mastectomy to other procedures that are less disfiguring, such as lumpectomy, followed by post-operative radiation and adjuvant hormonal therapy. Since DCIS is a heterogeneous lesion, a single therapeutic protocol is not quite effective for this lesion 4, and management protocols are determined based on the physician's judgement. Much of the controversy in management of DCIS is related to the fact that the survival rate of DCIS is about one hundred percent and there is no data yet demonstrating how the current treatment for DCIS directly affects its survival. Annual risk of local recurrence in DCIS patients who only undergo breast conserving surgery is about 1-2%.

The risk of axillary metastasis in DCIS is less than 4%, thus, axillary lymph node dissection is not necessary to be done. Although cytotoxic chemotherapy is not indicated in the treatment of DCIS, patients may benefit from hormonal therapy. Five years of hormonal therapy in patients with positive estrogen receptor results in a 30% reduction in the relative risk of local recurrence.

The natural history of DCIS is related to its pathologic grade. High grade lesions and positive or close surgical margins are two important predictive factors in DCIS recurrences.

The National Surgical Adjuvant Breast and Bowel Project (NSABP) protocol B06 showed a 43% recurrence rate in patients treated with local excision alone, half of which were invasive recurrences. The addition of radiation and careful cytological review of margins significantly improved the local control. In the NSABP B17 trial, the adjuvant radiation therapy decreased the rate of ipsilateral local recurrence about 60%. Although the benefit of post-operative radiotherapy is shown, some of the patients did not receive adjuvant radiotherapy due to their lack of compliance, aging, the distance between radiotherapy center and duration of the radiotherapy course.

Accelerated partial breast irradiation (APBI) is an alternative method for whole breast irradiation, which limits the exposure only to normal breast tissue areas. Intraoperative radiation therapy is a method of Accelerated Partial Breast Irradiation (APBI) where the whole dose of radiation is delivered to the identified tissue at the time of surgery and before the wound site is closed. It seems that this method of radiation therapy increases the patient's compliance and satisfaction.

According to the TARGIT-A study, intraoperative radiation therapy (IORT) is a great choice for certain women with early stage breast cancer. Many patients who were unable to complete the six week course of radiotherapy, chose radical mastectomy, even if the exposure access is easy. If it is shown that one session of intraoperative radiotherapy is equally as effective as standard radiotherapy, this problem would be resolved. IORT may be effective for selective patients after BCS. There is limited data on the efficacy of IORT in the management of DCIS. In this study, we evaluated the recurrence rate as DCIS or invasive breast cancer in patients with DCIS who had undergone BCS and IORT.

Methods

This study was done between 2012 and 2017 at the Cancer Research Center of Shahid Beheshti University of Medical Sciences, Tehran, Iran. A total of 38 patients with pure DCIS and with DCIS and Paget's disease of breast were treated with breast conserving surgery and IORT at Khatam-Ol-Anbia Hospital, Tehran, Iran. Patient factors recorded included age, age at diagnosis, tumor size, tumor histologic grade, marital status, family history, tumor differentiation, sentinel and axillary lymph node status, surgical margins, estrogen and progesterone receptor status and whether hormonal therapy was received by patients or not.

According to the IRAN IORT consensus IRIOeRT criteria (table 1), patients received either the radical dose (21 Gy) radiotherapy or the boost dose (12 Gy) to the tumor bed during surgery. Four patients, who
were candidates for boost radiotherapy, had received radical radiotherapy due to their problems with access to and distance from the radiotherapy center. One of our patients was under 40 years old who had requested IROIoRT for her treatment. The initial goal of the study was the assessment of ipsilateral breast DCIS or cancer recurrence status. Assessing the overall survival rate of patients was the secondary goal.

**Results**

Breast conserving surgery was performed on all of the 38 patients. Patients’ age had a median of 55 years (range 33-76) and the histological size had a median of 1.8 cm (range 0.3-5). It is notable that in 8 cases, the exact size of the mass could not be determined by the pathologist. Family history was positive in 23% of cases, and 11.11% in a first-degree family member.

Tumor-free surgical margins were confirmed by pathology in 97.3% of cases, except in one patient in whom deep margins were involved. Lymph nodes extracted as sentinel lymph node were negative in patients who underwent this surgery.

The median number of lymph nodes extracted per patient was 1 (range 0-12). High grade DCIS was reported in 65.7% cases, with 47.3% necrosis. Estrogen Receptor (ER) and Progesterone Receptor (PR) were positive in 68.4% and 50% respectively. Ki-67 as proliferative index was about 20% or more in 42.1% and in 28.9% of cases, was unknown. The lesion types are described in table 2.

IORT as boost dose was delivered to 5 patients (13.6%) and one (20%) of them had recurrence later on. The patient with recurrence had extensive retro areolar micro calcification. Radiotherapy dosed at of 16 Gy was delivered to the nipple-areole complex. Furthermore, IORT as radical dose was delivered to 31 (81.5%) patients, with a recurrence rate of 12.9% (4 cases). Overall, local recurrence was documented in 5 cases (13.1% of patients) with the mean follow up of 31 months (range 8–56 months) and mean age of 50 years. The pathology of recurrence was reported as DCIS in 3 cases and invasive breast cancer in the remaining two.

Distant metastases and mortality were not observed in the studied patients and all patients were alive.

Mastectomy and immediate reconstruction were performed in 4 of the cases with a recurrence and simple mastectomy was done in the remaining one case.

All five patients with recurrence had tumor-free margins in previous pathology reports (table 3). Average tumor size was 1.9 cm (range 0.7-4 cm). Four patients had high grade lesions and one patient had a low-grade lesion without necrosis. Comedo-necrosis was observed in 3 cases. The case with low grade lesion had close superficial margins. The first pathology report of 3 of the cases were pure DCIS, one with DCIS and LCIS and the other, DCIS with Paget’s disease. All extracted lymph nodes were negative. Four cases with recurrence received full radiotherapy and one patient received boost IORT plus external radiotherapy. Four patients had positive ER/PR receptor status. Ki-67 marker in 2 of the 5 patients with recurrence was over 20%. Moreover, two patients had positive family history and 4 of them had received hormonal therapy. Table 3 demonstrated the characteristics of the patient and tumor.

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**Table 1. IROIoRT consensus for radical IOeRT**

BCS and IOERT
DCIS is a heterogeneous disease. The treatment strategy is controversial due to its excellent prognosis. The main purpose of treatment is to choose a management plan which reduces local recurrence and does not create unnecessary morbidity.

According to literature, most local recurrences of DCIS are in the lumpectomy cavity. It seems that intraoperative radiation to tumor bed proves to be sufficient for selected cases and local treatment can be completed in one session to increase the patient's compliance.

Breast conserving surgery with or without adjuvant radiotherapy are the treatments of choice for DCIS; however, it depends on the size of lesion, grading and margin status. The recurrence rate in ipsilateral breast decreased by 50% in DCIS patients when administering radiotherapy after breast-conserving surgery.14

According to literature, most local recurrences of DCIS are in the lumpectomy cavity. It seems that intraoperative radiation to tumor bed proves to be sufficient for selected cases and local treatment can be completed in one session to increase the patient's compliance.

Although the women who had received intraoperative radiation therapy had higher rates of local recurrence, data on the effectiveness of IORT in DCIS patients is not adequate.

In a study conducted by Solin et al., it was shown that the 12-year rate of developing an ipsilateral breast event for DCIS cases who had been treated with excision without radiation was 14.4% and for patients with low- or intermediate-grade lesions, 2.5 cm or less in size and 24.6% for patients with high-grade DCIS, 1 cm or less in size. The 12-year rate of developing invasive breast cancer for DCIS cases created with excision without radiation was 7.5% and 13.4%, respectively for the low or intermediate grade lesions, 2.5 cm or less in size and high grade lesions, 1 cm or less in size.

A study conducted by Donker et al. evaluated recurrence rate and outcomes during a 15-years follow up in DCIS patients who had undergone breast conserving surgery with or without radiotherapy, from the EORTC 10853 Randomized Phase III trial. This study showed that development of a local recurrence was seen in almost one in three non-irradiated women after local excision for DCIS. Radiotherapy nearly halved the risk of local recurrence.

Polgár et al. reviewed a retrospective series of 10,194 patients. The 10-year rate of local recurrence with and without radiotherapy were 9 - 28% and 22-54% respectively. In four large randomized controlled trials (NSABP-B-17, EORTC-10853, UKCCCR, Swe DCIS; 4,568 patients.), 50 Gy whole-breast radiotherapy significantly decreased the 5-year local recurrence rate from 16 - 22% to 7 - 10% respectively. In a recent meta analysis of randomized trials, Polgár concluded that addition of radiotherapy to breast conserving surgery reduces the risk of both invasive and in situ recurrences by 60%.22

### Table 2. Patients and tumor characteristics

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<tr>
<td>Intermediate</td>
<td>3</td>
</tr>
<tr>
<td>Low</td>
<td>9</td>
</tr>
<tr>
<td>Ki-67</td>
<td></td>
</tr>
<tr>
<td>&lt;20%</td>
<td>11</td>
</tr>
<tr>
<td>≥ 20%</td>
<td>16</td>
</tr>
<tr>
<td>ER</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>26</td>
</tr>
<tr>
<td>Negative</td>
<td>11</td>
</tr>
<tr>
<td>PR</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>19</td>
</tr>
<tr>
<td>Negative</td>
<td>18</td>
</tr>
<tr>
<td>Free tumor margins</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>37</td>
</tr>
<tr>
<td>No</td>
<td>1</td>
</tr>
</tbody>
</table>
A meta analysis by Viani et al. on a total of 3665 patients with DCIS, reduced significantly in recurrence of invasive and DCIS ipsilateral breast cancer with an odds ratio of 0.40 without any differences in distant metastases. Viani reported more contralateral breast cancer after adjuvant radiotherapy, 3.85%, versus observation, 2.5%. The probability of contralateral breast cancer was 1.53 times higher (95% CI 1.05 – 2.24, P = 0.03) in the radiotherapy arms of the study.20

In the study conducted by Bijker et al., the local recurrence after 10 years was evaluated as follows: 74% of patients with DCIS who were treated with local excision and 85% of patients who were treated by local excision and radiotherapy were recurrence free in the 10-year period (log-rank P<0.0001; hazard ratio = 0.53). Based on their research, DCIS and invasive local recurrence reduction rate was 86.8%. No death or distant metastases were observed. A summary of research studies containing outcomes of IORT in patients with DCIS is available in table 4.

Table 3. Characteristics of patients with tumor recurrence

<table>
<thead>
<tr>
<th>Patient</th>
<th>Surgical Margin</th>
<th>Age</th>
<th>First Pathology</th>
<th>ER/PR</th>
<th>Ki67</th>
<th>Family History</th>
<th>Tumor Size</th>
<th>Grade</th>
<th>Lymph Node</th>
<th>Radiation Type</th>
<th>Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>Yes</td>
<td>33</td>
<td>DSIC+Paget's</td>
<td>Positive</td>
<td>15%</td>
<td>No</td>
<td>4 cm</td>
<td>High</td>
<td>Negative</td>
<td>Radial</td>
<td>Invasive</td>
</tr>
<tr>
<td>Patient 2</td>
<td>Yes</td>
<td>50</td>
<td>DCIS</td>
<td>Positive</td>
<td>20-25%</td>
<td>Yes</td>
<td>3 cm</td>
<td>High</td>
<td>Negative</td>
<td>Radial</td>
<td>Invasive</td>
</tr>
<tr>
<td>Patient 3</td>
<td>Yes</td>
<td>47</td>
<td>DSIC+LCIS</td>
<td>Negative</td>
<td>10%</td>
<td>No</td>
<td>1 cm</td>
<td>Low</td>
<td>Negative</td>
<td>Boost</td>
<td>DCIS</td>
</tr>
<tr>
<td>Patient 4</td>
<td>Yes</td>
<td>64</td>
<td>DCIS</td>
<td>Positive</td>
<td>30%</td>
<td>Yes</td>
<td>1 cm</td>
<td>High</td>
<td>Negative</td>
<td>Radial</td>
<td>DCIS</td>
</tr>
<tr>
<td>Patient 5</td>
<td>Yes</td>
<td>56</td>
<td>DCIS</td>
<td>Positive</td>
<td>15%</td>
<td>No</td>
<td>0.7 cm</td>
<td>High</td>
<td>Negative</td>
<td>Radial</td>
<td>DCIS</td>
</tr>
</tbody>
</table>

* SSM: Skin sparing mastectomy

Table 4. Summary of similar studies (similar inclusion criteria)

<table>
<thead>
<tr>
<th>Author’s name</th>
<th>Number of cases</th>
<th>Follow-up length (Months)</th>
<th>Local recurrence</th>
<th>Primary histologic grading (cases with recurrence)</th>
<th>Systemic recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current study</td>
<td>38</td>
<td>38</td>
<td>38</td>
<td>High 4/ low 1</td>
<td>0</td>
</tr>
<tr>
<td>Rivera et al.</td>
<td>35</td>
<td>35</td>
<td>35</td>
<td>High 1/ intermediate 1</td>
<td>0</td>
</tr>
<tr>
<td>Rashtian et al.</td>
<td>23</td>
<td>23</td>
<td>23</td>
<td>High 1</td>
<td>0</td>
</tr>
</tbody>
</table>

In conclusion, There is not enough data on the effectiveness of IORT in DCIS management. Although there is not a large number of cases in our study, the finding of this study showed 13.1 percent local recurrence in a median follow up of 31 months. There was no involvement in the contralateral breast, distant metastasis or death in the study population., distant metastasis, or death. Further studies with more cases and longer follow up periods are needed for better evaluation of the effectiveness of IORT in management of DCIS.

Conflict of Interest

This study did not use any financial support from the pharmaceutical or medical instruments companies in any steps of design, implication, and report.

References

ARTICLE INFO
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ABSTRACT

**Background:** Molecular classification of breast tumors has identified the basal-like subtype, with high heterogeneity and very poor prognosis. These tumors are mainly triple negative, characterized by the expression of basal markers CK5/6 and EGFR. In this study, we sought to investigate the features, outcome, and therapeutic modalities of basal-like breast cancers (BLBC).

**Methods:** We retrospectively identified 90 BLBC patients diagnosed at the Department of Surgical Oncology of Salah Azaiez Institute between January 2009 and December 2013.

**Results:** The mean age of our patients was 50 years, and 15.5% had a family history of breast cancer. The mean tumor size was 43.8 mm. Histological examination revealed invasive ductal carcinoma in 88.9% of the cases, metaplastic carcinoma in 5.6%, and medullary carcinoma and adenoid cystic carcinoma in 2.2%. BLBC was most often associated with a high tumor grade (55.3% had a grade 3 tumor) and a high Ki-67 proliferative index. Vascular invasion was found in 31.1% of the cases. Regarding lymph node involvement, 42.9% had positive lymph nodes and 7.9% featured distant metastases. Surgical treatment was provided for 85 patients. It consisted of conservative surgery in 40 cases and radical surgery in 45 cases. Neoadjuvant chemotherapy was administrated to 23 patients, with a 13% complete pathologic response. The rates of overall survival and disease-free survival at 3 years for localized BLBC were 74.4% and 75.9%, respectively.

**Conclusion:** BLBCs are aggressive tumors associated with poor prognosis. Thus, to identify novel prognostic factors and therapeutic targets, prospective studies should investigate the epidemiological and evolutive profile of these tumors.

**Keywords:** Basal-like carcinoma, immunohistochemistry, prognosis

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**Introduction**

Breast cancer is the most common cancer and the second leading cause of death in women globally. Human breast tumors can be classified at the molecular level, with each molecular subtype being characterized by distinctive gene signatures and clinical outcomes. However, as standard microarray-based transcriptional profiling is not currently feasible in the clinic, immunohisto-chemistry provides a more practical approach to determining various subtypes of breast cancer by identifying protein products of the signature genes.

The various molecular subtypes of breast cancer include luminal A and B, marked by overexpression of estrogen receptor (ER) and its targets in the luminal epithelial layer of the mammary gland; human epidermal growth factor receptor 2 (HER2/ErbB2)-positive subtype, characterized by...
high expression of the HER2 oncogene; and triple-negative subtype, defined by negative expression of genes coding for estrogen, progesterone, or HER2.²

A subset of triple-negative cancers, distinguished by expression of genes characteristic of the outer or basally located epithelial layer of the mammary gland such as cytokeratin (CK) 5 and 17 and the epidermal growth factor receptor (EGFR/HER1), is classified as basal-like breast cancer (BLBC). Basal-like tumors are associated with an unfavorable clinical profile with a high risk of early metastatic relapse. Furthermore, currently there is no targeted treatment for BLBC, and the only validated systemic therapy is chemotherapy. Despite the use of recent patterns of chemotherapy, the prognosis remains poor, representing a challenge in clinical practice.³

The aim of our study was to determine the clinicopathological, therapeutic, and prognostic features associated with this type of breast cancer in the Tunisian population.

**Methods**

**Study population**

In a retrospective cohort study, we reviewed a total of 4120 breast cancer cases with complete immunohistochemical analysis registered in Salah Azaiez Institute of Cancer between January 2009 and December 2013. Only triple-negative breast cancer (TNBC) cases were eligible for inclusion in the study. Cases were excluded if there was no expression of basal markers (CK5/6), the patient was deceased, or had lost her eyesight.

**Variables**

The epidemiological, clinicopathological, therapeutic, and evolutive data were analyzed. The basal-like tumors in our study were defined by the absence of ER and PR expression, and the lack of high HER2 expression (a HER2 score of ≤ 2, with negative FISH testing).⁴ Cancer staging was carried out based on the TNM system. In patients who had undergone upfront surgical treatment, cancer staging was based on pathological findings; however, for cases receiving neoadjuvant chemotherapy, clinical and radiological staging was performed.

Tumors were graded using the Scarff-Bloom-Richardson (SBR) histological system. Sataloff and Chevalier’s pathological classification was chosen as the primary end point in the assessment of histological response in both the mammary gland and axillary lymph nodes.

Overall survival (OS) was defined as the interval between the date of diagnosis and either death or the date of the last follow-up. The other end point considered was disease-free survival (DFS), defined as the length of time from the date of diagnosis to the date of the first signs of progress confirmed by the investigator in the medical record, the date of death, or date of most recent news when the patient was censored.

**Statistical analyses**

The statistical analysis was performed using SPSS 21.0. Descriptive statistics (frequencies for qualitative variables and minimum, maximum, mean and SD for quantitative variables) were used to summarize clinical data and demographics of the patients. Estimations of the OS and FDS functions S(t) at 3 and 5 years were performed according to the Kaplan-Meier analysis and the log-rank test with stratification of our study population into 2 groups: localized and metastatic disease.

**Results**

**Clinicopathological characteristics**

Of the 4120 cases reviewed, 300 (11.3%) were TNBC, of which 90 (30%) expressed basal-like markers on immunohistochemistry and therefore were included in the study.

The frequencies of risk factors for breast cancer in our study sample are shown in Table 1. The median age at diagnosis was 50 years (range: 24-91 years; <40 years = 21%, 40-59 years = 21%, >60 years = 58%).

Forty-four patients were menopausal (48.9%). Fourteen patients reported having at least one first- or second-degree relative with breast cancer. The identification of BRCA mutation was not performed in any patient.

Table 2 illustrates the main clinicopathological characteristics of the study population. Combined mammography and ultrasound showed abnormalities in 97.5% of patients, of whom 72.5% had lesions that were highly suspicious of malignancy (BI-RADS category 5). Only 2.5% were known to be probably benign lesions (BI-RADS 3) and were then reclassified.

As for disease stage, 10.1% were classified as stage I, 53.9% stage II, 28.1% stage III, and 7.9% (n = 8) stage IV at first diagnosis. Almost half of the patients (51.1%) had a T2 tumor.

The metastases were especially visceral in the first position. Bone metastases accounted for 25%.

The majority of patients (85.6%) had an infiltrating ductal carcinoma, 2.2% had medullary carcinoma, 5.6% had metaplastic carcinoma and others histologic subtypes were identified in 6.6% of cases. Tumors were poorly differentiated and had high proliferation indexes, with 47 (55.3%) cases being grade 3 and 33 (44.7%) cases being grade II, with a mean Ki-67 index of 49%. Regarding lymph node involvement, 42.9% of patients had positive lymph nodes at initial diagnosis, and a lymphovascular invasion was found in 31.1% of cases.

Based on the immunohistochemical study, all the tumors had a triple-negative basal-like phenotype defined by lack of expression of the ER, PR, and
Table 1. Risk factors for breast cancer

<table>
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<th>Parameters</th>
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<tr>
<td>&lt; 11</td>
<td>12.4</td>
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<tr>
<td>≥ 11</td>
<td>84.6</td>
</tr>
<tr>
<td>Age at first pregnancy (y)</td>
<td></td>
</tr>
<tr>
<td>&lt; 30</td>
<td>87</td>
</tr>
<tr>
<td>≥ 30</td>
<td>13</td>
</tr>
<tr>
<td>Parity</td>
<td></td>
</tr>
<tr>
<td>Nulliparous</td>
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</tr>
<tr>
<td>Primiparous</td>
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</tr>
<tr>
<td>Multiparous</td>
<td>86.1</td>
</tr>
<tr>
<td>Hormonal contraception</td>
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</tr>
<tr>
<td>No</td>
<td>47.8</td>
</tr>
<tr>
<td>Yes</td>
<td>52.2</td>
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<td>Breast feeding</td>
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<tr>
<td>No</td>
<td>46.7</td>
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<td>53.3</td>
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<td>No</td>
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</tr>
<tr>
<td>Yes</td>
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<tr>
<td>≥ 25</td>
<td>69.2</td>
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</table>

Mean BMI = 30.32

Table 2. Clinical and histopathological characteristics (N = 90)

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<tbody>
<tr>
<td>Presentation</td>
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<td>Breast mass</td>
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<td>Pain</td>
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<tr>
<td>Nipple retraction</td>
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<tr>
<td>Screen-detected</td>
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<tr>
<td>Localization</td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>54.4</td>
</tr>
<tr>
<td>Right</td>
<td>43.3</td>
</tr>
<tr>
<td>Bilateral</td>
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</tr>
<tr>
<td>Tumor size (mm)</td>
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</tr>
<tr>
<td>≤ 30</td>
<td>45.6</td>
</tr>
<tr>
<td>&gt; 30</td>
<td>54.4</td>
</tr>
<tr>
<td>Mean size = 43.87</td>
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<td>T category</td>
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<td>13.3</td>
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<tr>
<td>T2</td>
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<td>T3</td>
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<td>T4b</td>
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<tr>
<td>T4d</td>
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</tr>
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<td>Adenoid cystic</td>
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<tr>
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<td>N+ (1-3)</td>
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<tr>
<td>N+ (4-9)</td>
<td>11.9</td>
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<td>N+ (&gt; 10)</td>
<td>13.1</td>
</tr>
<tr>
<td>Capsular rupture</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>74.1</td>
</tr>
<tr>
<td>Yes</td>
<td>25.9</td>
</tr>
<tr>
<td>Necrosis</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>44.7</td>
</tr>
<tr>
<td>Yes</td>
<td>55.3</td>
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<tr>
<td>Intraductal component</td>
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<td>No</td>
<td>67.8</td>
</tr>
<tr>
<td>Yes</td>
<td>32.2</td>
</tr>
<tr>
<td>Ki-67 (%)</td>
<td></td>
</tr>
<tr>
<td>≤ 14</td>
<td>13.6</td>
</tr>
<tr>
<td>&gt; 14</td>
<td>86.4</td>
</tr>
</tbody>
</table>
HER2 with positive staining for CK 5/6. FISH testing was needed in 12 cases to confirm the HER2 status, and we found a positive expression of androgen receptor only in 5 cases.

**Treatment details and outcomes**

As for treatment modalities, 85 (94.4%) patients received surgery, of whom 40 had conservative surgery (tumorectomy with axillary lymph node) and 45 received radical mastectomy with axillary lymph node dissection (Patey type mastectomy). Histological margins were clear in all patients with local disease.

Of 68 patients who had received adjuvant chemotherapy, 17 (25%) had anthracycline-based chemotherapy, and 35 (51.5%) had anthracycline followed by taxane. The 8 patients with metastatic disease had received an anthracycline-based regimen as the first-line for patient with metastatic diseases.

Radiation therapy was indicated in 69 nonmetastatic patients. Palliative radiotherapy was delivered in 2 patients with painful bone metastasis.

After a median follow-up of 49 months, 12 of the 82 nonmetastatic patients experienced locoregional relapse and 19 patients had a metastatic recurrence. The maximum of recurrence occurred between the first and second year after diagnosis, with a median of 21 months, and 24 patients died.

Six patients of the 8 with metastatic disease at diagnosis experienced progression, and two patients responded to palliative treatment with tumoral stability and then progression. All the metastatic cases died with a median survival of 12.5 months (range 7-20). Of the 23 patients who had advanced tumors or inflammatory breast cancer, 19 had received anthracycline and 4 had received anthracycline plus taxane neoadjuvant chemotherapy. Only 3 (13%) patients had a pathologic complete response (pCR) following neoadjuvant chemotherapy according to Sataloff and Chevalier’s classification.

OS at 3 and 5 years were respectively 74.4% and 61.9% (Figure 1). After exclusion of patients diagnosed at a metastatic stage, OS raised to 81.9% at 3 years and 67.2% at 5 years (Figure 2). DFS rate for patients with localized disease was 75.9% at 3 years and 67% at 5 years (Figure 3).
Discussion

We analyzed the epidemiological, clinical, and therapeutic characteristics of BLBC in a sample of Tunisian patients. The demographic and clinical features of our sample were, to a large extent, consistent with the literature. The frequency of TNBC reported in the present work (11.3%) agrees with the previous reports (10%-17%). In the Chinese population, approximately 12.9% of breast cancers are TNBC.

In our work, however, the basal-like phenotype represented only 30% of TNBC, which is not in accordance with the literature. In fact, 80% of TNBC have a basal-like phenotype (TN-BL) and the remaining 20% are defined as TN non–basal-like (TN–non-BL) tumors. BLBCs were reported to present at a younger age compared with other subtypes (53 vs 58 years). The median age at diagnosis (50 years) in our study was younger than the average age mostly reported in the US population but close to the median age in Hispanic patients.

More than half of the subjects in our study (59%) were 40 to 59 years old, suggesting that there might be factors predisposing towards the development of this disease. BLBC occurs more frequently in premenopausal women compared with other breast cancer subtypes. In the current study, patients were premenopausal in 51.1% of cases. We found a 71.5% rate of family history of breast cancer in our cases. Unfortunately, data regarding BRCA1/2 gene rate of family history of breast cancer in our cases. We found a 71.5% rate of family history of breast cancer in our cases. Unfortunately, data regarding BRCA1/2 gene mutation in the literature, the basal-like type may be used as a criterion for genetic screening to improve the prognosis of this aggressive molecular subtype through a diagnosis at an early stage and the sensitivity of BRCA1-mutant TN-BLBC to PARP inhibitors.

Clinically, BLBC patients presented with large tumors with a mean tumor size of 43.87 mm and a high rate of nodal involvement (42.9%). Studies suggest that lower incidence of microcalcifications and peritumoral ductal carcinoma in situ may represent typical mammographic characteristics of BLBC. Because of its more aggressive biology, BLBC often manifests itself as an interval cancer (detected within 12 months after a normal screening mammogram). Histologically, basal-like tumors in our study were characterized by a high frequency of ductal histology (88.9%), greater histological grade (55.3%), and lymphovascular invasion (31.1%), which are in accordance with the literature.

Currently, there is no approved targeted therapy available for BLBC. Both adjuvant treatment and palliative therapy are limited to chemotherapy. TNBC generally has higher pCR rates than non-TNBC, and TNBC patients achieving pCR have better survival compared with TNBC patients who do not achieve pCR. The higher rate of response to neoadjuvant chemotherapy may be due to the typically high tumor grade and mitotic index of BLBC. However, it seems that only TN non-BLBC tumors achieve a pCR. In fact, in our series, pCR rate was 13% after neoadjuvant chemotherapy based on the classification of Sataloff and Chevalier.

Prognosis of BLBC remains poor compared with other subtypes. TN-BL tumors usually display aggressive metastatic behavior. These tumors respond to conventional chemotherapy but recur more frequently than hormone receptor–positive, luminal subtypes and have a high mortality rate.

In our series, 3- and 5-year survival rates were 81.9% and 67.2%, respectively. These results are similar to those reported by Liedtke et al. in 1118 patients over a 20-year period (1985-2004). BLBC is also associated with a higher risk of relapse when compared with other molecular subtypes, especially during the first 2-3 years of follow-up. Dent et al. reported that the risk of recurrence in BLBC patients peaked 1 to 3 years from the date of diagnosis. In the study of Luedtke et al., DFS rates at 1 and 3 years were 81% and 63%, respectively, for BLBC in localized stages compared with 90% and 76% for other molecular subgroups. In our study population, DFS rates at 3 and 5 years were 75.9% and 67%, respectively.

In the metastatic setting, the prognosis is extremely worse. It represented an aggressive entity associated with very rapid progression and mortality. The most common sites for BLBC metastases are the lungs, liver, and central nervous system.

Research suggests that cell cycle and DNA damage response are highly activated in BLBC and that tumor cells are results of defects in the homologous recombination repair system. Therefore, they are vulnerable to platinum salts or PARP inhibitors. However, we have to wait for the outcome of several current clinical studies in order to define the correct strategy for the management of BLBC.

In conclusion, we found that BLBC characteristics in Tunisian patients were consistent with the literature in terms of age at diagnosis, tumor grade, stage at diagnosis, and recurrence. BLBC is associated with poor prognosis and a high incidence of early metastatic recurrence.

Moreover, currently there is no targeted therapy available for this subtype of breast cancer. Therefore, novel molecular targets and tumor response to various treatments are open avenues of investigation. Also, since BLBC is perplexingly heterogeneous, research should strive to identify novel prognostic markers to aid in improving disease management in this population.

Conflict of Interest

None.
References


ARTICLE INFO

Methods:
This cross-sectional study was conducted in the Cancer Institute of Iran, affiliated with Tehran University of Medical Sciences, in 2015. Archived formalin-fixed, paraffin-embedded breast tumor blocks were evaluated to determine the AR status of the tumors. Demographic and pathologic characteristics of the patients were retrieved from the department of pathology database. Data were analyzed with SPSS 18.0.

Background:
Triple-negative breast cancer (TNBC) accounts for 15 to 20% of all breast cancers. These patients do not benefit from hormone therapy and other targeted treatments of breast cancer. Recently, researchers proposed the use of androgen receptor (AR)-targeted therapies in this subset of patients. The rate of AR expression in TNBC patients varies from 0 to 53%. AR positivity is associated with a better outcome for breast cancer patients. The purpose of this study was to evaluate AR status in TNBC patients and its association with other demographic and pathologic features.

Conclusion:
TNBC patients with AR expression tend to have lower tumor grades and higher rates of lymphovascular invasion.

Results:
Seventy-seven TNBC patients with the mean age of 45.3 ± 11.5 were assessed. Twenty-six patients (34%) showed AR expression, and 51 patients (56%) did not have AR expression. There was no significant correlation between AR status and age, tumor size, histopathologic type of tumor, or lymph node involvement. However, AR positivity had a statistically significant association with a lower tumor grade and lymphovascular invasion (P = 0.029 and P = 0.01, respectively).

Key words:
Triple-negative breast cancer (TNBC), androgen receptor (AR), histopathological features

Introducing
The American Institute for Cancer Research (AICR) reported 18 million newly diagnosed cancer cases worldwide in 2018. Lung cancer and breast cancer are the most prevalent cancers (excluding non-melanoma skin cancers) in men and women, respectively. Breast cancer accounted for 25.4% of newly diagnosed cancers in women in 2018. The first cause of cancer death in women in developing countries is breast cancer. In Iran, breast cancer contributes to 24.6% of all cancers and is the fifth cause of death in Iranian women.

Estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) expression are important predictive and prognostic factors for the management of breast cancer and are the basis of molecular classification of breast cancer subtypes. Triple-negative breast cancer (TNBC) is pathologically defined as breast tumors that do not express ER, PR, and HER2.
TNBC accounts for 15% to 20% of all types of breast cancer. It is a very aggressive tumor subtype with poor prognosis, as patients with TNBC do not benefit from hormone therapy and trastuzumab-based targeted therapy, and the only available systemic treatment for them is chemotherapy. 

As there is an absence of a well-defined targeted therapy for TNBC, recent gene expression studies focus on androgen receptors (ARs) in these patients.\(^5\) AR expression prevalence in all subtypes of breast cancer is approximately 70% to 90%, but it varies from 0 to 53% in TNBC patients.\(^7-8\)

Androgen signaling was first studied in prostate tumor cells, and flutamide - an androgen blocker - was used for prostate cancer treatment. The association between AR and breast cancer was demonstrated for the first time in the rat in 2001.\(^9\) This sparked interest in the use of androgen-blocking agents in the treatment of breast cancer. Bicalutamide, an androgen-blocking agent, has been studied in the breast cancer setting. It had paradoxical effects on ER-positive breast cancer and caused apoptosis in ER-negative breast cancer.\(^10-12\)

Although positive androgen receptor is associated with poorer response to neoadjuvant chemotherapy, it may be associated with better prognosis in TNBC patients.\(^7\) Novel androgen-blocking agents are introduced and can be beneficial for the treatment of AR-positive TNBC patients.

In this study, we evaluated AR status in TNBC patients in the Cancer Institute of Iran and its association with other demographic and pathologic features of the tumor.

**Methods**

**Study Design**

This was a cross-sectional study conducted in the Cancer Institute, affiliated with Tehran University of Medical Sciences in 2015. All patients diagnosed with TNBC between 2019 and 2014 were included. The study protocol was approved by the Research Ethics Committee of Tehran University of Medical Sciences.

Triple-negative breast tumors were identified in the pathology database of Cancer Institute and the paraffin blocks were selected for AR staining. Patients’ demographic data were retrieved from the pathology department database. Demographic data included age at diagnosis, histopathologic tumor type, tumor size (mm), grade, lymphovascular invasion status and the number of involved axillary lymph nodes. Androgen receptor status was assessed as mentioned below.

**Androgen receptor**

Archived formalin-fixed, paraffin-embedded breast tumor blocks were collected from the pathology department and Hematoxylin and Eosin staining was used to confirm the diagnosis and select the appropriate blocks. A commercially available antibody (Monoclonal Mouse Anti-Human AR, Clone 441 Isotype: IgG1 Kappa; Dako, Denmark) was used to determine the AR status. Microwave heating was used for antigen retrieval in all cases. Then, the slides were assessed and scored by the same pathologist using a light microscope. If more than 10% of tumor nuclei were stained, AR status was considered positive. Cytoplasmic and membrane staining were considered negative for the androgen receptor.

**Statistical Analyses**

Data were analyzed with SPSS 18.0 statistical software (SPSS Inc, Chicago, IL, USA). For evaluating qualitative variables, the chi-square and the Fisher exact tests were used. Also, quantitative variables were compared between the two groups using an independent \(t\) test. P values less than 0.05 were considered significant.

**Results**

Seventy-seven TNBC pathology blocks were collected and assessed for AR status. All patients were female, with the mean age of 45.3 ± 11.5 years at the time of diagnosis. AR expression was positive in 26 patients (34%), and 51 patients (56%) were AR-negative. Demographic and pathological characteristics of patients are shown in Table 1.

AR-negative status was more commonly observed in TNBC patients with higher tumor grade (\(P = 0.029\)). Also, lymphovascular invasion was associated with an AR-positive status (\(P = 0.010\)). Table 2 shows the distribution of demographic and pathological characteristics in AR-positive and AR-negative tumors.

**Table 1. Demographic and Pathological Characteristics**

<table>
<thead>
<tr>
<th>Variables</th>
<th>N(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD, y</td>
<td>45.3 ± 11.5</td>
</tr>
<tr>
<td>Tumor size, mean ± SD, mm</td>
<td>17 ± 36.5</td>
</tr>
<tr>
<td>Histopathologic type</td>
<td></td>
</tr>
<tr>
<td>IDC</td>
<td>64 (83%)</td>
</tr>
<tr>
<td>Medullary</td>
<td>7 (9%)</td>
</tr>
<tr>
<td>Papillary</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>Metaplastic</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>Tumor grade</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>II</td>
<td>28 (36%)</td>
</tr>
<tr>
<td>III</td>
<td>47 (61%)</td>
</tr>
<tr>
<td>Lymphovascular invasion</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>50 (65%)</td>
</tr>
<tr>
<td>No</td>
<td>27 (35%)</td>
</tr>
<tr>
<td>Lymph node metastasis</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>31 (40%)</td>
</tr>
<tr>
<td>No</td>
<td>36 (60%)</td>
</tr>
<tr>
<td>Androgen receptor</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>26 (34%)</td>
</tr>
<tr>
<td>Negative</td>
<td>51 (56%)</td>
</tr>
</tbody>
</table>

**Discussion**

This study showed that the frequency of AR expression in TNBC patients was 34%. There was no statistically significant association between AR
status and age, tumor size, histopathologic type of tumor, or lymph node involvement, although lower tumor grade and lymphovascular invasion were associated with a positive AR status.

These findings are similar to other studies. The prevalence of AR-positive status in TNBC tumors has been reported in various studies. In two recent review articles, AR expression rate in TNBC varied from 0% to 53%. A study from Iran examined the AR status in breast tumors in 2014 and found an AR expression rate of 64.3% in all tumors and 50% in TNBC cases. However, there were only 12 cases of TNBC in their study, which makes their results less accurate for this subgroup of patients.

Age has been associated with an AR-positive status in some studies. Two recent studies reported the association of AR-positive status with older age at the time of diagnosis. On the contrary, the previously mentioned study in Iran reported that patients with AR-positive tumors were younger than AR-negative patients. However, most studies declared that age does not appear to affect the AR positivity.

The present study did not show any association between tumor size and AR status. However, other studies reported that the smaller tumors were more likely to be AR-positive. Another study from Iran did not show any significant association between tumor size and AR status.

Some studies have reported a significantly lower rate of AR expression in metaplastic, mucinous, and medullary subtypes of breast cancer. In the study by Choi et al., the authors concluded that AR positivity was distinctively associated with an apocrine histopathologic type (P = 0.001). Our study did not show any association between the histopathologic type and AR expression. The most common histopathological type of tumors in our study was invasive ductal carcinoma, and the frequency of other types was not adequate for accurate evaluation.

In the present study, AR expression was associated with a lower tumor grade. This finding is similar to other studies. Park et al. reported that the expression of AR was significantly higher in tumors with lower grades (P < 0.001). In other studies, a significant association was found between AR positivity and a lower tumor grade.

Lymphovascular invasion is a predictor of more aggressive tumor behavior and might be associated with higher rates of AR expression. Our results are in concord with other studies showing that AR positivity is related with lymphovascular invasion. However, there are other studies that found an inverse correlation between AR positivity and lymphovascular invasion.

Lymph node involvement is one of the important predictive and prognostic factors for outcomes of breast cancer patients. We did not find a statistically significant association between AR expression and lymph node involvement (P = 0.231). Also, most studies confirmed the lack of a significant relationship between AR expression and lymph node involvement. In one study by Rakha et al., there was a significant association between AR expression and lymph node involvement (P = 0.03).

We did not have the data on Ki-67 for our study sample. Other studies have reported inconsistent results regarding AR status and Ki-67 relationship. A study by Pistell and colleagues evaluated 81 TNBC patients, and only 18.8% were AR-positive. AR positivity was associated with higher Ki-67 expression (P < 0.001) and lymphovascular invasion (P = 0.01) in their study. However, the study by Park et al. did not show any association between AR status and Ki-67.

In conclusion, AR positivity is associated with a lower tumor grade and positive lymphovascular invasion in TNBC. Further studies with larger study samples are required to evaluate the impact of AR status on patient outcome and the use of AR-based hormonal manipulations in TNBC patients.

**Conflict of Interest**

The authors have none to declare.

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**Table 2.** Comparing demographic and pathological characteristics between AR-positive and AR-negative groups

<table>
<thead>
<tr>
<th>variables</th>
<th>Positive (N=26)</th>
<th>Negative (N=51)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD, y</td>
<td>46 ± 10</td>
<td>45 ± 12</td>
<td>0.700</td>
</tr>
<tr>
<td>Tumor size, mean ± SD, mm</td>
<td>37 ± 19</td>
<td>34 ± 14</td>
<td>0.500</td>
</tr>
<tr>
<td>Histopathologic type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IDC</td>
<td>22 (85%)</td>
<td>42 (82%)</td>
<td>0.759</td>
</tr>
<tr>
<td>Medullary</td>
<td>3 (11%)</td>
<td>4 (8%)</td>
<td></td>
</tr>
<tr>
<td>Papillary</td>
<td>0 (0%)</td>
<td>3 (6%)</td>
<td></td>
</tr>
<tr>
<td>Metaplastic</td>
<td>1 (4%)</td>
<td>2 (4%)</td>
<td></td>
</tr>
<tr>
<td>Tumor grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>1 (4%)</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>14 (54%)</td>
<td>14 (27%)</td>
<td>0.029</td>
</tr>
<tr>
<td>III</td>
<td>11(42%)</td>
<td>36 (71%)</td>
<td></td>
</tr>
<tr>
<td>Lymphovascular invasion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>22 (85%)</td>
<td>28 (55%)</td>
<td>0.010</td>
</tr>
<tr>
<td>No</td>
<td>4 (15%)</td>
<td>23 (45%)</td>
<td></td>
</tr>
<tr>
<td>Lymph node metastasis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>13 (50%)</td>
<td>18 (35%)</td>
<td>0.213</td>
</tr>
<tr>
<td>No</td>
<td>13 (50%)</td>
<td>33 (65%)</td>
<td></td>
</tr>
</tbody>
</table>
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Diagnosis and Management of Metastatic Breast Cancer During Pregnancy by a Multidisciplinary Team: A Case Report

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ABSTRACT

Background: When breast cancer is diagnosed during pregnancy or within the first year after delivery, the condition is named as pregnancy-associated breast cancer (PABC). Breast cancer during pregnancy is a devastating situation for the patient, her family, and the medical team. Providing guidance for diagnosis and treatment of PABC, we report a case along with review of the literature.

Case presentation: Here we present a 31-year-old pregnant woman with low back pain who was referred to the gynecology ward. She was at 25 weeks and 6 days of pregnancy. After workup, it was discovered that she had a lytic lesion in her spine. Further workup revealed that she had metastatic breast cancer with the pathology of invasive ductal carcinoma. After consultation with a multidisciplinary team (a gynecologist, an oncologist, a radiotherapist, a hematologist-oncologist, and a neurosurgeon), we terminated the pregnancy and put her on radiotherapy for the spine metastasis and systemic therapy. Also, we reviewed 36 pregnant patients with primary or recurrent breast cancer who were managed with outpatient chemotherapy, surgery, or surgery plus radiation therapy. Care was provided by medical oncologists, breast surgeons, and perinatal obstetricians.

Conclusion: Since there are no sufficient data in the literature to guide the development of standard protocols for management of PABC patients (specially in metastatic disease), pregnant women must be followed up by a multidisciplinary team, and each case should be managed considering the gestational age and the stage of cancer.

Introduction

Breast cancer is the second most prevalent malignancy affected by pregnancy. Breast cancer in a pregnant woman is more distressing for the patient and her family than in a nonpregnant woman. The management of pregnancy-associated breast cancer (PABC) requires a multidisciplinary team as well as psychological support. The incidence rate for PABC is estimated to be 1 in 3000 pregnancies.1

Breast cancer is usually hormone-dependent; therefore, abortion is often recommended during the first trimester to avoid tumor growth due to estrogen and progesterone increase. However, termination of pregnancy does not seem to improve patient survival.2,3 Because of advanced maternal age, the incidence of PABC is expected to increase.4,5 Due to dense breast tissue during pregnancy, examination of breasts is difficult, which can prevent a breast mass from being detected by both the patient and the physician.6,7 Ultrasonography is the first approach when facing a breast mass in a pregnant woman.8-11 Mammography is less sensitive and has a high false-negative rate, but it also plays a key role in
Here we present a case of PABC. Our aim is to show that PABC should be followed up by a multidisciplinary team and that each case should be evaluated separately depending on the gestational age and stage of cancer.

Case presentation

A 31-year-old pregnant woman came to our hospital with low back pain, lower limb paralysis and walking inability. She had had the backache since 2 months before presenting to the hospital, and a rheumatologist had given corticosteroid under the diagnosis of ankylosing spondylitis. Her gestational age was 25 weeks and 6 days.

After workup by the neurosurgery team, lytic lesions were found in the spinal MRI in T10 to L4. There was no palpable mass in the breast in the physical examination.

Laminectomy and decompression were performed as soon as possible, and the pathology report suggested metastatic carcinoma of breast origin. Sonography demonstrated a 23×15 mm lesion in the left breast and a 26×86 mm lymph node in her left axillary. Then, core needle biopsy of the breast was done and the pathological examination showed invasive ductal carcinoma ER positive and PR positive and HER2-negative.

She had a family history of breast cancer in her 30-year-old sister. Metastatic workup showed isolated spine metastasis. Chest x-ray and abdominal and pelvic sonography were normal. The next step was radiotherapy to the spine, so pregnancy termination was inevitable. The medical consultation team including a neurosurgeon, a radiotherapist, an oncologist, and a gynecologist gathered for decision making. Finally, after consulting with patient and her husband, cesarean section was performed. At the 27th week of pregnancy, just one day before radiotherapy and after corticosteroid administration, a baby girl weighing 450 g with Apgar score 5 was delivered.
The mother was then treated with radiation therapy and chemotherapy, and surgery of breast was not necessary at that time. After treatment, that patient was followed up for .... months. There is no recurrence was found during the follow up period. Also, the baby is normal with no significant problem.

**Discussion**

Breast cancer is one of the most common cancers in women and can invade many other organs. The goal of treatment for breast cancer in pregnant and nonpregnant women is the same, namely, to control the tumor locally and preventing the disease from spreading in the body. During pregnancy, some treatment modalities should be modified because of adverse effects on the fetus.

Radiation therapy is contraindicated during pregnancy and is not considered a safe treatment. The main risks associated with this treatment are the increased odds of bearing babies with mental retardation (when administered after the 8th week of pregnancy) and an increased risk of childhood cancer.

Rovera et al. reported six breast cancer patients who were diagnosed during pregnancy (median age: 34 years; range: 28–44 years) and six other patients whose breast cancer was discovered during breastfeeding. In all cases, the histological type of tumor was invasive ductal carcinoma, 10 patients with grade 3 and 2 patients with grade 3. Ten patients underwent breast-conserving surgery. Eleven of 12 patients received adjuvant chemotherapy and 1 patient received both adjuvant and neoadjuvant therapies. In 3 cases, radiation therapy was also performed after delivery. In all cases, healthy babies were born. Nine of 12 patients were alive and disease-free after a median follow-up of 20 months (range 3–52 months). The other 3 patients died of systemic progression of the disease. In conclusion, there is not sufficient evidence to help with the development of standard protocols. Pregnant women must be followed by a multidisciplinary team.

Berry et al. managed 24 pregnant patients with primary (n = 22) or recurrent (n = 2) breast cancer with a combination of outpatient chemotherapy regimens, surgery, or surgery plus radiation therapy over an 8-year period. Of the 22 patients with primary breast cancer, 18 received modified radical mastectomy and 2 were treated with segmental mastectomy with postpartum radiation therapy. A median of 4 cycles of combination chemotherapy was performed during pregnancy, with no chemotherapy-related antepartum complications. The mean gestational age at delivery was 38 weeks. All of the neonates had normal birth weights and were healthy. The authors concluded that treatment of breast cancer with chemotherapy during the second and third trimesters of pregnancy is completely safe.

Our case was a stage IV breast cancer patient with isolated spinal metastasis. Because she needed radiotherapy, we terminated the pregnancy to avoid possible radiotherapy side effects on the fetus. Although the gestational age was 25 weeks and 6 days, waiting for the development of the lungs in the fetus was impossible.

In conclusion, management of PABC patients requires a multidisciplinary team as well as psychological support. Diagnosis of cancer during pregnancy remains an unusual event. However, its possibility should always be considered, and all cases should be referred to specialized centers so that the best decision is reached through counseling and appropriate medical and psychological support is provided. Also, we should consider the parent's preferences. The diagnosis of breast cancer during pregnancy has a high psychological impact on the patient's life, her family, and even the multidisciplinary team. The difficult management of this situation necessitates advice from other specialties to make the best decision. The decision of the patient, the stage of cancer, and gestational age should always be considered.

**Acknowledgments**

The authors thank Firoozgar Clinical Research Development Center (FCRDC), Firoozgar Hospital, Iran University of Medical Sciences, for their assistance.

**Ethical Consideration**

In accordance with medical ethics committee requirements, written informed consent was provided by the patient for the publication of this article and the accompanying images.

**Conflict of Interest**

None of the authors has any potential conflict of interest.

**References**


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How people die remains in the memory of those who live on.”
   Cicely Saunders (1918-2005)

Everybody dies; some at home and some in a hospital. Lucky people die in situations where they may receive both physical and emotional care. End-of-life care is a part of palliative care provided in the last days of patients’ life to allow them to die with dignity. End-of-life care priorities include communicating about prognosis, discussing the medical futility, assisting with decisions on invasive procedures such as cardiopulmonary resuscitation or mechanical ventilation, and planning for prudent pain and symptom management. While patients are considered the center of the care, their relatives are commonly forgotten. Questions such as what they should be expecting in the next hours or days, or what they should know about dying, death and after, remain unanswered.

Ms. N. was a 73-year-old woman with metastatic breast cancer. She was referred to the palliative clinic in the final days of her life with advanced breast cancer. She was disoriented, experiencing a lot of pain and discomfort along with other complications secondary to brain metastasis. Her children were informed of her prognosis and her comfort was their request. Ms. N. was admitted to the hospice that day and passed away peacefully at 1:00 a.m. next day, surrounded by her five children.

The on-call physician arrived with some delay to sign the death certificate. Having looked through the half-open door of the room and heard the sounds of crying, the doctor might have thought that stepping inside may be an unnecessary intrusion into the family’s need for privacy. The ambulance crew arrived to transfer the body to the morgue before Ms. N.’s grieving children had finished their mourning rituals.

As the body was being transferred to the morgue by ambulance, the atmosphere completely changed in front of the morgue when one of her sons noticed something; “Look! My mother is alive; she is peeing,” he shouted at the driver, and before anybody had time to digest what he had said, he hastily opened up the shroud.

The next few minutes were the most disturbing moments for the family and the staff. At the family’s desperate cry, the ambulance staff was coerced to transfer the body to the ED. Ms. N.’s naked body was subjected to resuscitation and given CPR at her children’s request.

Proper professional communication with a family who has just lost a beloved one is a very delicate matter. Signing the death certificate is only the technical part of a physician’s job. Examining the dead body with respect and empathizing with the family and supporting them would be the fully humane and professional duty of the care provider.

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Even when a death is expected, coming into terms with death is difficult, especially for close friends and family. Some changes will happen after death, and it is very important to reassure close relatives or friends that these changes are quite normal. The body’s sphincters relax and cause the exit of the gas and stool from the rectum, the stomach’s secretion from the mouth, or the urine from the bladder. This might be insufferable for those who are not expecting these events. All health care providers should learn about the physical changes after death in addition to receiving bereavement training.\(^2\,^3\)

The family’s response to their loss may be emotional and, possibly, traumatic when the patient has been referred to palliative care services late. Building trust is crucial, as is an understanding of family dynamics. Responding appropriately requires sufficient time. The symptom relief should be started soon, comfort and dignity safeguarded, while the family is being cared for and prepared to lose the loved one. It should be exceptional for referral to a palliative care service in the last few days of life. Offering the best supportive and palliative care should be part of the responsibility of all cancer team members (surgeons, medical oncologists, radiotherapists), in addition to trying hard to control cancer.\(^3\)

Support for the staff and acknowledging how they struggle to deal with a stressful working environment, difficult patients, or their difficult family members are vital. The staff must feel supported and appreciated while they are striving to deliver the best care at the final hours of a dying patient. This experience is moving, valuable, and highly educational for the staff.\(^2\)

End-of-life care refers to providing treatment and care for people who are nearing the end of their life, and support for their family members. End-of-life care is not palliative care but is an important part of it. It goes without saying that caring for dying persons and their families is demanding and very stressful, but when this goes well, it is extremely rewarding!

"The soul has been given its own ears to hear the things the mind doesn’t understand"

Rumi

Aethical Consideration
For the sake of confidentiality, the names of people and places were removed and are anonymous. Details which could have resulted in the identification of the case were not disclosed.

Conflict of Interest
None.

References

Support Care Cancer 2017; 25:933.
ARTICLE INFO

Methods: A comprehensive literature search of PubMed between 1996 -2019 that was made was made for case series and randomized studies with at least 2 years of follow-up in term of clinical and cosmetic outcomes, quality of life, and treatment costs.

Results: Technological advances have made various APBI modalities, including intracavitary and interstitial brachytherapy, intraoperative radiation therapy, and external-beam radiation therapy, more accessible in the community. Mature data from several randomized and prospective nonrandomized trials have contributed to the development of consensus guidelines for selecting the most appropriate candidates ABPI.

Conclusion: APBI represent an attractive treatment option for appropriately selected patients with early breast cancer. Irrespective to various techniques used for APBI it is very important to select the most appropriate patient population according to reliable guidelines for this treatment strategy that could be non-inferiority to whole breast irradiation especially in high-volume radiation centers with long waiting lists and for patients who live far away from the radiotherapy centers.

Key words: Accelerated partial breast irradiation, brachytherapy, intraoperative, external-beam, local control

Introduction

Breast cancer is the most prevalent female malignancy worldwide. Nowadays, more patients present with early-stage breast cancer because of breast screening and mass education programs, and the majority of them undergo breast-conserving surgery (BCS). In addition to tumor control and survival, the breast conservation approach is important in terms of cosmetic outcomes, which is associated with improvement in emotional adjustment of the patient with early-stage breast cancer. Whole-breast irradiation (WBI) is almost always recommend as an adjuvant treatment in patients undergoing BCS. Whole-breast irradiation following BCS can reduce the risk of local recurrence to very low levels comparable to those achieved with mastectomy.
In spite of the many benefits of WBI, the treatment is also associated with some disadvantages. For one thing, it is relatively complex and expensive and needs physical and human resources. Another major disadvantage of WBI is that the treatment is highly inconvenient as it usually includes 6 to 7 weeks of daily high-dose radiation treatments to the whole breast, which, aside from radiation-related discomforts, may require patients to miss work or undergo other significant lifestyle alterations (such as temporary lodging expenses or separating from their family, friends, and other supporters). In fact, a negative relationship has been observed between the distance from a patient’s home to the nearest radiation facility and the tendency to use breast conservation therapy, and some patients have refused BCS simply because of difficulties in accessing to radiation therapy facilities.

WBI has some late complications such as fibrosis, lymphedema, cardiac toxicity, radiation to the contralateral breast, and secondary malignancy. However, newer EBRT technologies such as three-dimensional radiotherapy, intensity-modulated radiotherapy, deep inspiration breath hold, and prone position techniques, have significantly contributed to decreased complications because of better dose conformity and delivery to the target volume and normal tissue sparing. Yet, there are still some complications remaining. Here we provide the rationale for using accelerated partial breast irradiation (APBI) and an overview of various APBI techniques in term of clinical and cosmetic outcomes, quality of life, and the cost of treatment. We also review the current guidelines for selecting suitable breast cancer patients for APBI.

Methods
We conducted a comprehensive search of PubMed from 1996 to 2019 for case series or randomized studies that had used various APBI techniques and followed up the patients for at least 2 years in terms of the clinical and cosmetic outcomes, quality of life, and costs of treatment.

Results and Discussion
The rationale for Using APBI
It has been argued that since ipsilateral breast tumor recurrences (IBTR) develop in and around the tumor bed in 44%-86% of cases, focusing the radiation to the areas with high potential of recurrence may be a better approach compared with WBI. Thus, much of the surrounding tissues, including the uninvolved ipsilateral breast, contralateral breast, heart, lungs, and skin, could be spared. This could result in better cosmetic outcomes as well as reduced toxicity.

The early experiences in APBI came from the UK in the 1990s. The first randomized trial was conducted in Christie Hospital from 1982 to 1987. The study enrolled 708 patients, 355 of whom were treated with WBI and 353 with APBI. Inclusion criteria were being younger than 70 years, having a tumor size of \( \leq 4 \) cm, and having undergone lumpectomy with negative margins. The WBI group received 40 Gy in 15 fractions to the whole breast and the axillary, infraclavicular, and supraclavicular regions. The APBI group received 40-42 Gy in 8 fractions delivered by electron beam over 10 days to the tumor bed only. After a median follow-up of 8 years, both groups had the same survival rate (72%); however, the local recurrence rate was significantly greater in the APBI group than in the WBI group (25% vs 13%). The conclusion was that APBI was possible but would need more rigorous patient selection criteria.

In another trial, conducted by Guy’s Hospital in the late 1980s, 27 patients underwent BCS and axillary dissection followed by low dose rate (LDR) brachytherapy, where iridium 192 needles were used to deliver constant focal radiation of 55 Gy over 5 days to a 2-cm margin around the tumor bed. At 6-year follow-up, 37% of patients treated with limited irradiation versus 16% of patients treated with WBI had developed local recurrences. The authors speculated that the inclusion of subjects with known risk factors, such as positive margins and node-positive disease, might have underlain the high rate of local relapse in partial irradiation.

Other APBI trials were conducted at Careggi Hospital (Florence, Italy), the Royal Devon and Exeter Hospital (Exeter, England), and Guy’s Hospital (London, United Kingdom) around the same period, all reporting high rates of local recurrence compared with WBI.

Once the feasibility of APBI was demonstrated, studies were designed to establish the factors and conditions associated with a higher risk of recurrence in patients treated with APBI. Among these factors were younger age, positive margin status, larger tumors, high nuclear grade, extensive ductal carcinoma in situ, invasive lobular carcinoma, involved nodes, and lymphovascular invasion. Table 1 demonstrates selected nonrandomized phase 1/2 clinical trials of APBI.

APBI Techniques
APBI is administered in 3 modalities including brachytherapy (BT), intraoperative radiotherapy (IORT), and external-beam radiotherapy (EBRT).

Brachytherapy
Most of the basic experiences of APBI come from BT. As noted earlier, most preliminary studies on APBI had used BT modality. There are two methods for BT: multicatheter interstitial BT (MIB) and intraluminal (balloon) BT. According to GEC-ESTRO Breast Cancer Working Group, published in 2009 (Table 2), patient selection criteria for APBI are...
Table 1. Selected nonrandomized phase 1/2 clinical trials with interstitial brachytherapy with longer follow-up

<table>
<thead>
<tr>
<th>Reference</th>
<th>APBI Technique</th>
<th>Patient Number/Median Follow-up</th>
<th>Patient Characteristics</th>
<th>Radiotherapy Dose</th>
<th>Cosmetic Results and Locoregional Failure Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ochsner Medical Institution</td>
<td>MIB</td>
<td>50/75 mo</td>
<td>T ≤ 4 cm; negative inked margin; LN+ = 3</td>
<td>LDR = 45 Gy/4 d HDR = 32 Gy/8 fr</td>
<td>GECR = 75% in both arms LRF = 4% (8%)</td>
</tr>
<tr>
<td>William Beaumont Hospital</td>
<td>MIB</td>
<td>199/60 mo</td>
<td>T ≤ 3 cm; age ≥ 40; no extensive DCIS or ILC; negative margin ≥ 2 mm</td>
<td>LDR = 50 Gy/5 d (112 seeds) HDR = 32 Gy/8 fr or 34 Gy/10 fr</td>
<td>GECR = 90% LRF = 1.2%</td>
</tr>
<tr>
<td>Strnad et al.27</td>
<td>MIB</td>
<td>274/64 mo</td>
<td>T &lt; 3 cm; age ≥ 35 y; negative margin ≥ 2 mm; HR+; G1-2</td>
<td>PDR = 50 Gy/3.5 d HDR = 32 Gy/8 fr</td>
<td>GECR = 90% LFR = 1.2% and 2.9%</td>
</tr>
<tr>
<td>Rabinovich et al.30</td>
<td>MIB</td>
<td>98/135 mo</td>
<td>T &lt; 3 cm; LN+ = 0-3</td>
<td>LDR = 45 Gy/3.5-5 d HDR = 34 Gy/10 fr</td>
<td>GECR = 68% LFR = 4%</td>
</tr>
<tr>
<td>Shah et al.31</td>
<td>MIB</td>
<td>199/144 mo</td>
<td>T1-T2; HR+; LN+ = 1-3; margin negative</td>
<td>LDR = 50 Gy/8 d HDR = 32 Gy/8 fr HDR = 34 Gy/10 fr</td>
<td>GECR = 90% LFR = 5%</td>
</tr>
<tr>
<td>Ott et al.32</td>
<td>MIB</td>
<td>274/64 mo</td>
<td>T &lt; 3 cm; age ≥ 35 y; negative margin ≥ 2 mm; HR+; G1-2</td>
<td>PDR = 50 Gy/3.5 d HDR = 320 Gy/8 fr</td>
<td>GECR = 92% LFR = 2.3%</td>
</tr>
<tr>
<td>Polgár et al.33</td>
<td>MIB</td>
<td>5/132 mo</td>
<td>T1N0-N1mi; no extensive DCIS or ILC; negative margin ≥ 2 mm</td>
<td>HDR = 30.3 Gy/7 fr HDR = 36.4 Gy/7 fr</td>
<td>GECR = 78% LFR = 2.3% (at 12 y = 9.3%)</td>
</tr>
<tr>
<td>MammoSite Breast BT Registry Trial</td>
<td>Single lumen Catheter</td>
<td>1449/63 mo</td>
<td>T ≤ 3 cm; age ≥ 40; no extensive DCIS or ILC; negative margin ≥ 2 mm</td>
<td>HDR = 34 Gy/10 fr</td>
<td>GECR = 90.6% (at 84 mo) LFR = 3.8%</td>
</tr>
<tr>
<td>Sawaki et al.34</td>
<td>IORT (Electron beam)</td>
<td>26/26 mo</td>
<td>T &lt; 2.5 cm; age ≥ 50 y; surgical margin &gt; 1 cm; LN−</td>
<td>19-21 Gy at the 90% isodose line fibrosis (G1 = 88%, G2 = 7%), hematoma = 34%, infection = 15% necrosis = 11% LFR = 0</td>
<td></td>
</tr>
<tr>
<td>Kraus-Tiefenbache et al.35</td>
<td>IORT (KV x-ray beam)</td>
<td>24/12 mo</td>
<td>(stage I or II; previous RT to breast (7 second primary and with local recurrence) 20 Gy to the applicator surface</td>
<td>No severe acute side effects or complication LFR = 4%</td>
<td></td>
</tr>
</tbody>
</table>

**MIB**, multicatheter interstitial brachytherapy; **DCIS**, ductal carcinoma in situ; **ILC**, invasive lobular carcinoma; **HR**, hormone receptor; **LDR**, low dose rate; **PDR**, pulse dose rate; **HDR**, high dose rate; **GECR**, good or excellent cosmetic result; **LFR**, local failure rate.

Table 2. Patient selection criteria for accelerated partial breast irradiation from selected organizations

<table>
<thead>
<tr>
<th>Age</th>
<th>Tumor size</th>
<th>Margin</th>
<th>ER/PR status</th>
<th>LN status</th>
<th>Histology</th>
<th>Other Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>GEC-ESTRO27</td>
<td>&gt; 50 y 45-50 y (cautionary)</td>
<td>≤ 3 cm</td>
<td>Negative (&gt; 2 mm)</td>
<td>any</td>
<td>pN0 by SNB or AND DCIS, IDC ILC (cautionary)</td>
<td>No LVSI, no multicentric, no ECI</td>
</tr>
<tr>
<td>American Breast surgeon</td>
<td>&gt; 45 y</td>
<td>≤ 3 cm</td>
<td>Ink margin negative, ≥ 2 mm for DCIS</td>
<td>any</td>
<td>p by SNB or AND N0 DCIS or IDC</td>
<td>Multifocal ok if T ≤ 3 cm Focal LVSI, no genetic mutations</td>
</tr>
<tr>
<td>ABS29</td>
<td>&gt; 60 y (suitable) &gt; 50 y (cautionary)</td>
<td>≤ 2 cm (suitable) 2-3 cm (cautionary)</td>
<td>&gt; 2 mm (suitable) &lt; 2 mm (cautionary)</td>
<td>Positive (suitable) Negative (cautionary)</td>
<td>pN0 (1-1, by SNB or AND P0) IDC non ILC (suitable) ILC and no pure DCIS (cautionary)</td>
<td>No LVSI, no multicentric, no genetic mutations</td>
</tr>
<tr>
<td>ASTRO30</td>
<td>&gt; 50 y (suitable) 45-50 y (cautionary)</td>
<td>≤ 2.5 cm</td>
<td>Negative (&gt; 2 mm) &gt; 3mm for DCIS</td>
<td>any</td>
<td>pN0 by SNB or AND IDC and low/intermediate DCIS ILC (cautionary)</td>
<td>ECI ≤ 3cm No or focal LVSI</td>
</tr>
</tbody>
</table>

**SNB**, sentinel node biopsy; **AND**, axillary node dissection; **DCIS**, ductal carcinoma in situ; **IDC**, invasive ductal carcinoma; **ILC**, invasive lobular carcinoma; **LVS**, lymphovascular space invasion; **ECI**, extensive component invasion.

as follows: being older than 50 years with unicentric, unifocal nonlobular carcinoma ≤ 3 cm in dimension, pN0, with no lymphovascular invasion (LVI) or an extensive intraductal component (EIC), and having a negative surgical margin of ≥ 2 mm. In addition, GEC-ESTRO suggested APBI for high-risk patients in the context of clinical trials. The GEC-ESTRO consensus is based on at least 19 studies investigating oncologic outcomes, which revealed that there was no difference in local recurrence between APBI and WBI, and also 17 studies surveying cosmetic outcomes, which all showed acceptable cosmetic outcomes except for one study that showed higher adverse effects with MIB administration. Furthermore, the consensus was made based upon different BT techniques including low dose rate (LDR)-BT, pulse dose rate BT, high dose rate (HDR)-BT, and MammoSite BT. The results of studies showed that, during a follow-up period of more than 4 years, the local failure rate of...
APBI was similar to that of WBI, with the annual failure rate of APBI being less than 1%.

In addition, the American Brachytherapy Society (ABS) released a consensus statement on APBI using MIB in 2017 based on two large randomized clinical trials, e.g., the GEC-ESTRO trial (which recruited 1118 patients) and a study by the National Institute of Oncology of Hungary (enrolling 258 patients), and 19 nonrandomized trials. The ABS’s findings were similar to GEC-ESTRO’s statement in terms of patient selection criteria, oncologic outcomes, and cosmetic adverse effect of APBI.

A guideline issued by ESTRO-ACROP in 2018 addressed MIB treatment planning, different methods of catcher insertion, and dose constraints and also answered the questions about using APBI as boost or salvage. Selecting patients who could receive boost was based on trials such as the EORTC “boost vs no boost” phase 3 trial (1989-1996) and a systematic review by board members of the GEC-ESTRO Breast Working Group, which characterized suitable high-risk patients. The ESTRO-ACROP guideline suggested HDR-BT schedules such as 7 × 4.3 Gy and 8 × 4 Gy, twice a day for 4-5 days according to the GEC-ESTRO trial, a European multicenter, randomized, phase 3 trial which recruited stage 0-IIA breast cancer patients aged 40 years and older. The aim of this trial was to compare WBI with MIB APBI in terms of both oncologic and cosmetic outcomes. It revealed that not only late subcutaneous toxicities in two treatment modalities were not different, but also cumulative grade 2-3 late toxicity rate after 5 years was around 4% lower in APBI. Late toxicities such as telangiectasia, fibrosis, fat necrosis, pain, and arm lymphedema were similar in the two treatment modalities. However, skin hyperpigmentation was lower in MIB compared to WBI. Furthermore, the rate of excellent-to-good cosmetic outcome for both treatment modalities was the same 92%. In another study, the cumulative incidence of local recurrence was around 1.4% with APBI and 0.92% with WBI at 5-year follow-up; however, the difference was not statistically significant. According to GEC-ESTRO Breast Cancer Working Group (II) guidelines on APBI using MIB, the total size of safety margin should be 20 mm, with clinical target volume being limited to the chest wall and 5 mm below the skin.

Table 3 summarizes recently published randomized studies using brachytherapy APBI techniques.

### Accelerated Partial Breast Irradiation Using EBRT

EBRT could be done with three-dimensional conformal external-beam irradiation (3D-CRT) using photons, mixed photons and electrons, or protons. Unlike BT and IORT, EBRT can be delivered at local facilities. Although the method requires irradiation of larger areas of the breast compared with the other two methods, the irradiated volume can be reduced by using intensity-modulated radiation therapy (IMRT).

<table>
<thead>
<tr>
<th>Trial</th>
<th>Number of Patients / Median Follow-up</th>
<th>Inclusion Criteria</th>
<th>Radiotherapy Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>GEC-ESTRO (MIB)</td>
<td>1328/10 y</td>
<td>Age ≥ 40 y; T ≤ 3 cm; pN0-Nmi; stage 0, I, II; DCIS, ductal, or lobular carcinoma; margin ≥ 2 mm</td>
<td>HDR: 32 Gy/8 fr or HDR: 30.3 Gy/7 fr or PDR: 50 Gy/2.6-3 d vs WBI: 50 Gy with a boost of 10 Gy</td>
</tr>
<tr>
<td>National Institute of Oncology (Hungary) (MIB)</td>
<td>258/10.2 y</td>
<td>pT1, pN0-1mi M0; G1-2; nonlobular; margin ≥ 2 mm</td>
<td>HDR: 36.4 Gy/7 fr vs WBI: 50 Gy</td>
</tr>
<tr>
<td>TARGIT - A (IORT-photon x)</td>
<td>3451/5 y</td>
<td>Age ≥ 45 y; T1, small T2, N0, N1; ductal; nonlobular; no EIC</td>
<td>20 Gy in 1 fraction, IORT low-energy X-rays (50 kV) vs WBI: 50 Gy with a boost of 10 Gy</td>
</tr>
<tr>
<td>ELIOT (IORT-Electron)</td>
<td>1305/5.8 y</td>
<td>Age ≥ 48 y; T ≤ 2.5 cm; N0, invasive carcinoma</td>
<td>21 Gy in 1 fraction, IORT, electrons up to 9 MeV vs WBI: 50 Gy with a boost of 10 Gy</td>
</tr>
<tr>
<td>Florence study (EBRT+IMRT)</td>
<td>520/5 y</td>
<td>Age &gt; 40 y with early BC suitable (T &lt; 2.5 cm)</td>
<td>IMRT: 30 Gy/10 fr vs WBI:50 Gy with a boost of 10 Gy</td>
</tr>
<tr>
<td>RAPID Trial (EBRT-3DCRT)</td>
<td>2135/3 y</td>
<td>Age &gt; 40 y; T ≤ 3 cm; IDC and DCIS breast cancer</td>
<td>3D-CRT: 38.5 Gy/10 fr (twice daily) vs WBI: 42.5 Gy/16 fr or 50 Gy ± boost</td>
</tr>
<tr>
<td>UK IMPORT LOW trial (EBRT-3DCRT)</td>
<td>2018 (674 WBI, 673 RD-WBI, 669 PBI)/6 y</td>
<td>Age ≥ 50 y; T1, small T2, N0, N1; ductal</td>
<td>3D-CRT: 40 Gy/15 fr or 36 Gy/15 fr vs WBI: 40 Gy/15 or 36 Gy ± boost</td>
</tr>
<tr>
<td>NSABP B-39/RT0G 0413 (NRG Oncology) (MIB)</td>
<td>4216/10.2 y</td>
<td>Age &gt; 40 y, stage 0, I, or II</td>
<td>HDR: 34-38.5 Gy/10 fr (twice daily) vs WBI: 42.5 Gy/16 fr or 50 Gy ± boost</td>
</tr>
</tbody>
</table>

**Table 3. Summary of recently published randomized studies using different APBI techniques**

**MIB, multicatheter interstitial brachytherapy; IORT, intraoperative radiotherapy; EBRT, external-beam radiotherapy; IMRT, intensity-modulated radiotherapy; 3D-CRT, 3-dimensional conformal radiotherapy; DCIS, ductal carcinoma in situ; ILC, invasive lobular carcinoma; HR, hormone receptor; LDR, low dose rate; PDR, pulse dose rate; HDR, high dose rate; GECR, good or excellent cosmetic result; LFR, local failure rate; RD-WBI, reduced-dose whole-breast irradiation; IDC, invasive ductal carcinoma**
In 2006, a review of data from several preliminary clinical studies using three-dimensional conformal EBRT pointed to technical feasibility, satisfactory cosmetic results, and acceptable recurrence rates of the method. However, several single-arm studies have reported poor cosmetic outcomes in approximately 20% of patients treated with EBRT-based APBI. These conflicting results may be attributed to variations in planning techniques or prescribed radiation doses.

Anbumani and colleagues assessed the feasibility of EBRT-APBI using dosimetric parameters comparable to those used in HDR-BT planning. Analysis of pulmonary and cardiac dosimetry data showed that EBRT was associated with lower percentages of lung and cardiac tissue volume receiving doses of 20 Gy and 5 Gy, as well as more homogenous dose distribution. Their data suggested that EBRT planning for APBI was technically feasible.

Another study was done by Mózsa and colleagues, who reported the 5-year results of EBRT-APBI after BCS in 44 low-risk breast cancer patients between 2006 and 2011. The patients received 3D-CRT using 3-5 noncoplanar fields with a total dose of 36.9 Gy in 9 fractions. After a median follow-up of 58.2 months, only 1 (2.3%) local recurrence occurred (the 5-year actuarial rate was 3.7%), and there was no regional or distant failure. Cancer-specific and overall survival rates were 100% and 95.1%, respectively. Acute side effects, late side effects, and cosmetic outcomes were also evaluated in the study, which was comparable to other APBI modalities.

In another trial, 142 patients ≥ 40 years of age with stage 0-II breast tumors measuring ≤ 2.5 cm without lymph node involvement received 38.5 Gy in 10 fractions over 5 consecutive days using 3D-CRT. The median cavity, clinical target volume, and breast volume were 16.9 cm³ (range 1.6-203 cm³), 75.1 cm³ (range 4.1-443 cm³), and 744 cm³ (range 150-3551 cm³), respectively. The margin around the lumpectomy cavity was 10-15 mm. The median cavity to breast ratio was 2.6 (range 0.16-14). Twenty-six patients showed no signs of toxicity; tenderness was observed in 70 patients, hyperpigmentation in 62, and induration in 45. The results suggested that acceptable toxicity could be achieved in 3D-CRT APBI by decreasing the volume of irradiated normal breast tissue.

Kumar et al. compared APBI using EBRT with hypofractionated WBI in early-stage breast cancer patients in a prospective cohort study. They assessed 390 patients aged 40 years or older with T1N0, ER-positive breast cancer who received lumpectomy followed by radiation treatment. Of them, 96 patients received EBRTAPBI with 38.5 Gy in 10 fractions, twice daily, while 294 patients received hypofractionated WBI with 42.56 Gy in 16 fractions with or without a 1-3 fraction boost. Patients were adjusted for age, histology, and margin status in treatment groups. At a median follow-up of 4.2 years, no difference was observed in the rate of local recurrence between the two treatment modalities.

Ott and colleagues conducted a prospective phase 2 trial for APBI over a 6-year period. They enrolled 72 patients aged ≥ 50 years with histologically confirmed breast cancer or pure ductal carcinoma in situ (DCIS). Inclusion criteria were having a tumor size ≤ 3 cm, clear resection margins ≥ 2 mm, and no axillary lymph node involvement. Patients whose mammograms showed a multicentric invasive growth pattern or had residual diffuse microcalcifications postoperatively, an extensive intraductal component, or vascular invasion were excluded. They underwent 3D-CRT APBI at a dose of 38 Gy in 10 fractions for 1-2 weeks and were followed up for a median of 25.5 months. Three-year local recurrence rate was 2.1%. Early toxicity (grade 1 dermatitis) was reported in 25 (34.7%) patients, and no late side effect of grade 3 or higher was observed. Excellent-to-good cosmetic results were seen in 96.7% of patients. They concluded that APBI by means of EBRT radiotherapy is a good option with low toxicity for a selected subgroup of patients.

Olivotto et al. compared cosmetic and toxicity results of APBI using 3D-CRT with those of WBI in a multicenter randomized trial between 2006 and 2011. They enrolled 2,135 breast cancer (tumor size ≤ 3 cm) patients aged > 40 years who had undergone BCS and assigned them to either 3D-CRT (38.5 Gy in 10 fractions twice daily) or WBI (42.5 Gy in 16 fractions or 50 Gy in 25 daily fractions ± boost irradiation) treatment group. At 3-year follow-up, patients treated with 3D-CRT showed significantly greater adverse cosmetic side effects and grade 1/2 toxicities compared with those treated using WBI.

Other randomized trials using EBRT for APBI are summarized in Table 3.

Newer Techniques of EBRT in APBI

With recent technological advances in radiation therapy, newer methods have been developed to be used in APBI for better normal tissue sparing and dose delivery. One of these methods is proton therapy. The use of proton beams has some physical advantages over photon beams, as it is associated with minimal entry, exit, or scattered radiation dose, deposition of radiation dose over a more limited range of depth, and, consequently, reduced side effects. Wang and colleagues evaluated the use of multiple proton beams in EBRT by comparing a proton therapy planning with 3D-CRT photon APBI. The absolute reduction of dose constraints in target volume was the same in both methods, but proton therapy was associated with a significantly lower exit dose to the normal breast, lung, and heart.
tissues.\textsuperscript{52} Bush and colleagues reported the 5-year results of a phase 2 trial of APBI by means of proton beam radiation in 100 patients with invasive nonlobular carcinoma, with a dimension of \leq 3 cm, who had undergone BCS with negative margins and no lymph node involvement. The surgical bed was irradiated at a dose of 40 cobalt Gy equivalents in 10 fractions, once daily, over 2 weeks. IBTR-free survival, disease-free survival, and overall survival rates were 97\%, 94\%, and 95\%, respectively. There were only 7 cases of grade 1 telangiectasia at 5-year follow-up, and the cosmetic outcome was evaluated as good to excellent in 90\% of the patients.\textsuperscript{53} In another study, 30 patients undergoing proton therapy (30 cobalt Gy equivalents in 6 fractions over 5 consecutive days) after BCS were followed up for a median of 59 months. All of the patients were alive at the last follow-up, with no cases of IBTR or local or distant metastasis, although the percentage of patients with a good-to-excellent cosmetic outcome decreased from 83\% at the end of treatment to 69\% at 3-year follow-up.\textsuperscript{54}

Another method of delivering APBI is stereotactic radiotherapy (SRT) (e.g., CyberKnife\textsuperscript{TM}). SRT has some advantages over 3D-CRT as it is characterized by pinpoint accuracy, offers real-time tracking and respiratory motion management, and is able to deliver higher doses of radiation with significantly lower radiation scattering to surrounding tissue. In one trial conducted at Georgetown University Hospital, 10 patients (aged \geq 48 years) with DCIS or invasive nonlobular carcinoma with a maximum diameter of 2 cm underwent partial mastectomy with \geq 2-mm negative margins, followed by EBRT using CyberKnife. The patients received a total dose of 30 Gy in 5 fractions for 5 consecutive days. The cosmetic results were rated as good or excellent in all 10 patients at a median follow-up of 1.3 years. Although it was concluded that CyberKnife could be used as a tolerable and reliable device to deliver APBI, the small sample size and short follow-up period were among the study limitations.\textsuperscript{55}

Intensity-modulated radiation therapy (IMRT) is another technique in APBI that is proposed to decrease late toxicity by improving radiation homogeneity. A phase 3 trial was conducted at the University of Florence to compare treatment outcomes of WBI and APBI using IMRT. Patients received either WBI (n = 260; 50 Gy in 25 fractions plus 10 Gy boost to the tumor bed) or APBI using IMRT (n = 260; 30 Gy in 5 nonconsecutive fractions). At a median follow-up of 5 years (interquartile range: 3.4-7 years) there was no difference between the groups in IBTR or survival rate, although the IBTR group had significantly better toxicity and cosmetic outcomes.\textsuperscript{56} A second analysis of the data from the same trial was published recently, with focus on the patients with DCIS who had undergone APBI using IMRT (n = 22). At a median of 9.2 years of follow-up, the incidence rate for contralateral invasive cancer/DCIS, distant metastasis, and late toxicities, breast cancer–related death, and 5- and 10-year IBTR was zero. The 10-year overall survival rate was 90.9\%, and cosmetic results were rated good to excellent in 21 of the 22 patients.\textsuperscript{41}

In conclusion, APBI has been studied in phase 1-3 trials with different EBRT techniques and protocols in more than 1000 patients during the past decades, yielding comparable, or even better, outcomes to those of WBI.

\textit{Intraoperative Radiation Therapy in APBI}

Intraoperative radiation therapy (IORT) is a type of APBI given in a single fraction after lumpectomy during the surgery. IORT has many advantages over WBI, including patient convenience, decreased irradiation of normal tissues, patient compliance\textsuperscript{21, 57, 58}, and higher breast-related quality of life.\textsuperscript{59}

There are two IORT techniques for APBI: electron beam therapy and kilovoltage X-ray beam radiation therapy. The first widely available IORT device, IntraBeam\textsuperscript{®}, was introduced in 1998. Since then, several mobile linear accelerators for IORT have been developed. While IntraBeam\textsuperscript{®} and Xoft\textsuperscript{®} are kilovoltage photon systems, Mobetron\textsuperscript{®}, Novac-7\textsuperscript{®}, and LIAC\textsuperscript{®} generate megavoltage electron beams. (Table 1 demonstrates some phase1-2 IORT trials.)

IntraBeam\textsuperscript{®} (Oberkochen, Germany) and Xoft\textsuperscript{®} Axxent Electronic Brachytherapy System use spherical applicators, or balloons, that allows for delivering uniform doses of radiation directly to the surgical bed. Delivering APBI using these systems is normally achieved in 20 to 35 minutes in a single application, which is significantly time-effective when compared with the conventional EBRT.

The Mobetron, Novac, and LIAC systems are mobile linear accelerators that produce high-energy electron beams. The Mobetron device is inserted into the surgical cavity for the delivery of electron radiation. An acrylic resin-copper disk may be placed between the breast tissue and the underlying muscle to protect the thoracic wall.

IORT enjoys several advantages over other methods of APBI. The target tissue is directly visible in this method, which guarantees that the high-risk tissue gets complete treatment while avoiding the risk of marginal miss. Also, it provides the chance of getting a BCS for those women who otherwise would choose a mastectomy because of having no access to radiotherapy facilities or being unable to undergo a several-week radiotherapy regimen. Besides, it is associated with a favorable toxicity profile and may offer overall survival benefits owing to a reduced dose deposition in cardiopulmonary.\textsuperscript{60} A major downside to IORT is that there is no final...
pathologic data on the tumor size, histology, margins, and nodal status available, which may necessitate an additional course of WBI later, thereby offsetting the low-toxicity benefits of IORT. However, studies show that IORT as a tumor bed boost is safe and is associated with acceptable toxicity.60

IORT has been compared with WBI in two large prospective randomized trials.61, 62 The first one, TARGIT-A, enrolled 3451 patients (aged ≥ 45) with unifocal invasive ductal carcinoma (≤ 3.5 cm in diameter). The patients in the WBI arm received 50 Gy over 3-5 weeks with or without a lumpectomy bed boost, while the IORT arm received 20 Gy via a 1.5-5–cm balloon applicator delivering 50 kV-energy X-rays to the tumor bed.61 The 5-year IBTR rate was higher in the IORT group compared with the WBI arm (3.3% vs 1.3%). However, the rate of non–breast cancer mortality was significantly lower for the IORT group (1.4% vs 3.5%) Also, IORT was associated with a significantly lower rate of severe skin complications (0.2% vs 0.8%).63 Another paper reporting the late toxicity results from the same trial found no significant difference in fibrosis, breast edema, retraction, lymphedema, or pain between the two treatment arms.64 Telangiectasia was reported at a similar rate (17%) for patients who received IORT plus WBI or WBI but was not reported after IORT alone. Also, IORT alone has less considerable breast and arm symptoms.40

In the second trial, known as the ELIOT trial, 1305 patients, aged 48 to 75, with a tumor size of ≤ 2.5 cm were enrolled and treated with either WBI (50 Gy + 10 Gy boost) or IORT (21 Gy).42 In this study, IORT was performed using a mobile linear accelerator that produced high-energy electrons beams through an applicator inserted in the lumpectomy cavity. The researchers observed a significantly higher 5-year IBTR rate for the IORT arm compared with the WBI arm (4.4% vs 0.4%). There were 14 new ipsilateral breast carcinomas in the IORT arm versus 0 in the WBI arm. On the other hand, 5-year IBTR rate in lower-risk women (tumor size ≤ 2 cm, grade 1 or 2, estrogen receptor positive, ≤ 3 positive nodes) was 1.7%. These patients are considered most suitable for receiving IORT.42

In the IORT group, toxicity was lower. Skin adverse reactions were notably lower compared to WBI. A subgroup of patients voluntarily underwent a follow-up spiral computed tomography. At this subgroup, the pulmonary fibrosis was more prevalent in patients who had received WBI. Fat necrosis, conversely, occurred at a higher rate in the IOERT group (15% vs 7%).

**Patient-Reported Quality of Life and Cost of Treatment**

Quality of life is an important consideration for patients when they are choosing their breast cancer treatments. Bitter and colleagues63 and Schäfe et al.64 analyzed self-reported cosmetic outcomes for the treated breast and quality of life for patients treated with WBI or APBI and found better cosmetic satisfaction and quality of life among patients who had undergone APBI.

**APBI, in comparison with WBI, has socioeconomically different results. APBI methods are generally considered more cost-effective. Shah et al. estimated that treatment with 3D-CRT APBI, IMRT APBI, and MIB APBI was associated with, respectively, $6.0 million, $2.0 million, and $0.7 million cost saving per 1000 patients compared with treatment using WBI. Comparing the costs of different APBI modalities, they found that, after allowing for nonmedical costs and costs due to recurrences, MIB APBI and 3D-CRT APBI would cost $54698 and $49009, respectively, per quality of life year.65 A study by Grobmyer and colleagues also estimated that treatment costs associated with IORT were significantly lower compared with WBI ($1857 vs $9653).66 Alvarado et al., too, reported that IORT would bring about greater cost efficiency and quality of life outcomes compared with WBI if used for appropriate patients.67

However, the cost-effectiveness advantage of IORT might fade away when compared with 3D-CRT APBI. A cost-per-QALY analysis from the TARGIT-A and ELIOT trials found that, after incorporating additional medical costs, nonmedical costs, and cost of recurrences, 3D-CRT APBI had a lower overall cost compared with IORT.68

In conclusion, APBI represents an attractive treatment option for appropriately selected patients with early-stage breast cancer, especially in high-volume radiation centers with long waiting lists and for patients who live far away from the radiotherapy centers. Irrespective of the technique used for APBI, it is very important to select the most appropriate patient population for this treatment strategy. According to the guidelines, the most suitable patients to treat with APBI are those with a low-grade tumor less than 3 cm negative node status, and negative margins. Table 2 demonstrates patient selection criteria developed by various authoritative organizations.

There are many ongoing phases 3 trials that are testing the noninferiority and equivalence of various forms of APBI against WBI. Among various APBI methods, interstitial brachytherapy and IMRT seem to have the strongest data supporting their utilization, as they offer the most acceptable local control and cosmetic results.69 However, patient selection remains one of the most important considerations, and this should be performed in a high-volume referral center and by experienced and trained hands.

**Conflict of Interest**

None.
References

12. Magee B, Swindell R, Harris M, Banerjee SS.


Background: The carcinogenic effect of exogenous steroid hormones on the breasts is a matter of debate, causing confusion for physicians at the time of making prescriptions. This article, as part of a quadruple series about exogenous sex hormones and breast disorders, reviews the association of breast cancer and hormone replacement therapy (HRT) in the general population, women with benign breast disorders, women with personal or family history of breast cancer, and BRCA carriers.

Methods: We accomplished an extensive search of the literature by using relevant keywords to identify pertinent cohort studies, clinical trials, and reviews. Then, we extracted all points regarding the question.

Results: An extensive literature exists on the risk of breast cancer following HRT in the general population, and HRT has been mentioned as a risk factor for breast cancer, especially in recent, long-term users of combined formulations. However, there is still no consensus about it. Conversely, few studies have considered challenging issues like the use of HRT in breast cancer survivors and high-risk women.

Conclusion: HRT up to 5 years can safely be used for management of menopausal symptoms in healthy women, and those with low-risk benign breast disorders. On the contrary, its use in high-risk women should be limited to refractory menopausal symptoms after describing potential harms to the patient.

Introduction
Breast tissue is under the influence of endogenous sex hormones, and a definite association between breast cancer and these substances has been acknowledged. Hormone replacement therapy (HRT), consumption of synthetic sex hormones for combating natural or iatrogenic menopause, is used by nearly 30% of women in the USA and the UK. Although HRT was at first highly praised for its positive effects on the cardiovascular system, osteoporosis, and other postmenopausal problems, it has subsequently been recognized as a risk factor for breast cancer (BC).

The first author of this paper has practiced as a surgeon in women’s hospitals for more than 18 years and has always been consulted by her colleagues and friends about breast-related issues associated with exogenous hormones. An extensive literature exists on the subject, but results and recommendations are extremely variable, with each work addressing only one of the topics regarding the breast, e.g., high-risk patients only, or BC survivors. A concise review of how various forms of exogenous sex hormones can affect the breasts of women with different conditions would probably help practitioners in this regard.

This perspective led to a series of reviews on the...
Types of HRT

Estrogens can be prescribed alone for HRT, commonly referred to as estrogen replacement therapy (ERT), or in combination with synthetic progestins, known as combined HRT (CHRT). ERT was the first and predominating HRT used before 1975, but because of the revealed increased risk of endometrial cancer, CHRT was begun in order to oppose the adverse effects of estrogen. Both the progestin component and the type of estrogen vary by country. In European countries, estradiol and testosterone-like progestins are more prevalent, while the use of conjugated estrogens and medroxyprogesterone-acetate prevail in the USA.

Results and Discussion

1. HRT in the general population

Epidemiologic studies have been carried out since 1974 to assess the relationship between HRT and BC risk in menopausal women. First works did not show any association, except for one that reported a doubling in BC risk with 15 years or more of HRT. From 1980 onward, more studies pointed to an increased BC risk with long-term use of HRT, although not very useful in clinical practice because of inconsistency. Thereafter, results of large-scale population-based works were gradually disseminated. Results from extensive studies published between 1985 and 1989 showed a wide range of relative risk (RR), from 0.6 to 5.3, for different lengths of use. Each study had its own limitations and biases, and the only confident inference was an increased risk of BC with long-term HRT.

In 1993, the Women’s Health Initiative (WHI) was launched as a national study in the USA, with multiple objectives regarding health issues in postmenopausal women, including BC prevention. The project enrolled more than 160,000 women between the ages of 50 and 79 years in several clinical trials or observational studies and has continued the follow-up of consenting participants through extension studies (https://www.whi.org). The announcement of WHI’s results showing increased rates of BC secondary to HRT caused a great decline in HRT use among women in the USA and, after some time, other countries. This was generally followed by decreasing rates of BC, endorsing the HRT-BC relationship. Multiple studies have been performed using data from WHI since then, and parallel studies have been carried out in other centers. Also, multiple reviews have gathered and reanalyzed the results of previous works. Nonetheless, the huge bulk of published data is still awaiting reliable conclusive interpretation. While most researchers admit a definite increase in BC risk caused by HRT, albeit probably small, some question the association, linking the decline in BC incidence to less frequent screening or other conditions.

Moreover, some studies have failed to demonstrate a significant difference between ever-users and never-users of HRT or any association between HRT and BC risk. Still, there are studies that have shown HRT use to be associated with increased BC risk only for women older than 55 years.

Regarding the type of HRT used, some studies demonstrated that ERT did not increase BC incidence, acknowledging an association exclusively for CHRT, or found a higher effect for CHRT compared with ERT. In contrast, a study in Mexico City found that only ERT increased BC risk in both Hispanic and non-Hispanic women. Similarly, one study reported that formulations containing higher doses of estrogens were associated with higher BC risk, and another one concluded that CHRT would reduce BC risk when used for 8 years or more.

Higher duration of HRT has been associated with higher risk of BC. Nevertheless, some researchers reported no association between duration of HRT and BC risk.

Recent HRT use has also been suggested to be positively associated with the risk of BC. It was shown that in women who had stopped HRT for two, five, or ten years, the risk of BC had almost dissipated, although there is also evidence to the contrary.

Regarding the features of breast tumors developed in women undergoing HRT, most studies suggest that the tumors are more likely to have less aggressive biological behavior. However, some authors argue against this view. Also, breast tumors appearing in women who had undergone HRT have been shown to be associated with better survival, but this outcome has been linked to earlier detection due to stricter screening in women.
receiving HRT than taking HRT itself. On the other hand, some studies demonstrated similar or worse BC survival in previous HRT-users versus non-HRT-users.

Logically, if hormones are going to activate hormone-dependent cancer, they should generally affect tumors expressing receptors for those hormones. This notion has been validated through numerous studies reporting a higher frequency of hormone receptor–positive (HR+) tumors in HRT users. A number of studies, however, have found similar tumor HR status in HRT users and nonusers, or even less HR positivity in the former group.

Many studies have also attempted to define the pathologic type of tumors that were seen in women who had undergone HRT. They reported higher rates of invasive lobular carcinoma in HRT users versus nonusers.

The above review contains contradictory points, but, overall and for practical use, it is most probable and most prudent to consider HRT as a risk factor for BC, while being more cautious about CHRT. Accordingly, the National Institute for Health and Care Excellence (NICE) guidance states that, depending on the length of treatment, CHRT may increase the risk of BC, while ERT does not, or causes a slight increase (http://pathways.nice.org.uk/pathways/menopause). It must be emphasized, however, that the risk associated with HRT is not as serious as that associated with inherent or lifestyle elements such as high BMI, late first full-term pregnancy, and high mammographic breast density. Then again, although the risk imposed on an individual woman would be low, physicians should be aware that frequent use of HRT would lead to high increments of BC incidence in the population. Also, decision regarding prescription of HRT must be balanced against the efficacious control of menopausal adverse effects, while prescribing short-term HRT should be preferred. According to the British Menopause Society consensus statement, short-term (5 years or less) use of HRT for management of menopausal symptoms in the general population surpasses its adverse effects regarding BC.

2. HRT in benign breast disorders

BBDs are heterogeneous lesions with varying levels of risk for BC, including fibrocystic changes (FCC) (no risk), fibroadenomas (FA) (very low risk), and papillomas and precancerosous lesions like atypical hyperplasias (AH) (moderate risk to high risk). Overall, the most common benign lump of the breast is FA, while the most frequently seen BBD is FCC. Both of these disorders are hormone dependent and undergo cyclic changes in concord with normal breast tissue.

AH includes atypical ductal hyperplasia (ADH) and atypical lobular hyperplasia (ALH). These are borderline lesions which are differentiated from in situ carcinomas by quantitative histologic criteria. Both are infrequent lesions, and their main concern is about a 3- to 5-fold increase in the risk of cancer.

The association of HRT with any of these benign lesions has not been studied extensively. One study mentioned a lower frequency of FCC in women taking HRT. Among studies investigating benign proliferative epithelial lesions, two detected an increased incidence, and one found no association.

The effect of HRT on FCC has been assessed slightly more than other BBGs. A positive association has been reported with ERT, which grows stronger with long-term use—a 5-fold increment was seen for 10 years or more of ERT.

Research about the influence of HRT on FAs is rare. Only two studies, published in the 1980s, were found that showed an increased incidence of FA with ERT.

AH, a high-risk lesion of the breast, has been studied for potential association with HRT. HRT was shown to stimulate epithelial hyperplasia of breasts with atypia, and one study reported a strong association between HRT and AH incidence. Conversely, another study failed to demonstrate this relationship for any type of HRT and use for any length of time, and a more recent study showed a reverse association between HRT and AH. Importantly, HRT did not increase the risk of subsequent BC in AH or other BBGs.

In summary, HRT might induce FCC and FA, but benignity of these lesions does not make them an obstacle toward HRT use when necessary. Association of HRT with AH has not been proved, and increases in malignancy rates have not been reported to date. Nevertheless, because these lesions are high-risk, and probably hormone-dependent, it seems wise not to prescribe HRT to patients with AH.

3. HRT in breast cancer survivors

Many women who have undergone treatment for BC suffer from hot flushes and other menopausal symptoms. This can be secondary to natural menopause, which is happening more frequently because of better survival. Also, menopausal symptoms can happen much sooner, and perhaps more severely, because of antiestrogen therapy in hormone-positive tumors, or for the cessation of menstrual cycles subsequent to chemotherapy. Nevertheless, because of hormone-dependency of BC, physicians are concerned that prescribing HRT to BC survivors may activate dormant cancer cells or induce new primary tumors in the ipsilateral or contralateral breast. A survey of BC patients showed that around 70% feared BC recurrence and did not want to undergo HRT despite high frequency of menopausal symptoms.

Researchers have studied the effects of HRT in BC survivors. HABITS was a randomized trial which was ended well in advance of its design because of high frequency of recurrence. The extended follow-up that
took place later confirmed this finding. However, the mortality of BC survivors was not shown to be augmented by HRT in the participants, and data about recurrence were not enough to provide accurate conclusion because of early closure. In contrast, several other studies demonstrated that HRT did not worsen the prognosis of BC, in terms of recurrence or mortality in BC survivors. Interestingly, a few studies have even mentioned a more favorable outcome in BC survivors who had received HRT.

Two meta-analyses also found conflict between the results of observational studies, which displayed no increased risk, and randomized trials, which revealed increased rates of recurrence with HRT, in BC survivors.

Given the contradictory findings of the studies, it is advisable that caution be exercised in prescribing HRT to BC survivors. Accordingly, the NICE guidance recognizes personal history of BC as a contraindication to HRT. Somewhat less strict, Health Canada’s Canadian Breast Cancer Initiative and the British Menopause Society do not recommend routine HRT in BC survivors and encourage the use of alternative nonhormonal treatments in symptomatic women, recommending short-term, low-dose HRT only for retractable symptoms after informing the patient about the potential hazards.

4. HRT in groups at higher risk of breast cancer

4.1. Family History of Breast Cancer

A family history of BC is one of the most important risk factors of the disease. Using HRT in these women is challenging as it may increase the BC risk. While having a first-degree relative with BC has been associated with a higher risk of BC in women undergoing HRT, results presented by some researchers are not in favor of any additive effect of HRT on the risk conferred by family history.

The British Menopause Society recommends that menopausal symptoms of women with a family history of BC should be managed with nonhormonal options in the first place and that short-term, low-dose HRT should only be used in intractable cases who have been informed about possible risks. Also, NICE guidance recommends that women with a family history of BC should become aware of the increased risk of BC with treatment duration before undergoing HRT.

4.2. BRCA mutations

Carrying mutated BRCA1 or BRCA2 genes is a very strong risk factor for BC. Whether HRT can further increase the risk in these women is of utmost importance because many undergo bilateral oophorectomy as a risk reduction measure and suffer from hot flushes or other menopausal symptoms thereafter. The few studies that have evaluated the question have not shown any increment in BC risk due to HRT in BRCA carriers. More recent works have confirmed the safety of short-time ERT but have been more guarded about CHRT. Although primary results are reassuring, data are insufficient to yield convincing conclusions; and further study is necessary in order to allow safe prescription of HRT in defective gene carriers. For the time being, NICE guidance interdicts HRT in women with mutated BRCA genes.

Table 1 summarizes the existing knowledge about the restrictions of HRT use in different breast conditions.

<table>
<thead>
<tr>
<th>Breast condition</th>
<th>Action to take about HRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Yes</td>
</tr>
<tr>
<td>BBD</td>
<td>Yes for low-risk lesions; No for high-risk lesions* except for short-term, low-dose HRT only in intractable cases, and the patient must know about potential risks.</td>
</tr>
<tr>
<td>BC survivor</td>
<td>No</td>
</tr>
<tr>
<td>FH</td>
<td>Yes, but the patient must know about potential risks.</td>
</tr>
<tr>
<td>Mutant BRCA</td>
<td>No, except for short-term, low-dose HRT only in intractable cases, and the patient must know about potential risks.</td>
</tr>
</tbody>
</table>

* Like atypical hyperplasia of the breast. BBD = benign breast disorder; BC = breast cancer; FH = family history; HRT = hormone replacement therapy.

In conclusion, despite numerous studies about HRT in general women, no definite conclusion can be reached about the actual effects on BC risk. Short-term (up to 5 years) HRT for managing menopausal symptoms is reasonable in these women, as well as in women with low-risk BBDs. For groups at higher risk, including women with a personal or family history of BC, carriers of BRCA mutations, or lesions with high-risk pathology in the breast, HRT is not advisable.

Conflict of Interest
None

References


Systemic Therapy in Local Recurrence of Breast Cancer, Report of a Case and Decision Making in MDT Meeting

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ABSTRACT

Background: Locoregional recurrence of breast cancer has significantly decreased over the last decades, particularly due to effective systemic therapy. While there is little controversy regarding local management of locoregional recurrences, in light of previous systemic treatment, additional chemotherapy regimens and their benefit to the patient are still subject to debate in tumors boards.

Case Presentation: A 45-year-old woman was referred to our tertiary care center with a local recurrence of breast cancer 9 years after modified radical mastectomy for a ypT2N2a invasive ductal carcinoma. She received neoadjuvant treatment consisting of FEC-D (5-FU-epirubicin-cyclophosphamide, followed by docetaxel) for hormone receptor positive, HER-2-neu negative cancer in 2009, as well as adjuvant radiotherapy and tamoxifen for 9 years. After R0 resection of the hormone receptor positive, HER-2-neu negative recurrence in 2019, adjuvant therapy with ovarian suppression and an aromatase inhibitor was undertaken. A multigene assay identified a recurrence score at 37 and benefit from chemotherapy > 15%.

Conclusion: After reviewing history, imaging and pathology, members of the multidisciplinary team recommended treatment with Taxotere and cyclophosphamide (TC) x 4 for our patient. Response to neoadjuvant chemotherapy, namely achievement of pathologic complete response, is also associated with decreased locoregional recurrence rate. The recurrence can be symptomatic or detected by physicians at routine follow up.

One of the most important issues in the treatment of such a disturbing and worrisome condition is the selection of the best and the most effective therapeutic options. The role of local treatment options especially surgical resection of the breast cancer recurrence has been well known in treatment of locoregional relapse. On the other hand, radiation therapy may be administered according to some parameters e.g. the previous history of radiation, time between the previous radiation therapy and the recurrence and the dosage of irradiation to the breast and chest wall during the primary tumor treatment. While there is little controversy recommending local...
Chemotherapy in BC recurrence

treatment of breast cancer local recurrence, recommendation to treat with systemic therapy is a matter of discussion in most tumor boards. There are two main questions in this field; whether the patient benefits from chemotherapy and what are the best therapeutic regimens recommended in this situation.

Case presentation

A 45 year-old woman was referred in April 2019 to our tertiary care center for late local relapse of breast cancer. She was initially diagnosed in 2009 with multicentric grade 1 hormonal receptor positive, HER-2-neu negative breast cancer. Family history was significant for breast cancer at an unknown age in her mother and a genetics consultation didn’t reveal a relevant genetic mutation. She had completed neoadjuvant chemotherapy consisting of FEC-D (5-FU-epirubicin-cyclophosphamide, followed by docetaxel) because of significant extent of the disease in the breast. In April 2010, she underwent a left-sided modified radical mastectomy without reconstruction. Pathology confirmed a principal focus of invasive ductal cancer of maximal diameter of 2.4 cm, along with a second focus of maximal diameter of 2.0 cm. Margins were negative and 4 of the 23 lymph nodes examined were positive for disease. Her disease was classified as ypT2N2a. Adjuvant treatment consisted of radiotherapy to the chest wall completed in July 2010 and tamoxifen for a total projected duration of 10 years. Physical examination and annual imaging were not significant until February 2019, when a 6 mm distortion at the mastectomy scar was reported as BIRADS 4 on MRI. An ultrasound performed in March 2019 identified a 4x5 mm hypervascular lesion on Doppler situated deep to the mastectomy scar. The lesion was biopsied and reported as grade 2 invasive ductal carcinoma, ER 10-20%, PR 70%, HER-2-neu negative. A chest/abdomen/pelvis CT scan confirmed the absence of metastases. On bone scan, there were no signs of bone metastasis. In April 2019, a PET scan revealed reactive lymph nodes that were negative for disease on biopsy. At this time, she was referred to our center and resection was planned. She underwent a resection of the recurrence including part of the pectoral muscle on May 24th, 2019. Pathology confirmed a grade 3 invasive ductal cancer of 1.5 cm, ER 1-5% PR 40% HER-2-neu negative. Closest margins were 5 mm. Since the recurrence occurred while the patient was still on tamoxifen, adjuvant treatment options included ovarian suppression with a GnRH agonist and an aromatase inhibitor. The patient’s personal preference was bilateral salpingooophorectomy, which she underwent in June 2019. The question of further chemotherapy remained. To quantify her benefit from adjuvant chemotherapy treatment, a multigene assay (Oncotype DX) was requested, even though it is not a standard indication. Her recurrence score was 37, with a recurrence risk at 9 years with only tamoxifen or aromatase inhibitor of 25% and an absolute benefit of chemotherapy > 15%. Of interest, her receptor status was evaluated by Oncotype DX as ER negative, PR positive, Her-2-neu negative. Her case was presented to the tumor board.

Question

Our specific question to the tumor board regarded the appropriate adjuvant chemotherapy regimen in a patient with an R0 resection of a late recurrence of breast cancer, hormone receptor positive, HER-2-neu negative, status post neoadjuvant chemotherapy consisting of FEC-D 10 years ago.

Discussion

Chemotherapy use has substantially contributed to the decrease in locoregional recurrence rate observed over the past decades. In a review of fifty-three randomized controlled trials from 1990 to 2011, chemotherapy’s correlation with decreased locoregional recurrence was significantly larger than endocrine therapy (P= 0.49 vs. P= 0.24, P for interaction <0.001). Similarly, a review of NSABP adjuvant systemic therapy trials demonstrated a decrease in both distant metastasis and locoregional relapse with systemic treatment. Increasing use of chemotherapy poses the challenge of deciding whether or not to treat the recurrence with further systemic treatment and if so, with which regimen.

Few studies have examined the question of adjuvant systemic therapy after locoregional recurrence. GBSG-6 and PACS 03/0003 trials both closed early due to low accrual. One of the earliest trials completed is the Swiss Group for Clinical Cancer Research (SAKK) trial. Patients with favorable characteristics, namely estrogen-receptor positive, disease-free interval more than 12 months and three or less nodules each less than 3 cm in diameter, were randomized to tamoxifen or observation. Further local relapses were seen more frequently in the observation group and translated in poorer disease-free survival (DFS) compared to the tamoxifen group (hazard ratio (HR) 0.57, 95% CI 0.39-0.84, P= 0.004). Overall survival (OS) was similar. Interestingly, the impact of tamoxifen on DFS was significant for postmenopausal patients only, while premenopausal patients had similar DFS in both arms of the study.

The International Breast Cancer Study Group (IBCSG) CALOR study is a cornerstone trial addressing the question of adjuvant systemic therapy in isolated locoregional recurrence of breast cancer. This international multicentric trial randomized 162 patients with completely excised isolated locoregional recurrences to chemotherapy or no chemotherapy. Chemotherapy regimen choice, including anti-HER2 treatment, was left to physician’s preference, but four courses of a...
multidrug regimen were recommended. Endocrine therapy was provided to patients with estrogen-receptor positive disease. 45% of patients received an Anthracyclin-based regimen, 19% received docetaxel or paclitaxel alone, 15% received Taxane-based chemotherapy and 11% received capecitabine alone. After a median follow-up of 4.9 years, 5-year DFS was 69% with chemotherapy and 57% without (HR 0.59, 95% CI 0.35–0.99, P = 0.046). Chemotherapy reduced distant and further local failure. Subgroup analysis revealed the DFS difference to be more significant for estrogen-receptor negative disease compared with estrogen receptor positive disease. The hazard ratio for 5-year DFS with versus without chemotherapy for estrogen-receptor negative disease was reported as 0.32 (95% CI 0.14–0.73) compared to 0.94 (95% CI 0.47–1.89) for estrogen-receptor positive disease. 5-year OS was superior for chemotherapy patients (88%) versus those who didn’t receive chemotherapy (76%) (HR 0.41, 95% CI 0.19–0.89, P = 0.024). Multivariable analysis further confirmed that chemotherapy was significantly associated to 5-year DFS (HR 0.49, 95% CI 0.29–0.84, P= 0.0098).

The final analysis of the CALOR trial was published in 2018.7 It reinforced the benefit of chemotherapy for estrogen-receptor negative disease, but not for estrogen-receptor positive disease. Interaction of treatment by estrogen-receptor status was reported as HR 0.26 (95% CI 0.11–0.60) for receptor-negative recurrence versus HR 0.87 (95% CI 0.46-1.64) for receptor-positive recurrence, P= 0.024. Overall, the observation of DFS events still favored chemotherapy, though marginally statistically insignificant (HR 0.62, 95%CI 0.38-1.02).

Despite the clear benefit of adjuvant systemic treatment for estrogen-receptor negative recurrence, the lack of benefit for estrogen-receptor positive recurrence is not as clear. Estrogen-receptor positive breast cancer can further be classified in luminal A and luminal B according to index of proliferation and molecular profile. As demonstrated by Belkacemi et al., prognosis and recurrence rates differ between the two subtypes.10 The question of benefit of adjuvant chemotherapy for luminal B disease, as is the case of our patient, is thus still unelucidated.11,12 Furthermore, our patient recurred while on tamoxifen. In CALOR’s final analysis, it is stated that the efficacy of chemotherapy could not be assessed in patients who recurred with estrogen-receptor positive disease while on endocrine therapy because of the low number of patients in this cohort.7

The trials outlined earlier point to the fact that locoregional recurrence should be managed according to the endocrine molecular characteristics of the recurrence. Moreover, discordance in breast cancer subtype between primary and recurrent breast cancer can affect survival and treatment selection.12 In that context, the use of genomic signatures for future therapy is of interest.6 It is with that thought that an Oncotype DX score on the recurrence specimen was requested for our patient. The absolute benefit of chemotherapy was estimated to be above 15%. Interestingly, there was discordance regarding ER status between the biopsy and excision specimens and Oncotype DX. ER status was 1-5% at our institution, but Oncotype DX reported an ER negative tumor. As discussed during the multidisciplinary meeting, this was attributed to different pathology lab technique. In the case of receptor negative disease on initial pathology, no Oncotype DX would have been requested; the patient would have received chemotherapy. Regardless, a question would have remained: what regimen should we provide?

In CALOR’s discussion,9 authors mention that choice of chemotherapy in the trial followed certain principles: if patients had previously received cyclophosphamide, methotrexate and fluorouracil or no chemotherapy, they had an Anthracyclin-based regimen; if they previously received anthracyclines, they were given Taxanes; finally, those who received Taxanes got capecitabine. Our patient previously received FEC-D and so, members of the tumor board advised that chemotherapy with possible cardiac toxicity be preferably avoided. A Taxane-based regimen, namely TC x 4, was hence selected by our multidisciplinary team. As for endocrine therapy, our patient will be switched to an aromatase inhibitor.

As Conclusion, the question of adjuvant chemotherapy for breast cancer recurrence is a subject of debate among many multidisciplinary tumor boards. Though recent trials have proven the benefit of systemic treatment for estrogen-receptor negative disease, estrogen-receptor positive subtypes, i.e. luminal A and B, have been less well investigated. In light of patient history, imaging, pathology and genomic analysis of tumor recurrence, members of our multidisciplinary tumor board elected to administer further chemotherapy consisting of TC x 4 to our patient.

Ethical Consideration
The ethics committee from CHUM Hospital was consulted and it was suggested that written or verbal consent be obtained. Verbal consent was obtained from the patient whose case inspired the discussion.

Conflict of Interest
None.

References


Background: Telling bad news to the patients after a diagnosis of breast cancer is one of the most important duties of a physician. The aim of this study was to explore breast cancer patient's preferences regarding how to receive bad news.

Results: The age of participants ranged between 28 and 58 years. Nine patients had undergone mastectomy and the remaining 6 had received conservative surgery. The minimum time between the diagnosis and receiving the news of cancer was 1 month, the maximum 15. Altogether, 250 codes were extracted after content analysis and categorized into 7 categories and 43 subcategories. The main categories were the method of disclosure of bad news, medical information, communication skills, emotional support, family involvement, the setting, psycho-spiritual care, and the word “cancer.”

Methods: A group of 15 women with breast cancer were purposively recruited to this qualitative study. Semi-structured in-depth interviews were conducted to identify the patients' preferences through content analysis.

Conclusion: Knowing about patients' preferences regarding the methods of breast cancer diagnosis disclosure can help physicians to effectively deliver bad news. Therefore, it is necessary that the clinicians be informed about the themes that the patients consider important while delivering bad news to patients.
not create further stress in the patient. They maintain this approach while communicating with the patient’s close relatives, showing proper reaction to the patient’s emotions while discussing life expectancy and adverse outcomes.

Despite the challenges and difficulties involved in effective disclosure of bad news, it can undoubtedly increase cancer adjustment in patients. Although there are a variety of protocols for breaking bad news, physicians always need to know how to inform the patients and what kind of information they are supposed to disclose.

The first step to do this would be to ask patients what they need to know. Studies have shown that the majority of patients are willing to know if they have cancer and whether their disease could be cured. About 91% of cancer patients in a study in China believed that patients should become aware of the truth about the nature of their disease. Patients require information about their clinical diagnosis because they believe the truth can help them plan for the rest of their lives and recover from the disease. Butoco et al. found that patients tended to be alone with their physician at the time of receiving the bad news and get the doctor’s expert opinion about their life expectancy, while Marwit et al. observed that patients would prefer to receive such information in the presence of their close family through honest and transparent conversation.

Fujimori et al. recognized that patients’ preferences in receiving the bad news consist of four components: setting, manner of communicating, what and how much information to disclose, and emotional support. Patients expect the clinician to spend enough time communicating with them about the diagnosis, treatment, and its effects on their daily function. The patients prefer that the doctors refrain from using scientific jargon while giving bad news and provide clear explanations easily understandable by the patient and her family.

Another factor found to be important to patients is emotional support, which includes making an empathic statement after delivering bad news. They expect the physicians to understand their emotions and those of their family when the news is being given and talk to them with an appropriate and kind tone. In fact, providing emotional support, spending an appropriate amount of time to fully answer their questions, and providing useful information for understanding cancer are all considered crucial by patients.

Given the psychosocial differences between genders, it seems reasonable that men and women have different preferences and expectations in terms of receiving bad news. For instance, women tend to be more sensitive in receiving bad news and prefer to get it from their physicians.

Breast cancer is the most common cancer among women in the world. It is also one of the main causes of cancer-related death among women. Hence, consideration of the way the bad news is communicated to the patients is of utmost importance. The purpose of this study was to explore breast cancer patients’ preferences for receiving bad news.

Methods
A qualitative method was used to identify the preferences of female patients in how to receive the news of their breast cancer. Application of the qualitative method here has been principally due to grave significance of the disclosure event from the standpoint of women with cancer. Consequently, the content analysis method was deemed appropriate to analyze the data gathered.

The target population for this study was women with breast cancer in Tehran. Fifteen women were purposively selected from among the women admitted to one of the referral hospitals affiliated with Tehran University of Medical Sciences (2016 to 2017). Subjects were recruited from different age groups and various educational backgrounds to increase validity of the data. Written informed consent was obtained from each participant.

The ethics committee of Tehran University of Medical Sciences approved this study. For all the eligible participants, semi-structured in-depth interviews were performed and recorded in a proper setting. The interviews started with a short introduction to the subject and main purpose of the research, followed by general questions regarding the patients’ experiences of receiving bad news from their physicians. Afterwards, more specific questions were asked including “Could you give me an example?” or “Could you explain it?” We also asked the following questions: How did you become aware of your disease? How would you have preferred to receive this news? In your opinion, which factors must be taken into account in giving the diagnosis news by the treatment team? The interviews were continued until the saturation point was reached, with each taking 110 to 120 minutes on average.

The Graneheim and Lundman method was applied to qualitatively analyze the data. At first, the audio files were transcribed and then the transcripts were reviewed several times till a general understanding of them was obtained. Afterwards, the materials were transformed into condensed meaning units (sentences and paragraphs extracted from the participants’ remarks). These units were then abstracted as codes. The primary coding was performed after multiple thorough reviews were done, and the meaningful units were explained and named. These units included words, phrases, or larger chunks from the transcripts. The researchers revised the data line by line to finally code each sentence. As such, maximum possible codes were specified so that it was ensured that all the information had completely been extracted. Then, the coded data were compared and categorized. At
Table 1. Categories and subcategories of breast cancer patients’ preferences regarding receiving bad news

<table>
<thead>
<tr>
<th>Row</th>
<th>Category</th>
<th>Subcategory</th>
<th>Examples of Participants’ Remarks</th>
</tr>
</thead>
</table>
| 1   | The method of disclosing bad news | • Telling the truth step by step  
• Making the proper introduction for telling the diagnosis  
• Preparing the patient  
• Telling bad news indirectly  
• Informing the patient about the diagnosis and treatment process  
• Giving a chance to choose between mastectomy and breast-conserving surgery after news disclosure  
• Answering the patient’s questions | • They should prepare the patient little by little so that they do not panic (a 45-year-old patient receiving mastectomy).  
• They should make an introduction and prepare the patient; it is much better than just directly telling them, especially for those with malignant tumors (a 31-year-old patient receiving mastectomy).  
• My doctors just told me they had to remove my breast in the first visit and gave me no chance to decide (a 31-year-old case receiving mastectomy). |
| 2   | Medical information           | • Telling about breast cancer  
• Telling about treatment options and their side effects  
• Informing about disease control  
• Explain the recommended diet  
• Telling about the fertility implications of the disease  
• Discussing statistics of breast cancer patients and the chance of cure  
• Telling about hair loss and change of appearance in chemotherapy  
• Informing about recurrence and prognosis | • I think anyone who has cancer should first know what it is and how it can be cured and if there is any treatment for it (a 35-year-old patient receiving mastectomy).  
• I preferred that my doctor tell me about the treatment options and their effects on me and my fertility. I would like to know about the proper diet during the treatment period, about the side effects of chemotherapy and changes in my appearance (a 31-year-old patient receiving breast-conserving surgery). |
| 3   | Communication skills          | • Talking kindly and gently  
• Using understandable words  
• Showing respectful manners  
• Communicating to build trust  
• Providing relief and peace  
• Making the treatment seem natural  
• Giving realistic reassurance to patients  
• Understanding patients and their family  
• Showing empathy  
• Interacting in a way to give hope | • When they told me the news, I panicked; but the doctor’s words and tone relieved me and encouraged me to go on (a 37-year-old patient receiving mastectomy).  
• I really felt awful but my doctor inspired me and told me he would do everything he could, and this raised my hopes (a 40-year-old patient receiving breast-conserving surgery).  
• I cried a lot when they told me I had to be operated on and might undergo chemotherapy. But the doctor calmed me down and said he understood me and would stay by my side and everything was going to be all right (a 47-year-old patient receiving mastectomy). |
| 4   | Family involvement and support | • Presence of family and relatives during disclosure of bad news  
• Talking with the patient’s family first  
• Using the family support to decrease the negative feelings induced by the bad news | • If they first tell a relative, it will be better. It is no good just saying “your test results are bad, and you have to start [the treatment] right away” (a 45-year-old patient receiving mastectomy).  
• If they hadn’t just told me and first had talked to my husband to tell me later or if they had told one of my relatives first, it would have been better for my mood. The way they talked to me gave me a huge shock and I was crying for two or three days (a 31-year-old patient receiving mastectomy). |
| 5   | Setting                       | • The doctors’ availability  
• Respecting patients’ privacy by asking the residents and other members of the treatment team to leave the room when disclosing the diagnosis  
• Devoting enough time for the patient  
• Providing a comfortable and peaceful environment  
• Telling the truth in a private, quiet setting | • One feels better with their doctor, but when there are residents and other patients in the room, it gets really difficult, particularly when everybody is looking at you in a weird way, like you have cancer; when you are alone with your doctor and the setting is peaceful, there will be a positive feeling (a 33-year-old patient receiving mastectomy).  
• If they had told me the news in the doctor’s office, I would have been feeling better; better than in the hospital. There were 3 or 4 residents standing by that could not fully explain matters. But in the office, it is much better. I mean, in a quiet place to talk to us for half an hour (a 45-year-old case receiving breast-conserving surgery). |
| 6   | Psycho-spiritual care         | • Using psychotherapy service after disclosing bad news  
• Physicians’ concern about patients’ mental state  
• Providing palliative care  
• Invoking God at the time of breaking the news  
• Reminding patients that death is always decided by God  
• Being considerate of religious beliefs of patients | • There was no psychologist or anyone to relieve me there. But women prefer to talk. They like to tell their problems to someone, someone who could understand them (a 33-year-old patient receiving mastectomy).  
• I suppose doctors must somehow know psychology and have some knowledge of it; they should be able to figure out the patient’s capacity for the bad news at first sight. They should know how to speak. I mean they should be aware of how to handle each case (a 47-year-old case receiving mastectomy).  
• They told me life is in the hands of God and only in God we have to trust. Saying this relieved me (a 35-year-old patient receiving breast-conserving surgery). |
| 7   | The term “cancer”             | • A frightening and stressful term  
• Its association with death  
• An incurable disease | • Just mentioning “cancer” is terrible by itself; you know, it is huge! It scares people. (A 54-year-old patient receiving breast-conserving surgery).  
• They tell us we have cancer, and we think we are going to die because we believe we die when we get cancer (a 45-year-old patient receiving mastectomy). |
this stage, related categories were identified and reclassified into new categories.

Following the initial coding, and to ensure the credibility of the data, they were given back to the participants for member checking and confirmation. To ensure the correctness of the codes, such measures as the external check (by specialists in breast cancer and medical ethics), immersion, and prolonged engagement were taken.

**Results**

In the present study, 15 women (age: 28-58) with breast cancer were interviewed. Nine of the participants had undergone mastectomy, 6 breast-conserving surgery. The time between diagnosis and receiving the bad news ranged from 1 to 15 months. Regarding educational status, 8 women had a high school certificate or a lower degree, and 7 were university graduates. Overall, 250 codes were extracted through content analysis and categorized into 7 categories and 43 subcategories (Table 1).

*The Method of Disclosing Bad News*

This category was one of the main concerns of patients and included 7 subcategories. In our setting, patients preferred that the news be given step by step, and the physician prepare them for receiving the news. To be indirectly informed of the details of their diagnosis was one of these preferences. In fact, it was very important to them that the doctor talk about diagnosis, management, prognosis, concerns, and questions and that they give them enough time to make a decision about the method of surgery (mastectomy or conservative surgery).

*Medical Information*

The other preference for the patients was receiving relevant medical information when the bad news is being broken to them. The patients would prefer to receive information on the following topics: the nature of breast cancer, treatment methods and their side effects, their diet during the treatment, effects of chemotherapy on their hair and appearance, and disease progression and recurrence.

*Communication Skills*

According to patient interviews, the physicians are expected to demonstrate good communication skills while delivering the bad news of cancer diagnosis. As shown in Table 1, there are 10 subcategories in this category. Patients prefer physicians to adopt a gentle approach and use an easy-to-understand language. Attention to the individual preferences of patients is required in order to create effective communication. Showing care and respect for the patient while opening a conversation about the fatal nature of cancer was very crucial, according to patients. Moreover, they expected to be understood as well as being heartened while the news is being given to them. Undoubtedly, showing empathy toward patients would encourage them to comply with the treatment after they are informed of their disease.

*Family Involvement and Support*

This category encompassed 3 subcategories (Table 1). Participants preferred that their close family be present while they are receiving the news. Owing to the potentially supportive role of close relatives, the patients believed that involving them could reduce the negative effects of the bad news.

*Setting*

Paying appropriate attention to the setting (time and place) was among the patients’ preferences in receiving the bad news. Five subcategories were identified for this category. Such factors as availability of the doctor, asking the residents and other members of the treatment team to leave the room, allowing the patient to ask questions and taking sufficient time to answer those questions, and arranging a private and quiet place without interruptions were the major topics here.

*Psycho-spiritual Care*

Another major concern of the patients was psycho-spiritual care, which consisted of 6 subcategories. Presence of a psychologist or a psychiatrist along with the physicians to provide psychological support and spiritual care during the disclosure of bad news was an expectation and preference of participants in this study.

*The term “cancer”*

Being careful with the use of the word “cancer” was another main preference of our participants, with 3 subcategories. Iranian patients consider this word to be frightening and very stressful as they associate this term with imminent death.

*Discussion*

The aim of this study was to explore breast cancer patients’ preferences in receiving bad news. The most important preferences of the patients were the method of truth-telling, medical information, communicative skills, emotional support, family involvement, setting, psycho-spiritual care, and the word “cancer.” These results are in line with those of Fujimori et al, who found that providing emotional support, giving medical information, and preparing a proper setting were important preferences of cancer patients regarding the disclosure of bad news.

The method of telling the truth was among the most important concerns to our participants. Indirect disclosure and preparing patients before giving the bad news, providing complete and transparent explanations about breast cancer, answering the questions of the patients and their relatives, and
giving patients the chance to select from among different treatment modalities were the most common participant preferences. According to the SPIKES protocol, one major aspect of the disclosure process is providing information which would be understandable for the patient and then checking whether the patient understood it, and, finally, avoiding the use of medical jargon. Therefore, following the strategy for breaking bad news and providing support to the patient could substantially reduce stress and uncertainty in women with breast cancer.

Another preference mentioned by the patients was receiving relevant medical information about their disease, treatment modalities, side effects, the chance of being cured, recurrence rate, and how breast cancer would influence their daily lives. Buckman believes that physicians should ask patients if they want to know the details of the medical condition and/or treatment and then provide medical information according to the educational level and socio-cultural background of patients, in small chunks using clear and simple language. Fujimori et al. found that young patients, women, and those with higher educational status are willing to receive more specialized information as to their disease and are more prepared to know the truth than other patients. Heydari et al. found that cancer patients need to get information on their disease and daily life. Therefore, the provision of realistic information by physicians within the disclosure process could decrease ambiguity in the treatment process.

Effective doctor-patient communication was another major concern to women with breast cancer in this study. Gebhardt et al. demonstrated that patient-centered communication skills could remarkably reduce patients’ stress and promote psychological adjustment in newly diagnosed breast cancer patients. Cao et al. discussed patient-centered communication strategies for giving bad news, saying that patients expected emotional support from doctors and that personalized disclosure would lead to higher levels of hope and trust in them. Previous studies have also emphasized emotional support and the establishment of a compassionate rapport as the main preferences of cancer patients during bad news disclosure.

Family involvement in the process of telling the truth was another preference of breast cancer patients in this study. Patients believe that the presence of their families at the time of receiving news about cancer diagnosis could reduce the negative impacts of the news. Studies have shown that family is the most important support system for cancer patients in Asia and Eastern Europe. Patients favor the involvement of their close relatives in the disclosure process as they can get help from them for decision making. Therefore, active involvement of families in the treatment process in a family-centered culture like Iran can considerably help cancer patients in the time of disclosure.

Another theme for the preferences of the study participants was the disclosure setting. Usually, patients expect physicians to spend enough time talking to them. Schofield et al. found that patients wanted to be alone in face-to-face interaction with their doctor to hear the diagnosis. Aminiighthashed et al. indicated that the bad news must be disclosed to patients in a calm and suitable place and after the routine working hours of medical centers. Hence, Iranian patients favor receiving the bad news in a private office setting, which is peaceful and without any interruptions or distractions.

Psycho-spiritual care was the other dimension of patient preferences identified in this study. They preferred to have a visit with a psychologist/psychiatric for psycho-spiritual care after receiving bad news about their diagnosis. Research shows that providing psychotherapy and spiritual care for cancer patients and their relatives can help them better adjust to the new situation. Furthermore, Iranian breast cancer patients who participated in this study preferred Islamic spiritual care as a coping strategy to help them confront and deal with bad news. Studies have shown that spirituality is an intermediary between stress and psychological adjustment to cancer. Therefore, considering the cultural and religious background of Iranian patients, it is highly recommended that this preference be respected.

Another dimension of the preferences of our patients was to avoid using the word “cancer.” Cancer patients and their families in Asia and the Middle East prefer not to use the term “cancer” as it implies an incurable disease, and thus invokes fear, anxiety, and pain in many patients. In Iranian culture, “cancer” is a taboo and “tumor” or “malignant mass” is used instead, because it is assumed that using “cancer” destroys the patients’ hopes and causes negative psychological reactions in them. It seems vital to change the trend and encourage the use of “cancer.” However, the word “cancer” or other alternatives should only be used by doctors after considering mental readiness of breast cancer patients for receiving bad news.

It must be noted that the findings of the present study may not be completely generalizable before further complementary quantitative studies. It is also recommended that cancer patients’ preferences be considered in a wider range in other studies with regard to such demographic variables as age, education, and occupation.

In conclusion, to inform the patients of the bad news, and in compliance with the international protocols, physicians need to be aware of the patients’ preferences regarding the way of receiving the bad news. The findings of this study could enhance the quality of doctor-patient communication.
with regard to the disclosure of bad news and help patients to better cope with the news of breast cancer diagnosis. That is why it is highly essential to incorporate the Iranian patients’ preferences obtained and gathered here into training programs for physicians.

Conflict of Interest
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Management of Carcinoma of Unknown Primary Involving Axillary Lymph Node (CUPAx)

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\textsuperscript{c} Department of Surgery, Alborz University of Medical Sciences, Karaj, Iran

**ABSTRACT**

**Background:** Cancer of unknown primary involving axillary lymph nodes (CUPAx) is a very rare type of cancer. There are still many challenges about the management and outcome of the disease. This retrospective study is an attempt to assess the overall survival and the outcome of CUPAx in Iranian women.

**Methods:** Based on inclusion and exclusion criteria, 20 patients primarily diagnosed with CUPAx referred to our breast multidisciplinary team (MDT) sessions between July 2010 and December 2016 were evaluated. The patients were categorized into three groups based on the types of treatment: mastectomy and radiation therapy, radiation therapy, and observation group.

**Results:** The mean age of the subjects was 52 ± 7.91 years (range: 42-74). The results manifested significant differences between the outcomes of three types of treatments. The patients who received both mastectomy and radiotherapy had a higher survival rate and no sign of the disease compared with other groups ($P=0.03$). The median survival time in the mastectomy group was 78 months and 23 months for the group with no mastectomy (95% CI: 7.64-38.36) ($P <0.001$).

**Conclusion:** The result suggested that mastectomy was effective in lowering the risk of disease progression in Iranian women diagnosed with CUPAx and highly suspicious breast origin. More studies on larger sample groups are needed.

**Introduction**

Cancers of unknown primary (CUPs) are a group of histologically confirmed metastatic cancer of which the primary site is undetectable even after a complete and standard diagnostic and pathologic workups. The incidence rate of CUPs is 3-5% of all solid malignant tumors.\textsuperscript{1} The most affected sites were the bones, liver, lungs, and lymph nodes. The CUP involving axillary lymph nodes (CUPAx) is a very rare case and the incidence rate is reported between 0.12 to 0.67 % of all diagnosed cancers.\textsuperscript{2,3} Some evidences manifest the incidence of CUP involving axillary lymph nodes is between 0.1 and 1 % of all patients with breast cancer.\textsuperscript{4,5} The primary site of CUPAx is most often hidden in the breasts; however lung, ovary, thyroid, pancreas, urogenital tract, or intestines are the other possible primary sites.\textsuperscript{6} The CUPAx affects women in the 6th decade of life with a mean age of 52 and the most frequent histology is ductal adenocarcinoma.\textsuperscript{7} About 23.4% of the CUPAx patients had a history of malignancy in their family.\textsuperscript{7}

Finding the primary source of CUPAx is a diagnostic challenge and requires extensive investigations. Magnetic Resonance Imaging (MRI) is widely utilized to this end,\textsuperscript{8,9} and it seems MRI is
one of the modalities with high sensitivity to detect occult breast cancer in CUPAx patients. Some studies on CUPs have reported that accuracy of fluorodeoxyglucose (FDG) PET ranges from 25% to 43%. The CUPAx belongs to favorable subsets of CUP which respond to local or systemic treatments with a longer survival term. Some studies have compared the prognosis of patients with CUPAx to early breast cancer patients. Montagna et al. did not find any significant difference in disease-free survival (DFS) and overall survival (OS) between occult breast cancer and early invasive cancer. Pentherodorakis et al. reviewed 14 studies (a total of 559 CUPAx patients) and concluded that the mean 5-year OS rate was higher or similar to stage II-III patients with breast cancer. The literature review by Lee et al. suggested that, with a 10-year survival ranging from 50% to 71%, prognosis resulted in better outcomes comparing with the cases diagnosed at stage II. Another report indicated that patients of CUPAx had 10-year overall survival of 96.8% in N1 feature and 82.6% and 80.8% in N2 and N3 cases respectively. There is no consensus on the management of CUPAx with suspected breast origin. Local therapy of the breast varies from observation to quadrantectomy, mastectomy, or whole breast irradiation. Many researchers have investigated the role of local breast treatment on the survival of the patients. Walker et al. reported that 10-year Cause Specific Survival (CSS) rate was 75.7% for patients who experienced breast conservative therapy (BCT) versus 73.9% for patients who experienced mastectomy. They concluded that, comparing with BCT, mastectomy had no effect on CSS.

The management of the axilla in CUPAx is less controversial. In a review by Pentherodorakis et al., the vast majority of practitioners routinely practiced axillary lymph node dissection (ALND) (level I and II); however, in smaller groups of cases, axillary excisional biopsy and irradiation of the axilla were applied. They reported that in-axilla failure rate after a level I/II ALND (<10%) was lower than excisional biopsy and/or axillary irradiation (20% to 50%).

The present study was an attempt to examine the long-term outcome of CUPAxin patients at Cancer Institute of Imam Khomeini hospital based on patients’ characteristics and treatment plans.

**Methods**

The records of patients filed in the Breast multidisciplinary team (MDT) sessions (Cancer Institute of Imam Khomeini Hospital) between July 2010 and December 2016 were retrospectively reviewed. The participants signed an informed letter of consent at the time of final follow up. In addition, the ethics committee of the hospital approved this study. Patients with CUPAx entered the study and their hospital charts were reviewed. Different types of data were retrieved including: history, physical examination, demographic characteristic, imaging studies (Mammography, Ultrasonography, MRI, and metastatic work up), pathology, IHC results (ER, PR, HER-2, TTF1, CK7, GCDFP15, CK AE1/AE3, and HMB45), and local and systemic therapies.

Breast MDT recommendation to all patients was ALND with systemic therapy before ALND. Either mastectomy and chest wall radiation or whole breast irradiation was recommended as local treatment of the breast. The final treatment would differ depending on patients’ priorities and principal physician’s decision.

The patients were categorized according to the local treatment of the breast into three groups: 1- mastectomy and radiation therapy, 2- radiation therapy, 3- no local therapy of the breast (observation group). In addition, all patients received chemotherapy.

Patients with incomplete data, primary lesion in the breast imaging, history of breast cancer in contralateral breast, evidence of distant metastasis, other cancers based on histologic results, and IHC of axillary lymph node were excluded. Standard followed up procedure was implemented and the outcome was categorized according to the last follow up. The final outcomes were no evidence of disease (NED), alive with disease (AWD), and dead of disease (DOD).

The collected data was analyzed in SPSS (version 13, Chicago, IL, USA). Categorical variables were expressed in number (%) and continuous variables were represented as mean ± standard deviation. Chi-squared test or Fisher’s exact test was used to compare categorical variables (P< 0.05). Kaplan-Meier approach was used to estimate the median survival from the time of diagnosis to the time of event (death or alive with disease) and overall survival was compared between treatment groups with a log-rank test.

**Results**

Between July 2010 and December 2016, 20 patients with primary diagnosis of CUPAx referred to our breast MDT sessions were selected based on the exclusion and inclusion criteria (n= 20). Four patients had a suspicious lesion in mammography or US. Biopsy of these lesions revealed three fibroadenomas and one cases of usual ductal hyperplasia. Five patients had suspicious lesion on breast MRI, which was detectable on targeted US. The biopsy of these lesions proved to be benign. Lymph node IHC results such as TTF1, CK7, CK 20, GCDFP15, CK AE1/AE3, and HMB45 were in line with breast cancer origin. Table 1 lists the patients’ characteristics. The mean age of the affected women was 52 ±7.91 years (range: 42-74) and 55% of them were in postmenopausal status.

Figure 1 illustrates the overall survival of all
patients who participated in this study. The mean survival time was 57.19 months (95% CI: 44.75-69.64).

Table 1. Patient’s characteristics (N=20)

<table>
<thead>
<tr>
<th>Variables</th>
<th>N (Range-%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age at diagnosis (range)</td>
<td>52 (42-74)</td>
</tr>
<tr>
<td>Median follow-up (range)</td>
<td>38 (14-78)</td>
</tr>
<tr>
<td>Laterality</td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>11 (55%)</td>
</tr>
<tr>
<td>Left</td>
<td>9 (45%)</td>
</tr>
<tr>
<td>Menopausal status</td>
<td></td>
</tr>
<tr>
<td>Premenopausal</td>
<td>9 (45%)</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>11 (55%)</td>
</tr>
<tr>
<td>Positive family history of malignancy</td>
<td>4 (20%)</td>
</tr>
<tr>
<td>IHC results of lymph nodes</td>
<td></td>
</tr>
<tr>
<td>Luminal A, B</td>
<td>12 (60%)</td>
</tr>
<tr>
<td>Her2-enriched</td>
<td>2 (10%)</td>
</tr>
<tr>
<td>Basal-Like</td>
<td>6 (30%)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td></td>
</tr>
<tr>
<td>Adjuvant</td>
<td>16 (80%)</td>
</tr>
<tr>
<td>Neoadjuvant</td>
<td>4 (20%)</td>
</tr>
<tr>
<td>Nodal Status</td>
<td></td>
</tr>
<tr>
<td>N1 (1 to 3 involved lymph nodes)</td>
<td>7 (35%)</td>
</tr>
<tr>
<td>N2 (4-9 involved lymph nodes)</td>
<td>13 (65%)</td>
</tr>
<tr>
<td>Lymph node pathology, n (%)</td>
<td></td>
</tr>
<tr>
<td>IDC</td>
<td>3 (15%)</td>
</tr>
<tr>
<td>Metastatic carcinoma</td>
<td>10 (50%)</td>
</tr>
<tr>
<td>Undifferentiated carcinoma</td>
<td>5 (25%)</td>
</tr>
<tr>
<td>Poorly differentiated carcinoma</td>
<td>2 (10%)</td>
</tr>
</tbody>
</table>

Data are presented as number and percentage in parenthesis.

Table 2. Patients’ information considering treatment and outcomes

<table>
<thead>
<tr>
<th>Treatment Type</th>
<th>Status of patients</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NED N=12</td>
<td>AWD N=7</td>
</tr>
<tr>
<td>Mastectomy + Radiotherapy</td>
<td>10 (76.9%)</td>
<td>3 (23.1%)</td>
</tr>
<tr>
<td>Radiotherapy alone</td>
<td>2 (50%)</td>
<td>1 (25%)</td>
</tr>
<tr>
<td>No local therapy</td>
<td>0 (0.0%)</td>
<td>3 (100%)</td>
</tr>
</tbody>
</table>

* P refers to Fisher’s exact test.

Figure 1. Overall survival of CUPAx in the present study sample.

Table 2 lists the number of patients with different treatments and outcomes. The significant differences between the outcome of three types of treatments are evident. The patients who received both mastectomy and radiotherapy have a higher survival rate and no evidence of disease compared with other groups (P=0.03). Categorizing the patients into two groups based on mastectomy revealed that 76.9% (10/13) of patients who received mastectomy had no evidence of disease and the complication occurred only in three patients (23.1%). However, 29% (2/7) of patients who did not receive mastectomy were alive without disease and the complication occurred in five patients (71%). This difference is also statistically significant (P=0.06) (Data not shown in the table). Survival time period comparison with Log Rank test manifested the median survival time of the mastectomy group was 78 months and 23 months for the other group (no mastectomy) (95% CI: 7.64-38.36); the difference is statistically significant (P <0.001).

There was a patient in the mastectomy and irradiation group with follow up of 42 months (total of 13 patients) with regional relapse in axillary
lymph node and another patient with liver metastasis. In the irradiation group with follow up of 25 months (total of 4 patients), one patient developed multiple bone metastasis and the other patient died from widespread visceral (ovary & lung) and bone metastasis at 44th month from her first presentation. Finally, in the group without any local treatment with follow up period of 22 months (totally 4 patients), one patient demonstrated local recurrence on the chest wall with ulceration, another one developed cervical lymph node metastasis, and the third patient developed multiple bone metastasis.

Discussion
The CUPAx is a rare clinical entity and it has been reported in case reports. There are also a few studies with large sample size. Breast is the most likely origin of CUPAx and ER or PR positive in IHC assay of axillary lymph node could support the origin of breast; still, negative results do not exclude the breast origin.

Twenty cases of CUPAx who referred to our cancer institute with the median follow-up of 38 months (range: 14-78) were studied. Interestingly, the mean age of subjects (52 years old) was similar to a large systematic review. The result suggested that mastectomy was effective in lowering the risk of disease progression and as a best modality, it should be recommend to all patients with CUPAx with highly suspicious breast origin.

Consistent to the present study, Sohn et al.’s investigation showed the overall survival in patients undergoing ALND only, breast conserving surgery, and mastectomy with ALND was not significantly different (P= 0.061). The authors believe that the statistical uncertainty of our result is due to the small sample size. However, Sohn et al. evaluated 142 cases and they reported the same results. Another study with 48 CUPAx cases revealed that the patients with ipsilateral radiotherapy and breast conservation therapy (BCT) or mastectomy had better 5-year local recurrence free survival compared with observation group. They did not evaluate the survival time for mastectomy and BCT separately. They recommended a standard radiotherapy to improve local control in patient with occult primary breast cancer. However, in the present study only one patient died from the disease and she only received radiation therapy. Therefore, we suggest only radiation therapy without considering surgery may be a threat to the patient’s health.

Another study in 2010 systematically reviewed published CUPAx case series and 24 retrospective studies enrolling 689 patients. Among the total of 446 patients managed with mastectomy, 72% of them histologically showed that the breast was the primary origin. The authors concluded that mastectomy or radiotherapy provided loco-regional disease control in 75% to 85% of cases. The effect of removing an occult primary on survival was unclear; however, these data supported mastectomy as an effective diagnostic modality. Our result was consistent with this systematic review so that mastectomy provided disease control in 77% of our cases.

A mini-review in 2015 recommended radiotherapy and adjuvant chemotherapy afterwards and/or hormone therapy depending on the risk factors for patients with CUPAx. The authors did not suggest mastectomy as an effective treatment. However, according to a survey by the American Society of Breast Surgeons (ASBS) in 2005, 43% of the experts preferred mastectomy, while 37% opted for whole breast irradiation, and 20% selected other treatments (including 6% that chose observation).

Finally, although there is a consensus about the necessity of ALND and chemotherapy in treatment of CUPAx patients, still the recommendations regarding the local management of the breast are controversial.

As shown by the results here and in the other studies, in CUPAx patients, local therapy of breast by mastectomy or radiation therapy is associated with better results in local control, distant metastasis, and overall survival. Larger prospective studies are required to address this question with more certainty.

Acknowledgement
We would like to show our gratitude to the breast multidisciplinary team of Cancer Institute of Imam Khomeini hospital.

Conflict of Interest
The authors declare that there is no conflict of interest.

References
6. Sohn G, Son BH, Lee SJ, Kang EY, Jung SH, Cho...
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ABSTRACT

Background: Although various Oncoplastic Breast Surgery (OBS) techniques have been introduced for various sizes of the breast and locations of tumors, surgeons are still faced with serious challenges for the tumors which have developed in special anatomic parts of the breast. A good instance of these challenges is with the tumors located far from the Nipple Areola Complex (NAC) especially in the upper inner quadrant. We aimed to assess the application of the newly introduced OBS technique (Cross Technique) for tumors in these locations.

Methods: The data of 95 patients who were suffering from breast cancer and operated with the Cross method were assessed in this prospective survey. Data was gathered regarding demographic variables, the size, location, and pathologic characteristics of tumors as well as the patients' BMI, breast circumference, and cup size. The patients were recruited to the study according to the inclusion and exclusion criteria and the study protocol which was approved by the research deputy surgery department in Tehran University of Medical Sciences. The data was then presented in a descriptive method.

Results: Nighty-five patients underwent oncoplastic breast surgery using the Cross method in a span of time from November 2015 to May 2018. The patients had a mean age of 48.2 (ranging from 25 to 70 years) as well as a wide range of breast circumferences and cup sizes (70 to 95 for the breast circumferences and A to E for the cup size). Clear surgical margins were obtained in 93 cases according to the permanent pathology reports. Complications were seen in 5 patients (2 slight hematomas and three ischemic skin flaps) all of which were managed conservatively. The most common histologic types of tumors were in situ and invasive ductal carcinoma (DCIS-IDC). The mean tumor size was 22.7 mm with a standard deviation of 9.2 mm and most of the tumors were positive for estrogen receptor (ER)/progesterone receptor (PR). In the surgery of axilla, an average of six lymph nodes were excised while 22 patients were found out to have axillary lymph node involvement.

Conclusion: Not only is the Cross method not only a reliable choice for tumors located in the upper inner quadrant (UIQ), but it can also be applied safely for the tumors in upper outer quadrant (UOQ) and upper central part of the breast, although the best application for the technique is the tumors located far from the nipple areola complex.

KEY WORDS
Oncoplastic breast surgery,
Cross technique,
breast tumor,
far from NAC
innovative approaches were proposed afterwards. Oncoplastic breast surgery (OBS) techniques are among the approaches that combine tumor removal procedure with a plastic surgery to reshape the breast.

OBS techniques are categorized into two different classes, corresponding to the mass of breast tissue being removed. Although various OBS techniques have been introduced for various sizes of the breast and locations of tumors, surgeons are still facing with serious challenges in certain cases. For instance, in cases with small-size breasts and tumors far from the nipple-areola complex (NAC), breast-conserving surgery can be quite challenging especially for the tumors in the upper-inner part of the breast. We have recently introduced a novel technique, called the “Cross” technique, to overcome some of the limitations of the current OBS techniques performed on tumors in the upper inner quadrant (UIQ).

The current study aimed to investigate the outcomes of the Cross technique in a larger population of breast cancer patients with tumors in the UIQ. Moreover, we have suggested the Cross technique as a suitable approach for tumors located far from NAC complex in regions other than the UIQ.

### Methods

The current work is a prospective study on 95 female with individuals affected by breast cancer, who were operated using the Cross method by the main author of this article. Data was gathered regarding demographic variables, the size, location, and pathologic characteristics of tumors, patients’ BMI, breast circumferences, and cup size. The protocol of the study has been approved by the research deputy of the department of surgery in Tehran University of Medical Sciences. Advantages and limitations of the planned operation (the Cross technique) were described in detail for all patients in the outpatient clinic. The patients had enough time to decide whether or not to participate in this study and to be operated using the Cross technique, having been fully informed of the advantages and limitations of this novel OBS technique. Finally, the patients submitted their written informed consent were selected to be included in this study.

The inclusion criteria were as follows: 1) Breast carcinoma had to be proved by the pathology report, 2) The tumor being located far from the distance between the peripheral part of the breast and the nipple was measured and divided to three parts and only the tumors located in the far one third were included, 3) The patient had to be an applicant for the breast-conserving surgery and further oncoplastic repair, and 4) The patients also were to give their consent to be operated using the Cross technique.

The exclusion criteria were; 1) having previous sessions of radiotherapy, 2) having a recurrent tumor, 3) patients with important genetic mutations like BRCA, 4) any indications for mastectomy, and 5) patients with large breast cup sizes, who had expressed their consent to be operated using level two oncoplastic surgery (reductive type).

### Surgical technique

The first step to prepare the patient for surgery was drawing the map of surgery on the breast in terms of tumor location as well as the proposed incision line in upright position. The skin incision line was drawn in a curvilinear pattern as close as possible to the areolar margin. This is in fact one of the most critical steps while using the Cross method, since an incision above the “Décolleté line” would result in a scar that is exposed by the neckline of the patient’s clothing. Surgery was then started by making the incision over the curvilinear line. Afterwards, the skin and subcutaneous tissue were dissected through Kooper ligament to separate the breast tissue from the overlying skin and subcutaneous tissue. The dissection was fan-shaped and performed in the quadrant where the tumor was located. Resection of the tumor was performed by cutting the breast tissue with safe margins of 1 cm with an elliptical incision in radial direction. Then, the tumor was removed with secured margins and sent to the pathology laboratory. The frozen section assessments were used only if there were suspicious margins of tumoral involvement.

Since the location of the tumor in most cases was not exactly under the skin incision, we placed metallic clips in the bed of the tumor resection to enable the radiation oncologist to accurately localize the tumor for radiation therapy. If the breast tissue defect was hard to be closed by the sutures. This maneuver helped the surgeon to do tension-free closure of the defect by facilitating the tissue flaps to slide on the pectoral plan. Then, the resection site was repaired in radial direction. As the next step of the operation, a closed suction drainage system was placed in the dissected area wherever the area of dissection was considerably large. Finally, subcutaneous tissue and skin were sutured properly with absorbable surgical sutures in circumareolar direction. The detailed methodology of the Cross technique is described in the original paper published by our team, introducing this novel approach.

### Statistical analysis

We analyzed the demographic data by IBM SPSS Statistics for Windows, version 22 (IBM Corp., Armonk, N.Y., USA). We verified the compliance of variables with normal distribution through probability graphics and the Shapiro-Wilk test. Data is presented as median, mean with standard deviation, or frequency.

### Results

Nighty-five patients underwent oncoplastic breast surgery using the Cross method from November 2015 to May 2018. The demographic data
of patients are presented in Table 1. Patients had a mean age of 48.2 ranging from 25 to 70 years. The breast circumference and cup size were measured. The range of measurements of breast circumference was from 70 to 95 and there were 6, 46, 33, 3 and 7 patients with brassiere cup sizes of cup sizes B, C, D and E respectively.

The clear surgical margins was obtained in 93 cases according to the permanent pathology reports. Five patients showed post-op complications. One patient showed skin flap ischemia, two others had small area of skin flap necrosis and the last two cases developed with slight hematoma after the operation. None of these patients needed reoperation and their complications were fully managed conservatively. No complication was observed in the remaining 90 patients.

Table 1. Demographic features of patients.

<table>
<thead>
<tr>
<th>Demographic features</th>
<th>Patient (n=277)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years, mean ± SD</td>
<td>48.2 ±11.6</td>
</tr>
<tr>
<td>Breast size, median (min-max)</td>
<td>80.0 (70-95)</td>
</tr>
<tr>
<td>Greater diameter in cm, mean ± SD</td>
<td>23.8 ±5.1</td>
</tr>
<tr>
<td>Specimen weight, mean ± SD</td>
<td>82.6 ±46.5</td>
</tr>
<tr>
<td>Laterality</td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>53 (55.8%)</td>
</tr>
<tr>
<td>Right</td>
<td>41 (43.2%)</td>
</tr>
<tr>
<td>Bilateral</td>
<td>1 (1.1%)</td>
</tr>
<tr>
<td>Tumor location</td>
<td></td>
</tr>
<tr>
<td>Upper outer quadrant</td>
<td>36 (37.9%)</td>
</tr>
<tr>
<td>Upper inner quadrant</td>
<td>17 (17.9%)</td>
</tr>
<tr>
<td>Lower outer quadrant</td>
<td>2 (2.1%)</td>
</tr>
<tr>
<td>Lower inner quadrant</td>
<td>1 (1.1%)</td>
</tr>
<tr>
<td>Upper central</td>
<td>34 (35.8%)</td>
</tr>
<tr>
<td>True lateral</td>
<td>1 (1.1%)</td>
</tr>
<tr>
<td>True medial</td>
<td>4 (4.2%)</td>
</tr>
</tbody>
</table>

Figure 1. The patient underwent oncoplastic breast surgery using the Cross technique in UOQ of the right breast after neoadjuvant chemotherapy. A and B: Before surgery (with wire localization). C and D: 20 days after surgery (before radiotherapy). E: 30 days after radiotherapy.
Figure 1 shows the breasts of a patient operated without any subsequent complications before and after the surgery and radiotherapy.

Pathologic features of the tumors are presented in Table 2. The most common histologic type was insitu and invasive ductal carcinoma (DCIS-IDC). The mean tumor size was 22.7 mm with standard deviation of 9.2 mm, and most of the tumors were positive for estrogen receptor (ER)/progesterone receptor (PR). In the surgery of axilla, an average of 6 lymph nodes were excised and 22 patients were proved to have lymph node involvement.

Table 2. Pathologic features of tumors.

<table>
<thead>
<tr>
<th>Features</th>
<th>Patients (n=95)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor pathologies</td>
<td></td>
</tr>
<tr>
<td>IDC</td>
<td>29 (30.5%)</td>
</tr>
<tr>
<td>DCIS</td>
<td>3 (3.2%)</td>
</tr>
<tr>
<td>DCIS-IDC</td>
<td>46 (48.4%)</td>
</tr>
<tr>
<td>ILC</td>
<td>4 (4.2%)</td>
</tr>
<tr>
<td>DCIS-LCIS</td>
<td>39 (41.4%)</td>
</tr>
<tr>
<td>Atypia</td>
<td>1 (1.1%)</td>
</tr>
<tr>
<td>NA</td>
<td>10 (10.6%)</td>
</tr>
<tr>
<td>Receptor Status</td>
<td></td>
</tr>
<tr>
<td>ER positive</td>
<td>59 (62.1%)</td>
</tr>
<tr>
<td>PR positive</td>
<td>56 (58.9%)</td>
</tr>
<tr>
<td>HER2 positive</td>
<td>17 (17.9%)</td>
</tr>
<tr>
<td>Lymph node involvement</td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>52 (54.7%)</td>
</tr>
<tr>
<td>N1</td>
<td>11 (11.6%)</td>
</tr>
<tr>
<td>N2</td>
<td>10 (10.5%)</td>
</tr>
<tr>
<td>NA</td>
<td>22 (23.2%)</td>
</tr>
<tr>
<td>Therapies</td>
<td></td>
</tr>
<tr>
<td>Neoadjuvant chemotherapy</td>
<td>14 (14.7%)</td>
</tr>
<tr>
<td>Adjuvant chemotherapy</td>
<td>77 (81.1%)</td>
</tr>
<tr>
<td>Adjuvantradiotherapy</td>
<td>91 (95.8%)</td>
</tr>
<tr>
<td>Adjuvant hormone-therapy</td>
<td>61 (64.2%)</td>
</tr>
<tr>
<td>Adjuvant target-therapy</td>
<td>18 (18.9%)</td>
</tr>
</tbody>
</table>

Discussion

We studied the outcome of a novel OBS method called the "Cross technique" in 95 patients with breast cancer. All patients enrolled in this study had tumors located in regions far from the NAC. No patients in this study experienced any kind serious complications that needed to be managed by re-surgery.

A line of studies has proved that OBS is a reliable choice in terms of survival rate and cosmetic outcomes, compared to traditional methods. However, the cosmetic outcome of this kind of surgery is affected by several factors, of which the most prominent is the tumor location. Various techniques have been proposed for tumors located in regions far from the NAC (UOQ, UIQ and upper central part), which are considered less favorable parts. From this point of view, Grisotti et al consider UIQ as "no man's land" where surgeries would probably lead to an NAC displacement and a visible scar. For instance, a study by Anderson and colleagues have demonstrated batwing mastopexy as a reproducible method. However, Batwing method has limitations such as a risk of NAC displacement and breast deformity. The Cross method was originally described to be performed on tumors in the UIQ, causing minimum deformity in the breast. In this study, we considered the Cross method to be performed on any tumor that lies far from NAC complex, especially in patients with small-size breasts.

A challenge to the planning of breast conserving surgeries is the resection of overlying skin of the tumor. The challenge is even more serious when the tumor is near the overlying skin. Studies have shown that the application of neo-adjuvant chemotherapy can make such tumors proper candidate for breast-conserving surgeries by decreasing the size of the tumors and increasing the distance of the tumor from the skin. So, in most patients the resection of the tumor overlying skin can be safely omitted during the operation. On the other hand, the traditional point of view was that for breast conserving surgery the skin incision should usually be placed over the tumor, however, in the Cross method the skin incision can be made within a considerable distance from the tumor, explicitly below the "Décolleté line".

Furthermore, using a single incision line in the Cross technique and avoiding sophisticated surgical incisions as happens in some other oncoplastic surgery techniques like lateral oncoplasty can have major advantages such as less tissue manipulation as well as a shorter time of healing and recovery for the patients. It has been shown that up to 18% of the patients were not completely satisfied with the cosmetic results of OBS techniques. Multiple studies have shown that a major factor influencing patients satisfaction is the length of the scar. One of the advantages of the Cross method is that it provides a decent access to the tumor and thus leads to a single and relatively small scar.

The other important factor for patients' satisfaction is the operation on the contralateral breast. In most reductive types of oncoplastic procedures, the patient usually has to have another operation on her other breast for the sake of symmetry. Nevertheless, most of the patients do not wish to undergo other surgeries to make the other breast symmetric. Even with respect to this viewpoint, the Cross technique is a favorable procedure for petotic and large breasts (larger than C breast) especially in case of patients who do not wish to be operated for the contralateral breast.

As an oncologic measure, the reoperation for the positive margins is of utmost importance. On the other hand, requiring a second surgery is another issue that would reduce patients' satisfaction dramatically. The average rate of positive margins ranges from 20 to 40 percent after the oncoplastic surgery in different studies. In the present study this rate was just two percent and only two patients were not completely satisfied with the cosmetic results of OBS techniques.
demonstrated the outcome as well as the advantages of the newly introduced OBS method, called the Cross technique. We showed that not only is the Cross method a reliable choice for tumors located in the UIQ, but it can also be applied safely for the tumors in UOQ and upper central part of the breast while the best application of the technique is in case of the tumors located far from the nipple areola complex.

**Ethical Consideration**
The patient signed the informed written consent for using her photo in the article.

**Conflict of Interest**
The authors declare no conflict of interests.

**References**
ARTICLE INFO

Background: Breast involvement during malignant lymphomas is a rare condition, whether in primary or secondary cases, whereas according to the literature, primary breast lymphomas represents merely less than 0.5% of the breast malignancies.

Case Presentation: The case was a 48 years-old patient referred to the clinic with contralateral breast diffuse large B cell malignant lymphoma. She had an operation for right breast mucosa-associated lymphoma tissue (MALT) lymphoma two-years earlier. The participant experienced surgical excision of the right breast mass and radiotherapy subsequently. Surprisingly, after two years she developed a mass on the left breast, for which we were not able to establish an evident relationship between the earlier MALT lymphoma and the second diffused B cell lymphoma.

Conclusion: Although, our report emphasizes on the undeniable role of the breast examination in prevention of catastrophic events, we are far from providing diagnostic approaches on breast MALT lymphoma, due to minimal case sizes and lack of adequate information and evidences.

Introduction

Breast involvement during malignant lymphomas is a rare condition, whether in primary or secondary cases. However, according to the literature, primary breast represents less than 0.5% of the breast malignancies. Among primary breast lymphomas, mucosa-associated lymphoid tissue (MALT) is a common subtype that affects almost one half of the victims. Mucosa-associated lymphoid tissue is the least developed tissue inside the breast that might be the leading cause of the MALT scarcity in the breast. Therefore, breast involved lymphomas result in 1.7% of the extranodal non-Hodgkin lymphomas. The present report is on a 48 years-old patient with contralateral breast diffuse large B cell malignant lymphoma, who had an operation for right breast MALT lymphoma, two-years earlier.

Case presentation

In July 2016, a 47-year-old woman underwent an excisional surgery (lumpectomy) for a slightly solid mass on the right upper quadrant of her right breast adjacent to the nipple. She was a non-smoker mother of six children with no history of any malignancy or chronic diseases, no history of using drugs, and no correlated familial history. Postoperative histopathological evaluations revealed dense monomorphic lymphoid infiltration of breast stroma with diffuse growth pattern, consisted of small to medium-sized lymphoid cells with rounded to slightly irregular nuclei. These features of the fibrofatty stroma were suggestive of a typical lymphoepithelial lesion and consistent with marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT). As observed during the surgery and later confirmed by postoperative pathological studies, none of the lymph nodes were involved, and she had N0 regarding TNM scoring.
She had an eventless postoperative recovery and received radiotherapy, subsequently. Afterwards, during the follow-up period, she received ultrasonographic examinations of the breast and tests in lab, including complete blood count and blood proteins level.

In February 2019 and during the routine ultrasonographic evaluation of the breast, the patient presented with a breast mass which reported to be a heterogenous hypoechoic area with tiny cystic components and microcalcifications between 2-3 o’clock position on the left breast near the nipple, which was 45*39*19 mm in size. According to the radiologist’s report, the mass had a breast imaging reporting and data system (BI-RADS) category of 4a. Although, the tissue diagnosis report indicated a lower probability of malignancy (between 2-10%), given the suspicious origin of the lesion, the patient was suggested to have a core needle biopsy.

Four months later, core needle biopsy was performed with the sonography guidance from the 1.5*1.0*0.2 cm mass which included dense infiltration of lymphocytes and lymphoid cells with nuclear atypia. Afterwards, the collected tissue was examined using microscope and the findings showed large irregular and vesicular nuclei for atypical cells, as well as conspicuous nucleoli and scant to moderate amount of clear to eosinophilic cytoplasm. Moreover, the atypical cells had positive reactions to CD20, CD43, LCA, BCL2, BCL6, and Ki67 in immunostaining test. However, there were no signs of irregular cells invasion to the epithelium. Considering the negative reaction of the cells to CD3, CD5, CD23, cyclin D1, CD21, CD10, and CK receptors, the overall diagnosis was diffuse large B cell type of malignant lymphoma. Laboratory tests provided no significant alteration in terms of CBC test components and blood protein electrophoresis, including albumin, Alpha, Beta, and Gamma.

Discussion

As a case report, a woman with resected right breast mass and diagnosed with breast mucosa-associated lymphoid tissue (MALT) lymphoma was introduced. The patient was also diagnosed with a contralateral breast mass two years later. To our knowledge, this is the first report of a case of breast MALT lymphoma with a contralateral diffused B-cell lymphoma, after first surgical excision and radiotherapy. Similar to our patient, the case described by Topalovski et al. (1999) suffered a contralateral breast MALT lymphoma recurrence two years after excisional treatment. Thus, it appeared that the reported case here was consistent with the hematogenous pattern of metastases for breast MALT lymphoma, considering the affected organs and tissues. However, histopathological evaluation revealed a diffuse B cell lymphoma on left breast. Furthermore, it is suggested that right breast is commonly affected by the development of MALT lymphoma, as detected in our patient.

Since its introduction by Isaacson, there has been a very few cases of mucosa-associated lymphoid tissue lymphomas; so that it represents only 5% of the all Non-Hodgkin lymphomas, which develops from specific immune cells including, T cells and B cells developing in lymphoid tissue structures. Although, the primary underlying etiology of the lymphomas, particularly in different organs (e.g. breast MALT lymphoma) is yet to be determined, it is known that immune system dysregulation and immunodeficiency are the culprits of lymphoma progress. In addition, MALT lymphomas are mainly believed to involve gastrointestinal tract tissue, while mucosa-associated lymphoid tissues are widely distributed along the alimentary tract, including Peyer patches, and vermiform appendix. Moreover, there is a relationship between them and chronic Helicobacter pylori infection. However, in extra-gastrointestinal cases, the persistence of chronic inflammatory reactions can lead to immune system dysfunction, autoimmunity, and further development of the lymphomas subsequent to Hashimoto's thyroiditis. Despite the fact that reported case developed breast MALT lymphoma in her 40s, non-Hodgkin lymphomas including MALT lymphoma are primarily developed during the 6th decade of life as recommended by the literature. With due attention to overall prevalence of the primary or secondary breast lymphomas that is extremely low, it is a challenging issue to deal with etiologic characteristics and risk factors of breast MALT lymphoma in patients. However, considering the hypothesis regarding the effect of the sex hormones on the development of the lymphomas in breast tissue, it is assumed that the age of the disease presentation might be in correlation with the sex hormones activity. However, the role of the sex hormones is still a topic of debate, following the controversial outcomes of the previous studies. On the other hand, simultaneous gastrointestinal tract involvement is a normal phenomenon in patients with breast MALT lymphoma, which also proves the probability of the secondary involvement of the breast tissue. However, the patient presented here had no manifestation of other organs’ involvement and the lymphoma was detected only in breast tissue either at first presentation or after recurrence.

In general, the disease mimics the constitutional and flu-like symptoms with rare cases of development of the lymphadenopathy. However, the mass palpation during the physical examination was the noteworthy finding before detailed workups. Similarly, the current case appeared in the clinic with a complaint of a mass on the right superolateral segment of the right breast. Furthermore, several imaging modalities were unable to provide an acceptable and reliable diagnosis of MALT.
lymphoma. Thus, our patient underwent ultrasonographic evaluation of the breast tissue, as the single imaging procedure. However, new studies have suggested positron emission topography (PET) scan to provide a promising advancement after diagnosis of the disease via biopsy to assess the distant metastasis.\textsuperscript{11,14}

Although, surgical excision of the mass and radiotherapy are the widely administered treatment techniques for breast MALT lymphoma, sometimes patients only receive radiotherapy as the sole treatment, which contributes to low relapse rate, particularly distant relapse.\textsuperscript{15} Based on this, the patient underwent surgical excision of the right breast mass and radiotherapy subsequently. Surprisingly, two years later she developed a mass on the left breast for which we were not able to establish an evident relationship between firstly presented MALT lymphoma and the second diffused B cell lymphoma. However, as previously mentioned, hormonal activity is capable of imposing lymphoma formation; therefore, it can be hypothesized that the two malignancy processes were mainly separate events. Still, the both might be induced by same underlying factors.

Unfortunately, our case had neglected the importance of mammographic screening and the first mass was detected during breast palpation. This is a common case for other women in the region that makes them vulnerable to late diagnosis and metastasis. Although, our report may emphasized on the role of the breast examination in prevention of catastrophic events, we are far from providing diagnostic approaches on breast MALT lymphoma, due to minimal case sizes and the need for further studies.

**Ethical Consideration**
The patient signed the written informed consent.

**Conflict of Interest**
The authors have none to declare.

**References**
The treatment of breast cancer is changing so much so that a recent JAMA 2019 editorial Breast Cancer Treatment did not even mention surgery or radiotherapy in the article. The management protocols change regularly making multidisciplinary management mandatory.

**Screening**

Screening protocols have helped to discover progressively smaller tumors, aided by the technical tools, such as tomosynthesis and more recently Artificial Intelligence. AI demonstrated better accuracy than experienced radiologists. There are several limiting factors at play in screening including age, cost, interval lesions and delivery of radiation. In prospect, focusing on high-risk population is obviously the solution with the liquid biopsies and young radiologists having to fundamentally rethink their procedures.

**Surgery**

Radical mastectomy with axillary dissection can no longer be considered the “gold standard”. Breast conservative surgery, oncoplastic repair, and fat transfers by lipofilling have completely changed the scene. Despite the scandals and anxieties associated with silicone prosthesis in the 80’s, Poly Implant Prosthesis (PIP) and more recently Anaplastic Large Cell Lymphoma (ALCL) and breast reconstruction are becoming more common, practiced most often with the prosthesis. Various autologous Latissimus dorsi flap procedures, TRAM, DIEP, Thigh SGAP have become more frequently used but need experienced surgeons in the microvascular anastomosis. These flaps are commonly associated with the prosthesis and/or fat transfers.

Robotic surgery, when available, is becoming popular by a single-port incision, limiting the size of the incision, which facilitates breast reconstruction through the same incision. The ultimate improvement will be the injection of a resorbable matrix in which the normal tissue of the patient will recolonize the texture. The follow-up process is still short and will need further validation.

Axillary dissection is progressively disappearing and the sentinel biopsy has generally replaced the classical axillary dissection, for the massive involvement. Absence of a valid method for determining the exact pathologic status of the axilla maintain the place of the information given by a surgical approach of the axilla, but recent pares of AMAROS and ACOSOG have demonstrated similar results of radiation compared to the completion of axillary dissection in positive sentinel node biopsy. Axillary dissection seems to be a late fight in the surgical process.

**Radiation therapy**

New equipment has dramatically improved post-operative radiation therapy. Cardiac and lung toxicity nearly vanished by the correct use of photons and electrons and the disappearance of the cobalt. Contouring the disease and the organ, coupling the treatment with breathing (VMAT), and IMRT are among the toxicity limiting improvements. Hypofractionation lessens the duration of the treatment duration and partial irradiation.

New techniques (CyberKnife, Proton, Hadron, Target) allow limited treatments as well as highly-focalized treatments on metastasis. Some countries are developing extensive expertise in localized treatments such as cryotherapy, with excellent results in localized diseases and metastasis.
**Biology**

Owing to the fact that certain specialties are on the verge of disappearance and the extreme outcome of multidisciplinary fields, biology is assuming a growing role, although its application is not yet completely known and its limits are not well explored. The TNM classification has given way to the molecular classification, but it must be recognized that apart from luminal A cancers and those on positive HER2, the other molecular subtypes pose more problems to the management than they solve.

Certainly, the commercially available molecular signatures on post-operative materials, or on a core biopsy, have a prognostic value and for some of them a predictive value. The cost of these signatures is still high and only available to patients with a good insurance coverage. Some countries are still reluctant to cover these tests despite their “cost-saving” value. The reduction of a number of unnecessary chemotherapies supports the cost-saving nature of these signatures.

Is it the time to say that it is too late for these signatures when the NGS (New Generation Sequencing) on the tumor and on liquid biopsies become commercially available? We will have to learn to justify our knowledge differently and soon.

While estrogen and progesterone receptors remain relevant, undoubtedly all physicians consider a tumor with 10% estrogen receptors as hormone positive. Furthermore, the tumor with the expression of both estrogen and progesterone receptors as high as 100% will also have the same name. Obviously, it is simplistic to consider the estrogen receptor as an indicator of prognosis and progesterone receptor as a predictive marker. It explains for example why we underestimate some "good and favorable tumors" that are recurring and follow some of the worst triple-negative tumors for the decades.

The tissue sampling of the recurrences or metastases has also demonstrated that tumors "evolve" under the effect of the treatment and/or over time, with a clonal evolution, although it is difficult to detect the source and time. Based on these recurrences, we currently do "in cascade" as evolution in their new location, new markers e.g. androgen receptors, Pi3K kinase, BRCA 1-2 mutation, deficiency in DPD, etc. depending on our therapeutic plan for a given patient.

Therefore, we face the same choices in the management of each new single patient. Should we continue to start the treatment according to the TNM staging and the molecular classification while waiting patiently, the eventual tumor recurrence and/or metastasis? These, once in two, will be discovered in the follow-up intervals. The cost of monitoring, consultations, transportation, and biological and radiological examinations is poorly assessed. The only thing we know for certain is that it reassures our patients, but it is required that visits be scheduled with time lapses to protect them from anguish. It seems that it would not scientifically sense.

The alternative would be to propose to each individual patient a complete assessment of the tumor cells in circulation (and/or DNA or RNA) in search of specific markers. It means that in the current state of our knowledge we would search for the most suitable molecules in circulation and monitor the evolution of the same marker in follow-up sessions by administering simple blood tests. The procedures are currently feasible in the USA (Foundation one, under the control of NYC Memorial), although they still cost thousands of dollars which is not affordable by most patients, hospitals, and insurance companies.

Accordingly, on the one hand, it is an already answered question because these tests exist and, we, as physicians, all want to do them for our close family members and loved ones, in order to offer them the best and the most adapted treatments. On the other hand, if all the unnecessary examinations of CA15-3, abdominopelvic X-ray, and chest and repeated blood tests, which have gradually given way to the more complex CT scans and recently PET scan, and above all the enormous physical examination (that is not reliable enough) will be taken to account, we will realize that the cost is not lower than the newer personal tests.

Economic studies are difficult to carry out in the field but they will be necessary because in the future we will have to be able to decide on the best treatments for our patients, without being permanently waiting for authorization from Ministry of Health for new drugs or, worst, receive temporary authorization expecting a hypothetic reimbursement.

Clearly, the main question is how we can manage this mass of genetic information. Of course, nobody has answered these questions and a new generation of physicians and scientists will have to answer it. It is easy to see how AI (Artificial Intelligence) is now an important field. There are AI reports in breast imaging for which our fellows in breast radiology should expect painful revisions. Our pathologists are also particularly exposed to these newer technologies and concepts in their traditional morphological activity. While the majority of their traditional activities are already supported by biological laboratories, historical conflicts between pathologists and biologists will be resolved in these "diagnostic units or platforms".

The resistance of the physicians against this new medicine can be understood, but it would not be so long before the patients reproach us for not having made the examinations in agreement with scientific findings at the time of the treatment. We would then be legally responsible for potential health hazards.

**Conflict of Interest**

The author has none to declare.

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New paradigm in Breast Cancer management


In terms of technical improvement, oncoplasty was performed through a collaboration between oncologic and plastic surgeons in the mid-1990s. However, at that time, oncoplasty was rather a novel advent than a common mainstream. In fact, depending on tumor’s site and breast topology, oncoplasty differed from one case to another and one center to another depending on the personal experience of the plastic surgeons. Gradually, the techniques were improved considerably, so oncoplasty was transformed from a concept to an approach and then to a group of standard techniques.

Initially, the "oncoplasty" term was introduced in medical terminology through the first half of the 1990s, and its main purpose was the treatment of breast cancer as R0 resection in addition to preserving a normal and symmetrical breasts appearance. Soon after, the techniques are extensively developed in the way that within 15 years the techniques are recognized as a standard modality in the surgical treatment of breast cancer according to the favorable cosmetic outcome and as a result less psychologic consequences.

In terms of technical improvement, oncoplasty was performed through a collaboration between oncologic and plastic surgeons in the mid-1990s. However, at that time, oncoplasty was rather a novel advent than a common mainstream. In fact, depending on tumor’s site and breast topology, oncoplasty differed from one case to another and one center to another depending on the personal experience of the plastic surgeons. Gradually, the techniques were improved considerably, so oncoplasty was transformed from a concept to an approach and then to a group of standard techniques. Within the past two decades, there has been a six-fold increase in the development of oncoplastic breast surgery techniques while the complications have been markedly decreased.

In Europe, the breast surgeons gently overtook and the role of plastic surgeons diminished. Then, breast cancer surgery fellowship programs have been developed in France, Italy and England to train competent surgeons to do almost all of breast cancer surgeries, including oncoplastic and reconstructive procedures.

In contrast, in the North America, there is still a prominent role of plastic surgeons, especially in reconstructive breast surgery. Thus, there is not a general and independent breast cancer surgery fellowship covering all oncoplastic and reconstructive breast surgeries in this part of the world though it has been established in some limited hospitals based on the annual ACGME (Accreditation Council for Graduate Medical Education) accreditation under SSO (Society of Surgical Oncology) supervision. Therefore, there are two different approaches to do oncoplastic and reconstructive breast surgery; performing the OBS and reconstructive surgery by an independent and fully trained breast surgeon or by a collaborative team consisting of oncologic and plastic surgeons. These following two options are being followed in numerous advanced cancer centers all over the world.

A few studies have evaluated oncoplasty applying in accordance with different fields, but there are no precise comparative results between plastic surgeons and breast surgeons in managing breast cancer yet. We discuss the subject according to the type of surgery, whether it is a reconstruction or oncoplastic
surgery. Typically, OBS is classified at two separate levels; Level I OBS, which is employed for breasts of small to medium size, when it would be predicted to excise less than 20 percent of the breast tissue. It contains resection of tumor and repairing the consequent defect by applying tissue displacement. Level I is appropriate for small tumors and following the procedure, the breast and nipple-areola complex position usually remains unchanged so that the breast shape would be very identical to the preoperative or a little smaller in size.

Table 1. Different types of oncoplastic and reconstructive surgery

<table>
<thead>
<tr>
<th>Type of surgery</th>
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<tr>
<td>Oncoplastic breast surgery</td>
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<tr>
<td>Level I</td>
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<tr>
<td>Level II</td>
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<tr>
<td>Breast Reconstruction</td>
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<tr>
<td>Tissue reconstruction</td>
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<tr>
<td>Free flaps</td>
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<td>Pedicled flaps</td>
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<td>Implant reconstruction</td>
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<tr>
<td>One stage</td>
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<tr>
<td>Two stage</td>
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<td>Mixed tissue and implant</td>
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Level II of oncoplastic surgery is applied in massive lumpectomy with skin resection in patients having large and/or pendulous breast, which need breast manipulation and mobilization of glandular tissues. At this level, oncoplasty is accompanied by larger incisions and noticeable asymmetry. In order to establish the symmetry, the opposite breast is commonly operated as a reductive mammoplasty, so it can be proper for patients who would like to reduce the volume of their large breasts during oncologic surgery.

Moreover, there are different techniques for breast reconstruction that mainly organize in three types: implant/expander, tissue, and the mixed reconstruction (table 1). Tissue reconstruction includes various techniques such as TRAM (transverse rectus abdominis myocutaneous), LD (Latissimus Dorsi) and DIEP (Deep Inferior Epigastric Perforators). TRAM and LD - also known as pedicled flap - are familiar and more commonly applied, but DIEP has been introduced in the recent two decades and replaced the TRAM flap in many situations.

**Oncoplasty**

In classic oncoplasty as displacement-replacement, the breast surgeons have gained valuable experiences that should be well used in learning and scoping new methods. The choice of technique widely depends on the surgeon's judgment of tumor characteristics, breast shape and patient's desire. In addition, breast cancer management is not limited to breast surgery and some other important considerations such as perioperative tasks, axillary staging, post-operative radiation, and systemic therapies must be managed. Indeed, the breast surgeons must have a leading role in implementation or consultation.

It seems that level I oncoplastic surgery techniques can be simply applied by the breast surgeons, but in level II that require challenging repairing or performing therapeutic mammoplasty, the role of the plastic surgeons in cooperation with breast surgeons would be more obvious.

Even in performing level II oncoplastic surgery, there are some potential advantages and disadvantages for each approach. The following topics can be considered as the advantages of more efficient and less confusing single surgeon (breast surgeon) approach:

- Better physician-patient communication,
- Easier time management for scheduling the operations,
- Decreasing the cost of surgical intervention,
- Clear responsibility of the surgeon for perioperative care and potential complications,
- Less ambiguity in case of confronting with a medico-legal problem.

On the other hand, some alternative advantages for team working (Oncologic and Plastic surgeon) approach are:

- Better planning for cosmetic considerations in the same breast as well as the contralateral breast,
- More profitable use of the operating agenda, and appropriateness for more extensive tumor excisions with safe margins.

Results from the American Society of Breast Surgeons Oncoplastic Surgery Committee 2017 Survey demonstrated widespread interest in doing oncoplastic surgery by non-plastic surgeons that revealed a safe oncoplastic surgery with its improved oncologic and aesthetic results would become available to the U.S. breast surgeon and ultimately to the patients. The article from Boston also confirmed that doing oncoplastic surgery by two groups of surgeons does not increase the risk of morbidity in breast cancer patients.

**Reconstruction**

Reconstructions are generally followed after different types of total mastectomy or poor cosmetic results of partial mastectomies. They are recognized as major and time-consuming surgeries, especially when performed as immediate breast reconstruction (IBR) and flap reconstruction. Nevertheless, IBR is a refined decision from the oncologic point of view though its indications are increasing recently. Nowadays, thanks to the effective systemic therapies, more patients are eligible to receive immediate breast reconstruction. On the other hand, decreasing the stage of the disease at the time of diagnosis has reduced the need for post-mastectomy radiotherapy, and it makes IBR more feasible.

For breast reconstruction planning, the surgeon
should consider that some essential prognostic factors could overwhelm the outcome of the reconstruction, e.g., the need for further radiation therapy, previous history of radiotherapy, the timing of the treatment, risk of recurrence, and the necessity of additional systemic treatments. On the other hand, reconstruction needs a holistic cosmetic perception of the techniques and outcomes in order to choose the best approach for each patient.

Although the breast surgeons can simply do the less complex surgeries like implant-based breast reconstruction or pedicled tissue flaps, the presence of a skillful plastic surgeon is crucial in free flap reconstructions. As mentioned earlier, apart from the methods, reconstruction is a large and time consuming surgery that in case of tissue flaps like DIEP, would be remarkably longer. Therefore, it seems better to perform the operations through an experienced team consisting of both oncologic and plastic surgeons, especially for the free flaps and more complex redo reconstructions. Moreover, it is crucial for a surgeon who does the breast reconstruction to be familiar with the different techniques for reconstruction and their best indications, to know the oncological considerations and surveillance of the patients.

In conclusion, it is important to consider that beyond the dualism of Plastic- Breast surgeon, a competent team of physicians who embrace both technical and aesthetic aspects, must play a leadership role in the breast cancer management. Any active surgeon in breast cancer management must be mastered in the doctrine of oncoplastic surgery and be able to make a choice among relevant techniques to achieve an excellent harmony between minimal breast aesthetic impairment and maximal oncological outcomes. Indeed, in the breast cancer surgery fellowship and the breast surgery course in the plastic surgery curriculum, the precise oncologic aspects of breast cancer management, team working, and multidisciplinary approach should be overemphasized before going through details of the sophisticated surgical techniques.

**Conflict of Interest**
None

**References**
ARTICLE INFO

Background: The effect of exogenous sex hormones on the risk of breast cancer has been shown for some compounds but for other compounds it is under detailed investigation. This study, as part of a quadruple of articles reviewing the consequences of using sex hormones in women with various breast conditions, discusses the prescription of non-oral hormonal contraceptives and miscellaneous exogenous steroid hormones.

Method: We browsed international clinical guidelines and carried out a comprehensive search in the literature by relevant keywords in order to extract data about the effects of hormone-releasing intrauterine devices, injectable depot-medroxyprogesterone acetate, contraceptive implants, cyproterone acetate, finasteride, and spironolactone on the breast.

Results: Studies are scarce for most of these compounds, and information comes mainly from researches about oral contraceptives and hormone replacement therapy. Although none is recommended for use in patients with breast cancer, administration in benign disorders of the breast, women with positive family history of breast cancer and general women is acceptable with minor risks.

Conclusions: Most non-oral hormonal methods of contraception and miscellaneous available hormone compounds prescribed for the treatment of hormonal disorders are safe for temporary use, except for women with breast cancer. For them, analogues of gonadotropin-releasing hormones may be considered a safe hormonal prescription.

Introduction

Because of the association of breast cancer with female sex hormones, prescribing hormonal combinations in women especially in those harboring a disorder in the breast usually goes with hesitation and uncertainty. In order to answer some questions that physicians have in this regard, four sequential articles have been written discussing the prescription of different hormonal compounds in various conditions regarding the breasts. The first and second parts scrutinized the effects of hormone replacement therapy (HRT) and oral contraceptive pills (OCP) on the breasts, respectively. In this third article, our approach is to non-oral hormonal contraceptives and to hormones that are usually prescribed in various hormone-related disorders for non-HRT and non-contraceptive purposes. These have been rarely addressed worldwide and hardly regarded to have initiated malignant changes in the breast. Meanwhile, practitioners who specialize on breast diseases are usually consulted about them by their colleagues. Therefore, in this section, we will discuss the effects of levonorgestrel-releasing IUDs (LNG-IUDs), injectable depot-medroxyprogesterone acetate, contraceptive implants, cyproterone acetate, finasteride, and spironolactone on the breast.

Key words: Breast Cancer, Finasteride, Implant, Intrauterine device, Medroxyprogesterone, Spironolactone.

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acetate (DMPA), progestrone implants, cyproterone acetate, finasteride and spironolactone.

Methods
We aimed to find valid data about the effects of miscellaneous hormones on the breasts. Because of interesting relevant literature about the effects on male breasts, we also searched and entered related data. We carried out a comprehensive search in Google Scholar and PubMed by using combinations of these keywords: “benign breast”, “breast cancer”, “conjugated estrogen”, cyproterone, “ethinyl estradiol”, etonogestrel, fibroadenoma, fibrocystic, finasteride, levonorgestrel, “male breast”, medroxyprogesterone, and “progesterone implant”. We extracted data from all pertinent works including cohort studies, clinical trials and reviews. We also browsed valid clinical guidelines including the International Agency for Research on Cancer (IARC), Monographs on the Evaluation of Carcinogenic Risks to Humans, the guidelines of the Society of Family Planning (SFP), the US Medical Eligibility Criteria for Contraceptive Use by the Centers for Disease Control and Prevention (CDC), and the US Selected Practice Recommendations for Contraceptive Use. All pertinent information was extracted from these references.

Results and Discussion

Depot-medroxyprogesterone acetate
The approval of the injectable form of depot-medroxyprogesterone acetate (DMPA) as a contraceptive method has taken a long gradual course from its synthesis in 1963 to its use in more than 100 countries now. This lag was partly due to the probability of increasing the risk of breast cancer, which is still a matter of debate. However, while some studies have shown an approximate 2.2-fold increased risk of breast cancer due to DMPA9,10,11, this association was shown to stop after discontinuation of the hormone, or not to existo.12,13,14 Thus, in addition to the general population, contraception using DMPA is permitted in women with benign breast disorders and even in those with positive family history (FH) of breast cancer. Nevertheless, its use is contraindicated in patients with breast cancer, and considering the theoretical hazards, in survivors of the disease.15,16

Progesterone Releasing Intramuraer Devices
Intrauterine devices (IUDs) are used for long-acting reversible contraception (LARC). Some types of commonly-used IUDs are those that release levonorgestrel, or LNG-IUDs.15,16 Despite the hormonal basis, levonorgestrel reaches very low levels in the serum of women who use these IUDs.17

Several large-scale studies have assessed the risk of breast cancer in women who use LNG-IUDs. They did not show an increased risk18,21, except for one research derived from a Finnish registry which revealed an unexpectedly higher risk.22 Therefore, according to SFP and CDC recommendations, LNG-IUDs should not be offered to women with present or previous breast cancer15,17, with the probable exception of breast cancer survivors on tamoxifen, where LNG- IUDs might counteract proliferative effects of tamoxifen on the endometrium.15,16,25,26 Use of these devices for contraception in women with benign diseases of the breasts and in patients with positive FH of breast cancer is recommended.

Contraceptive implants
One of the LARC methods consists of implanting flexible rods containing and gradually releasing progestins. These are easily planted under the skin of the arm or removed whenever needed. The etonogestrel implant is the most widely used method.15,16,26,27

Studies investigating the association of contraceptive implants with breast cancer risk are scarce. One study with a small sample size derived no increased risk14, while an ethnic-based research showed a significant rise in the risk of breast cancer in users of progestrone implants.12 Data of both studies should be considered with caution. Meanwhile, implants are not recommended as a method of contraception in breast cancer patients or survivors, while their use in benign breast disorders and women with positive FH is allowed.15,16

Non-contraceptive, non-HRT exogenous oral estrogen and progesterone compounds
Different formulations containing synthetic estrogens or progesterone, although mostly used as OCPs or for HRT, are sometimes used for the treatment of hormone-related conditions such as abnormal uterine bleeding, menstrual irregularity, endometriosis, or hirsutism. However, the effects on the risk of breast cancer and on benign breast diseases have not been studied specifically for this purpose. For example, medroxyprogesterone in the oral form as tablets, megestrol acetate and dydrogesterone are commonly used for the treatment of menstrual disorders. Megestrol acetate has been studied for this purpose in breast cancer survivors, and also as an appetite stimulator for reversing cachexia in patients with metastatic breast cancer. These works generally yielded positive results, but the effects on the prognosis of cancer have not been investigated.28 The effects of dienogest on the breast tissue when consumed for the treatment of endometriosis have been explored in a study. All patients had significant decrease of breast size and improvement of mastopathic changes.35

Suggestions for the use of progesterone and estrogen compounds for the treatment of the mentioned gynecologic disorders in women with different breast conditions can be deducted from recommendations for OCPs as discussed in the first article of these series and HRT as addressed in the second article. They are demonstrated in table 1.

Finasteride is an anti-androgen which functions by counteracting the action of 5α-reductase. It is mostly used in the treatment of prostatic hyperplasia, androgenic alopecia in women, and sometimes in hirsutism. While increased risk of male breast cancer has been attributed to finasteride in previous studies, this has not been confirmed in two recent works. Up to the present time, specific contraindication in women with breast disorders have not been defined.

Cyproterone acetate
Cyproterone acetate is a synthetic derivative of hydroxyprogesterone, which has a relatively high antiandrogenic as well as some antigonadotropic effects. It is usually used as part of the management of menstrual disorders and hirsutism, or contraception. It has also been used in prostate cancer. One of its minor side effects is breast discomfort.

While drugs with estrogenic or progestrionic properties are sometimes administered in intractable advanced metastatic breast cancer in women, cyproterone acetate has not proved effective in this setting. On the other hand, two studies have demonstrated beneficial effects for this compound in advanced cases of male breast cancer.

Cyproterone acetate is occasionally administered alone for the management of menstrual issues or hirsutism, but probable adverse effects on breast cancer risk, and also on benign breast disorders have not been studied in that setting. Therefore, the same recommendations for progesterone-only oral contraceptive pills can be followed for this medicine too.

Spironolactone
Spironolactone is an aldosterone antagonist with anti-androgenic effects that is commonly used for the treatment of hirsutism. Although its potential for increasing male or female breast cancer has been put forward in earlier studies because of some case reports or series, the association is not confirmed by other works. Until now, specific contraindication in women with breast disorders have not been defined.

Gonadotropin-releasing hormone Analogues
Analogues of gonadotropin-releasing hormone (GnRH) bind competitively to central GnRH receptors in the pituitary gland. They are among the pharmacological treatments for the treatment of menorrhagia and the premenstrual syndrome.

One of the common usages of this group of drugs is in the treatment of hormone receptor-positive premenopausal breast cancer, where they are administered in conjunction with tamoxifen or aromatase inhibitors, or for the preservation of ovarian function at the time of chemotherapy.

Therefore, this category of compounds seems an alternative for the treatment of some menstrual disorders when breast cancer is the concern.

In conclusion, most non-oral hormonal methods of contraception and other available hormone compounds prescribed for the treatment of hormonal disorders are safe for temporary use, except for women with breast cancer, for whom analogues of gonadotropin-releasing hormone may be considered a safe hormonal prescription.

Conflict of Interest
None.

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Seminarz in Oncology; 1986.
Background: There are several therapeutic options available for breast cancer treatment, now incorporating innovative targeted molecular therapies. Metastatic breast cancer is usually treated with chemotherapy and/or hormonotherapy. Metastatic breast cancer is usually treated with chemotherapy and/or hormonotherapy. Surgery has not been shown to improve survival. Adjuvant radiotherapy (RT) has been proven to be effective in the treatment of locally advanced breast cancer, reducing locoregional recurrence. The optimal treatment of internal mammary lymph nodes (IMN) metastases remains controversial.

Case presentation: A 48-year-old woman was diagnosed with invasive breast cancer with ipsilateral metastases to axillary lymph nodes and a contralateral IMN metastasis. This case was presented twice during the tumor board sessions of the Surgical Oncology Service at the Centre hospitalier de l’Université de Montréal (CHUM), Montréal, Canada.

Conclusion: Internal mammary chain dissection should be discussed in tumor board sessions on a case-by-case basis. There are no strong guidelines on the management of IMN metastasis in breast cancer, but there is growing evidence that these women should be treated with curative intent.

Question: Does the internal mammary chain (IMC) dissection could be used as a treatment approach in breast cancer with IMC metastasis?

Key words: Breast cancer, internal mammary node metastasis, lymph nodes dissection, radiotherapy, tumor board.

Introduction
Breast cancer affects 1 woman in 8 during their lifetime. In the last two decades, major advances have been achieved in breast cancer diagnosis and treatment, reducing mortality by 20%. Amongst others, the recent advent of innovative targeted molecular therapies, such as PARP and CDK 4/6 inhibitors, seems promising. Metastatic breast cancer is usually treated with chemotherapy and/or hormonal therapy if the hormone-dependent disease is present: surgery has not been shown to improve survival in stage IV disease. On the other hand, adjuvant radiotherapy (RT) has been proven to be effective in the treatment of locally advanced breast cancer, reducing locoregional recurrence rates and improving survival as well.

The majority of breast cancers (> 90%) demonstrate primary drainage to axillary lymph nodes. Their crucial contribution to staging, treatment and prognosis is well established and is widely accepted nowadays. The second group of lymph nodes, the internal mammary nodes (IMN), receive a significant proportion of primary drainage from breast cancer.
Case presentation

A 48-year-old premenopausal woman without notable medical, surgical and family history was referred to our institution with a six-centimeter mass located in the lower outer quadrant of the right breast. A core needle biopsy of the mass and axillary lymph node confirmed a grade 2 invasive ductal carcinoma with axillary metastases, with hormone-positive receptors and HER-negative status. A breast magnetic resonance imaging (MRI) demonstrated a neoplastic cutaneous extension with suspected pectoral involvement, suspicious level I, II and III right axillary lymph nodes, two suspicious right IMN with a diameter of 5 mm and one left IMN measuring 9 mm. The neoplastic cutaneous invasion was demonstrated by thickened skin adjacent to the tumor and accompanied by a cutaneous retraction zone. A positron emission tomography (PET scan) was performed, confirming hypermetabolism of the breast mass, right axillary nodes and left IMN, with standardized uptake values (SUV) of 12, 6 and 2.8, respectively. The pathology report of fine needle biopsy of left IMN revealed metastatic cells from breast cancer. The extension was assessed with thoracic, abdominopelvic and bone scans, and showed no distant metastasis except for the left IMN. (Figure 1)

The genetic work-up was negative. Chemotherapy with dose-dense AC (doxorubicin/cyclophosphamide) was initiated, followed by the first discussion at our institutional tumor board meeting. By mutual agreement, despite a stage IV breast cancer, given the limited disease to regional lymph nodes, curative treatment was continued. After a total of 5 months, neoadjuvant chemotherapy composed of dose-dense AC followed by weekly paclitaxel was completed with an excellent clinical and radiological response and complete normalization of the left IMN disease. After a second discussion, surgical oncology, thoracic surgery and plastic surgery combined their technical skills to perform a right modified radical mastectomy with partial excision of the pectoralis major muscle, a left internal mammary chain (IMC) dissection, and a right-breast immediate reconstruction with a latissimus dorsi flap for defect closure and reconstruction. The thoracoscopic approach was used for the left IMN removal which the patient clearly favored over watchful waiting or post-operative radiotherapy alone. Surgery was well tolerated without complications. Final pathology showed 5 out of 12 metastatic axillary lymph nodes, but a left IMC free of disease, corresponding to a pathologic stage IIIA (ypT1cN2a) according to latest AJCC
classification. Radiotherapy covering the right chest wall, right axillary and supraclavicular lymph nodes as well as both IMCs was initiated a few weeks after surgery. Since the breast cancer tumor was hormone receptor positive and the patient was premenopausal with a high residual burden of disease, Zoladex and Letrozole were started. Six months after surgery, follow-up clinical examination, as well as PET and thoracic scans, revealed no evidence of locoregional or distant recurrence. Bilateral breast MRI and mammograms are scheduled. (Figure 2)

Question
This case was presented at the weekly breast cancer tumor board session at the Centre hospitalier de l’Université de Montréal, Canada, gathering experts in the field, such as surgical oncologists, medical oncologists, radiation oncologists, radiologists and pathologists. Two main questions were debated. First, should we treat this patient with curative or palliative intent, given the contralateral positive IMN? Second, should we offer IMN dissection as an option to this woman after neoadjuvant chemotherapy?

Discussion
According to NCCN recommendations, inoperable, non-inflammatory, locally advanced breast cancer at presentation should be treated with neoadjuvant anthracycline-based chemotherapy, with or without a taxane. A monoclonal antibody such as trastuzumab and possibly pertuzumab for locally advanced breast cancer that is HER2-positive should be added to the preoperative systemic regimen. Surgical options following a clinical response to initial chemotherapy include 1) modified radical mastectomy or 2) partial mastectomy and level I/II axillary dissection. NCCN guidelines state that these patients, regardless of chosen local therapy, have significant local recurrence risks that warrant the use of adjuvant RT. Standard therapy includes RT to chest wall or breast and supraclavicular nodes. Based upon lower-level evidence (category 2B), there is an NCCN consensus that IMN radiation should be considered even without IMN metastasis. IMN should be included in the RT field if positive for cancer. Endocrine therapy consists of adjuvant therapy in the event of hormone-receptor positive disease.

Patients with metastatic breast cancer are unlikely to be cured of their disease and complete remissions are rare with current therapies. However, with advances in the multimodal treatment of breast cancer, patients can hope to live for many years nowadays. Although in many types of cancer removing the primary tumor provides survival benefits even in the presence of distant metastases, for metastatic breast cancer, most oncologists agree that aggressive local therapy is futile in terms of survival. On the other hand, there is increasing evidence that women with a solitary metastasis, or a few metastases at a single organ site, could live longer following surgical control of the metastatic disease. A recent study showed a durable response to therapy with a significant survival benefit in metastatic breast cancer patients treated with aggressive surgical removal of oligometastases. This subgroup of patients shared some important characteristics, such as an excellent response to systemic therapy before surgery and adequate locoregional treatment of breast and lymph nodes, in order to attain the status of no evidence of disease. HER2 and hormone-receptor positivity were associated with an improvement in overall survival.

Figure 2. PET Scan After Treatment, Showing the Excellent Radiological and Surgical Response.
and progression-free survival, respectively. These findings could potentially guide clinicians in their selection of patients for this novel approach incorporating curative metastasectomy.

After three randomized clinical trials failed to show any benefit in terms of overall survival between Halsted or extended mastectomy and radical or modified radical mastectomy while incurring significant operative morbidity, IMN dissection was abandoned. It is mandatory to note that only a small percentage of patients in those studies had positive IMN. Moreover, the diagnostic and therapeutic management of breast cancer patients at that time were different from the current management of the disease. A few retrospective studies tried to demonstrate OS and RFS benefits from IMN dissection, but these were underpowered. Following these publications, the interest of clinicians for IMN in breast cancer treatment had waned, and this issue was almost ignored for a few years. IMNs have regained popularity as a result of the development and increasing use of lymphoscintigraphy and the demonstration of the importance of locoregional control on long-term survival, among others. As a consequence of renewed interest, there has since been a small increase in studies on IMN in the early 2000s with ongoing interest. Literature has since demonstrated that elective biopsy of internal mammary chain sentinel nodes (IMCSn) affects cancer stage, prognosis, and overall management strategy. In the same vein, a recent study assessed the effect of IMCSn biopsy on OS and RFS. It showed that lower survival of patients with IMN metastases was attributable to distant metastasis. Predictive factors were suggested to determine who could be spared the possible RT side effects and who could benefit from this treatment modality. Recommendations from this group are to perform IMCSn biopsy for patients younger than 70 years old with a breast tumor larger than 1.5 cm. In their hands, the procedure was shown to be safe, with a low rate of complications. However, despite great advances toward uncovering the best indications for IMN biopsy and surgical resection, controversy still resides in that no modern clinical trials are assessing OS and RFS benefits from IMN dissection in patients with proven preoperative IMN metastases, without the distant disease.

On the other hand, recent studies demonstrated encouraging results on OS, RFS and distant metastasis-free survival of breast cancer patients with IMN metastasis treated with adjuvant RT after 10 years of follow-up. Nonetheless, concerns have been raised by multiple authors regarding long-term morbidity resulting from RT, such as cardiac toxicity and pulmonary fibrosis. There is no minimum threshold for the risk of cardiotoxicity with left-sided IMN radiation with the probability of major coronary events increasing proportionally with the mean dose to the heart. In our institution, radiation oncologists use a novel RT technique, namely helical tomotherapy (HT), in left-sided breast cancer or when IMN incorporation in the radiotherapy field is required. HT enables excellent conformity of dose distribution with treatment delivery from 360 degrees around the patient with coverage of complex zones while providing maximal noble organs sparing.

Breast cancer patients with IMN involvement should all be discussed at tumor board sessions on a case-by-case basis because there are no strong guidelines in current literature assessing IMN metastasis management. Patient’s age and comorbidities, molecular subtype and risk of distant micrometastases are all but a few examples of factors that we think should be included in the pro- and con discussions. Each proposed treatment should be evaluated according to expected patient benefit weighted against potential complications. Recent studies pave the way to prospective trials assessing predictors that would tip the scale towards choosing a more aggressive multimodal treatment, such as extended surgery to IMN.

For this patient with contralateral IMN metastasis, tumor board experts in the CHUM suggested IMN dissection during mastectomy, despite stage IV breast cancer. Arguments raised in favor of surgery were the lack of clear guidelines, age and overall health of the patient, limited disease to lymph nodes, luminal A molecular subtype, thoracoscopic minimally-invasive surgical approach, and patient’s concern about residual disease. Longer follow-up with serial and close imaging will be essential for this patient. At last, follow up 6 months after surgery, the patient has no locoregional or distant cancer recurrence.

Ethical Consideration
The ethics committee from CHUM Hospital was consulted and it was suggested that written or verbal consent be obtained. Verbal consent was obtained from the patient whose case inspired the discussion.

Conflicts of interest
The authors have no conflicts of interest to disclose.

References


ABSTRACT

Background: To determine the relationship between color and spectral Doppler features of breast cancers and their biomarkers.

Methods: From January 2017 to January 2018, 43 patients with breast cancer were enrolled. Age, the existence of color flow in the Doppler ultrasound, color flow pattern, tumor size, and immunohistochemistry (IHC) subtypes were recorded.

Results: Among 43 breast cancer patients, IHC profiles showed that 36 patients were estrogen receptor (ER) positive, 30 patients were progesterone receptor (PR) positive, and 12 patients were human epidermal growth factor receptor 2 (Her-2) positive. The prevalence of biomarker groups in this study were as follows: luminal A, 21 patients (48.83%); luminal B, 15 (34.88%); Her-2 amplifiers, 2 (4.65%); and triple negative, 5 (11.62%). Thirty-seven patients (86.04%) with malignant masses had detectable flow and six patients (13.95%) had no detectable flow. The ER-positive and PR-positive breast cancers had the highest vascular presence rate in color Doppler ultrasound, but it was not statistically significant. Maximum vessel diameter in the difference biomarker groups and Doppler color patterns with various biomarkers showed no significant differences.

Conclusion: Based on the results of this article, we could not predict the breast cancer biomarker groups using available Color Doppler features and indexes, so pathology with IHC is still required.

Introduction

Breast cancer is the main cause of cancer-related deaths in women worldwide and it has a diverse heterogeneous natural history with variable responses to different treatments.¹

Breast cancer is a highly heterogeneous disease with a wide variety of clinical presentations and behavior, which cause a range of responses to treatment and different prognosis.²³⁴ Breast cancer is different on a molecular level and traditional histological classification has limitations. Thus, new molecular classifications have been identified such as luminal-A, luminal-B, human epidermal growth factor receptor 2 (Her-2) amplified, and triple-negative.⁵ Current management of breast cancer has changed as molecular biology continues to evolve, and targeted therapies based on the genetic, hormonal, or immunohistochemical (IHC) subtypes of breast cancer are being used. Thus, determining IHC subtypes has great value.⁶ Clinically, luminal-A is the most prevalent subtype and Her-2 positive patients generally show excellent clinical outcomes when they receive an effective targeted therapy.
Several studies have investigated different imaging modalities to differentiate between these biomarker groups such as mammography, magnetic resonance imaging (MRI), and positron emission tomography (PET). Researchers have also extensively used gray scale ultrasound (US) to compare between receptor-positive and triple-negative tumors. Thus, the relationship between the IHC panel of breast cancers and imaging features is important and promising.

We aimed to determine the relationship between color Doppler images of breast cancer and the molecular subtypes.

![Figure 1. A 37-year-old woman with extremely dense breast tissue and an invasive ductal carcinoma in her right breast.](image)

**Methods**

The study protocol was approved by the ethics committee of Tehran University of Medical Science. Written informed consent was obtained from all patients before undergoing any procedures.

The lesions first were imaged with gray-scale sonography to evaluate their sonographic characteristics and to ascertain their Breast Imaging Reporting and Data System (BIRADS) score and the tumor diameter. Next, color and spectral Doppler sonography was performed on the suspicious (BIRADS 4 or 5) breast masses based on their grayscale characteristics with a 9- to 12-MHz linear array transducer of an Esaote My Lab Ultrasound machine. All the sonography procedures were performed by a single radiologist who was experienced in breast imaging and who is a faculty member at the university. Optimized parameters were set at a pulse repetition frequency of 750 to 1000 Hz and a low wall pass filter was used to detect low-velocity or low-volume blood flow. The color box included the lesion and a margin of normal...
neighboring breast tissue with slow scanning without probe pressure in the transverse plane. The color gain was adjusted to a level for the detection of small tumor vessels without background noise.

The existence of flow was considered to be a positive color Doppler test if at least one vessel was depicted inside the lesion or as a feeder beside it, and it showed an arterial flow pattern in simultaneous-pulsed Doppler imaging. If tumoral vascularization was detected, then a more thorough color Doppler study was performed. The cross-sectional size of the masses and the average vessel diameter were recorded. Spectral waveforms for up to three different vessels were measured and the resistive index (RI) was calculated. The calculations were performed by placing the machine's cursor on the flow obtained and selecting the best cycle from the Doppler waveform. The highest RI value obtained was used for analysis (Figure 1).

The color Doppler flow pattern in the patients was subjectively divided into four groups as follows:

- **Group 1**: no detectable flow (Fig. 2a);
- **Group 2**: a feeder vessel (Fig. 2b);
- **Group 3**: capsular peripheral flow (Fig. 2c); and
- **Group 4**: vessels in nearly the entire part of the mass (Fig. 2d).

All the data, as mentioned above, were recorded before the results for the biopsies on the lesions were gathered. These patients were then followed, if they had accessible malignant pathology after biopsy and were under surgical treatment with IHC results, they kept in the study. IHC results, which were performed on surgical samples, were all obtained in the same pathology department.

We excluded patients who: 1) did not wish to participate in the study; 2) had benign pathology results after biopsy; 3) were transferred to another hospital and we did not have access to their pathology results; 4) underwent neoadjuvant chemotherapy before surgery; 5) had multifocal or multi-centric masses; 6) had a mass larger than 5 cm in diameter (previous studies showed that there might be a difference between detecting vessels in lesions based on their size, so we exclude masses larger than 50 mm in diameter); 7) had cancer with malignant pathology other than invasive ductal; 8) did not have sufficient sufficient clinicopathologic data, and 9) had a non-mass appearance on

![Figure 2. Different patterns of color Doppler flow were seen among the patients in this study.](image)
sonography. Ultimately, 43 patients with cancer were enrolled in this study.

Estrogen (ER), progesterone (PR), and Her-2 expression in primary tumors were analyzed by IHC staining of formalin-fixed, paraffin-embedded surgically removed breast cancers. ER and PR were considered to be positive if tumors had more than 10% of nuclear-stained cells. Her-2 staining was scored on a scale of 0 to 3+, according to the Herceptin Test guidelines; Her-2 was considered to be positive when it was graded as 3+, while 0 to 1+ were considered to be negative. If the score was 2+, then the fluorescence in situ hybridization test (FISH test) was performed and samples with a >two-fold increase in expression were considered to be positive. ER or/and PR-positive, Her-2 negative tumors, which had Ki-67 ≥14% were considered to be luminal B. Based on the hormonal status, each patient was categorized into one of four distinct molecular subtypes: luminal A (ER and PR-positive), luminal B With positive (ER, PR and Her-2), Her-2-enriched (ER and PR-negative with Her-2), and triple-negative.

Statistical Analyses

Color and power Doppler findings, including RI and the average vascular diameter, were compared statistically among the different receptor groups using an analysis of variance (ANOVA). Similarly, t-tests were used to compare the mean and the Chi-square test was used to compare the distribution of the above-defined Doppler patterns in various receptor groups in malignant breast cancer. Data were presented as the mean ± standard deviation (SD). In all cases, P<0.05 was considered to be statistically significant. Data analysis was performed by SPSS (version 16.0) software [Statistical Procedures for Social Sciences; Chicago, Illinois, USA].

Results

There were 43 breast cancer patients whose data were analyzed. The mean diameter of their breast cancer tumors was 20.24 mm (range, 5–45 mm).

The patients’ mean age was 50.79±10.03 years (range, 23–72 years). IHC profiles showed that 36 patients (83.72%) were ER-positive, 30 patients (69.76%) were PR-positive, and 12 (27.90%) patients were Her-2 positive.

The prevalence of biomarker groups in this study was as follows: luminal A, 21 patients (48.83%); luminal B, 15 patients (34.88%); Her-2 amplifier, two patients (4.65%), and triple-negative, five patients (11.62%). Thirty-seven patients (86.04%) with malignant masses had detectable flow and six patients (13.95%) did not have detectable flow. The ER-positive and PR-positive types of breast cancers had the highest rate of vascular presence in color Doppler US, and 30 out of 36 (83.33%) ER-positive tumors and 25 out of 30 (83.33%) PR-positive tumors had the detectable flow, but there was no statistically significant difference (P=0.567 and P=0.649). The same was true for Her-2 receptor and no significant relationship was found between vascular presence and Her-2 positivity (P=1.000).

Maximum vessel diameter in color Doppler was measured for all masses with detectable arterial flow (in millimeters). The maximum vessel diameter in different biomarker groups was not significantly different (ER, P=0.385; PR, P=0.252; HER-2, P=0.811).

In the lesions that had detectable flow, spectral waveform Doppler was obtained, the maximum RI value was recorded in each mass, and the mean of each biomarker group was measured. There were no significant differences between the RI values for these groups (ER, P=0.599; PR, P=0.861; HER-2, P=0.802).

The malignant masses were classified based on different color mass Doppler patterns (no flow, feeder, capsular peripheral flow, and entire mass flow patterns). There was no significant relationship among these groups and with various biomarkers (ER, P=0.28; PR, P=0.58; HER-2, P=0.76). These defined groups and their relationship to the biomarker groups of breast cancers are summarized in Table 1.

Table 1. The relation of different flow patterns and biomarker groups

<table>
<thead>
<tr>
<th>Flow type in sonography</th>
<th>Biomarker groups</th>
<th>Herceptin</th>
<th>triple-negative</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>a</td>
<td>b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No flow</td>
<td>3</td>
<td>14.3%</td>
<td>3</td>
<td>20.0%</td>
</tr>
<tr>
<td>Feeder</td>
<td>5</td>
<td>23.8%</td>
<td>2</td>
<td>13.3%</td>
</tr>
<tr>
<td>Peripheral-capsular hyperemia</td>
<td>9</td>
<td>42.9%</td>
<td>6</td>
<td>40.0%</td>
</tr>
<tr>
<td>Whole</td>
<td>4</td>
<td>19.0%</td>
<td>4</td>
<td>26.7%</td>
</tr>
</tbody>
</table>

various biomarker groups in luminal A, luminal B, Her2 amplifiers, and triple-negative tumors for these kinds of flow patterns (P=0.53).

Discussion
Currently, breast cancer treatment depends on tumor IHC characteristics. These tests are not available everywhere and they are invasive and expensive. Therefore, researchers have investigated non-invasive methods such as imaging findings that may predict tumor IHC preoperatively to help with the patient’s treatment plan. In the literature, some studies have evaluated the correlations between various imaging methods, such as mammography, US, MRI, and PET, with histopathologic markers. Additionally, newer research also investigated the functional imaging characteristics to determine IHC biomarkers, which are promising but not practical to use in clinical centers worldwide.

Angiogenesis via secretion of angiogenic factors plays an important role in the growth, extension, and formation of metastasis in breast cancer. Thus, Doppler sonography may allow evaluation of vascularization to differentiate between benign and malignant breast lesions, and it may even predict tumor IHC.

Ultrasoundography is the most important adjunct modality to mammography that is used to screen and diagnose breast cancer, and it is available and inexpensive. It is also used to guide biopsy and breast interventions. Doppler US can be performed in the same session as the gray scale US and it is used in addition to B-mode US to differentiate between benign and malignant lesions. Breast cancer is a tumor that is usually located superficially, which is suited for Doppler sonography and easy penetrability with the linear transducer. US intravenous contrast agents were not available at our center for use in this setting, and using contrast agents is more expensive, time consuming, and slightly invasive compared to simple color Doppler sonography.

Jose et al. showed that, although malignant tumors have significantly more vascularization than benign tumors, malignancy in lesions without flow in color Doppler cannot be eliminated because vessels were unable to be detected in 32% of breast cancers.

There was no similar previous study that explored color Doppler in the different IHC breast cancer groups, so the development of a reliable decision-making non-invasive imaging method, which is a part of usual diagnostic process for patients with breast cancer and which predicts tumor molecular subtypes, is valuable.

Other imaging methods such as grayscale sonography, breast MRI, and PET were used by various researchers to differentiate between various biomarkers. Koo et al. showed that triple-negative tumors have a higher 18F fluorodeoxyglucose (FDG) uptake in FDG PET (1.67-fold) than luminal A tumors. Youk et al. reported that triple-negative, especially androgen receptor-positive triple-negative cancers, have more necrotic tissue than other cancers, which yields a high signal intensity in T2-weighted MRI images and a high apparent diffusion coefficient value. Yu-Sohn showed that the triple-negative subtype showed a higher incidence of masses on mammography compared to the other subtypes. Zhang proposed a team decision approach that integrated multiple decision trees based on special gray scale features of each subtype and they obtained high accuracy using their models.

Various Doppler sonography parameters have been analyzed to determine their usefulness in differentiating between breast cancer biomarker groups. Our analysis did not show significant differences in the RI, vessel diameter, and flow patterns with different biomarkers.

There were several advantages to this study. First, all patients had T1 (tumor ≤20 mm for the largest diameter) or T2 (tumor >20 mm but ≤50 mm for the largest diameter) masses based on the TNM staging of breast cancer. Second, all patients underwent surgery and IHC was performed on the surgical samples. Third, in contrast to previous studies where biomarkers were used to predict breast cancers, we did not only compare triple-negative tumors with other IHC groups. We included and compared all of the following biomarker groups: luminal A, Her-2 enriched, and triple-negative tumors. Fourth, a useful model of color Doppler pattern classification was introduced for breast cancers, which may be beneficial in future research.

The main limitation of the present study was missing some patients and arbitrarily excluding some patients, so that the number of patients was fairly small. For stronger conclusions, a future study with a larger sample size is required.

In conclusion, there was no significant association between tumor’s IHC and different color and spectral parameters of Doppler sonography.

Conflict of Interests
The authors declare that there is no conflict of interest.

Financial Disclosure
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15. CJ DO, EA S, EB M, EA M, al. e. ACR BI-RADS® Atlas, Breast Imaging Reporting and Data System 2013 [ ]


Background: This study aimed to investigate the effectiveness of short-term group logo-therapy on life expectancy and resilience of women with breast cancer.

Methods: This applied study is quasi-experimental and was designed by the use of pre-test and post-test. The population of study included all women with breast cancer, from which 30 women with breast cancer were randomly divided into experimental and control groups. To collect study data, The life expectancy scale and Connor-Davidson Resilience Scale (CD-RIS) were used. For data analysis, covariance analysis ANCOVA was used.

Results: The results showed that there is a significant difference between the scores of life expectancy between groups \(F= 485.012, p= 0.005\) and there is a significant difference between the mean scores of resilience among groups \(F= 2.051, P= 0.001\).

Conclusions: In general, it can be said that, group logo-therapy can help women with breast cancer to find meaning in their life, receive support from groups, and adapt themselves with diseases. Also, logo-therapy can be useful in breast cancer patient’s attitude towards hardships and problems and can increase their strength and resilience.

Key words: short-term group logo-therapy, life expectancy, resilience, breast cancer
A person can be subdued by destiny as long as he clutches to one requirement that is not fulfilled, which consequently makes one lose appreciation of the bigger picture. The opposite of loss of meaning is a pursuit of wisdom. Wisdom means to live in a hopeful spirit. Logo-therapy, by some writers, was called “the third school of psychotherapy by Vienna” and it refers to the meaning of human existence and emphasizes on the search for one’s resistance in regard to this concept. According to the principles of logo-therapy, trying to find the meaning of life is the most fundamental driving force of every person in their life.

Logo-therapy, by taking into account the transience of human existence rather than pessimism and isolation, invites humans towards effort, hope and activity. It expresses that suffering and undesirable destiny aren’t the reasons for people’s failure, but that failure occurs when life becomes meaningless. If we bravely accept suffering until the last minute of life, life will have meaning and the meaning of life can include even the potential meaning of pain and suffering. Humans against adverse conditions, risks and hardships often feel helpless and hopeless and, in many cases, they also try to accept risks and hardships, from which oftentimes unexpected results can be obtained. Diagnosis of cancer can cause personality crises in people. At this time, many factors can contribute to patients overcoming their illness. A psychological intervention such as group logo-therapy is a small world that symbolizes the real world in which the members participate with the aim of exploring themselves as individuals who have shared interests. This method is an explorative journey for achieving the ability to be with their true selves and expand their perspective toward themselves and their surrounding world and clarify what gives meaning to their present and future life. In this group, individuals feel that they can be with each other in meaningful ways of life, and ways of fighting diseases like breast cancer.

One way that logo-therapy can help women with breast cancer is to increase their resilience by adding more meaning to their lives. Creating meaning and logo-therapy can be considered important in people’s confrontation with life-threatening illnesses. Considering that recognizing and identifying the correct way to treat it are important aspects of care in cancer patients, logo-therapy can be used as an effective way by mental health professionals along with other therapies to improve the hope and depression of affected people.

Resilience is one of the essential concepts which increases the level of a person’s ability for resistance and rapid improvement during the decline of physical function in disease. Resilience is one of the major components that could provide one way or another a miracle for cancer patients. Resilience is a dynamic process through which people show positive adaptation, despite the traumatic and abnormal experiences. Mahmoudi, in his study, found that cancer patients who have had high resilience, show more sympathy toward themselves and it can be effective and important in the course of recovery. Investigators showed that the majority of people with cancer who had enjoyed a high level of resilience, show better health and physical function. Other studies showed that women with breast cancer have lower levels of resilience than other women. Furthermore, Li et al. showed that individual resilience might ease caregiver burden among the principal caregivers of breast cancer survivors, and family resilience tends to promote the survivors’ individual resilience. Therefore, individual resilience can be enhanced for breast cancer hope.

Among patients confronting serious illness such as advanced breast cancer, hope takes on multiple forms. In general, hope is the wish for, or belief in the possibility of a better future. Hope can also be a desire that a decision or intervention might produce a specific outcome. According to Coulehan, hopes differ from expectations in that hopes are always positive and maybe improbable. Therefore hope is an ability that helps people to reach the target despite the existence of difficulties in the way and helps the maintenance of motivation. Any person trying to achieve his or her respective goal considers various assessments, which manifest as the amount of hope in that person and finally lead to different behaviors. The useful role of hope, both before the problem (primary role) and after its occurrence (secondary role), has been determined. Women with breast cancer who have had mastectomy would lose a part of their body, which is a sign of their gender. This issue distorts the mental image of a person towards her own body and may lead to loss of confidence and feminine charm and then ushers anxiety and depression and despair for the patient. Failure of timely diagnosis and treatment of depression in patients with breast cancer has harmful results, including reduced quality of life, negative impact on the patient’s capacity to accept physical therapy, reduction of resilience and life expectancy, reduction of survival, and ultimately increase in patient’s death. Studies show that an increase of hope in breast cancer patients improves the resilience in women with breast cancer, which could help the recovery process. Also research about the effects of hope and resilience indicates a lack of research resources, which aims to increase resources and information about the resilience and the hope of patients with breast cancer. The results of one study indicate that group logo-therapy can be effective in reducing psychological stress and problems of divorced women and accordingly, group logo-therapy is an appropriate way to increase life expectancy and resilience of divorced women. Using...
this method, mental health professionals can improve the status of divorced women.\textsuperscript{14} Considering the importance of the psychological issues in women who have had breast cancer surgery, the present study was aimed to assess the effects of logo-therapy on life expectancy and resilience in cancer patients and, consequently, to present an appropriate strategy to improve life expectancy and resilience in this group of patients.

**Methods**

This applied study is quasi-experimental and was designed by the use of pre-test and post-test. Researcher investigates the effectiveness of short-term group logo-therapy on life expectancy and resilience of women with breast cancer. For data analysis, covariance analysis, ANCOVA via SPSS 20 software were used.

**Community and sample of the study**

The population of the study included all women with breast cancer who were referred to medical centers of Ardabil. Thirty people were selected as the sample of study by convenience sampling method and they were randomly divided into two groups of 15 subjects consisting of the experimental group and control group.

**inclusion criteria**

- Consent to participate in research
- No other mental illness
- Experienced of mastectomy and/or lumpectomy

**exclusion criteria**

- Withdrawal from research
- Mental illness

**Measuring tools**

Life expectancy scale: In this study, to collect data and measure variables of hope, the life expectancy test of Schneider 1991 was used. This scale has 12 items in which responses are classified by an 8-point Likert-type scale, from strongly disagree with score 1, and strongly agree with score 8. Here, eight is considered the lowest score, and 64 is regarded as the highest score. The thinking subscale includes four items of 2, 9, 10, and 12; subscale of routes consists of four items of 1, 4, 7, and 8; and four items of 3, 5, 6, and 11 were designed as trick questions. Scoring items of 1, 5, 7, and 11 as trick questions to increase the accuracy of the test will be deleted. So, the range of scores is between 8 and 64. The validity and reliability of this questionnaire were measured by two psychology professors of Isfahan University who tested sixty students of this university with it and determined an internal consistency of $a=0.68$. A significant relation between the questionnaire with positive affection $r=0.46$ and optimism $r=0.64$ shows the simultaneous validity of the questionnaire.\textsuperscript{14}

Connor and Davidson resilience scale CD-RIS: This scale was designed by two well-known theorists in this field, namely, Connor and Davidson and by reviewing research resources in the field of resilience.\textsuperscript{18} The questionnaire has 25 items in 5 categories, each rated on a 5-point scale 0–4, which is scored from strongly agree to strongly disagree. Mohammadi normalized the scale in 2005 in Iran. To determine the validity of the scale, the correlation of each score with the total scores, except item 3, was calculated, and it showed coefficients between 0.41 and 0.64. Afterward, scale items were factor analyzed by using principal components. Also, to determine the reliability Cronbach's alpha was used and the reliability was obtained about 0.89.\textsuperscript{20}

**Procedure**

Ethical considerations in this study include the freedom to participate and the security of patients' identities. The program of logo-therapy was done in 120 minutes in 9 sessions for five weeks in the experimental group as follows: In the first session, explaining the objectives and rules of the group, familiarity of members with each other and with the advisor, explanations in connection with features of post-traumatic stress disorder were performed. In the second session: awareness of treatment-seekers of the fundamental concepts of was explained. Activities: compact expression from the biography of Viktor Frankl and fundamental beliefs of logo-therapy were introduced. In the third and fourth sessions, patients' beliefs and acceptance were considered regarding their characteristics, considering spiritual freedom as a dimension of human existence. Then paradoxical intention training techniques were assigned to the teaching group. In the fifth session, patients were taught the meaning of life and love. In the sixth session, understanding the meaning of suffering and pain activities in group discussion about suffering and how to accept and bear it, were discussed. The seventh session included understanding the meaning of death, and group discussion about the transience of life, the reality of death, and its meaning. In the eighth session, understanding God's presence in the subconscious of humans and group discussion about the presence of God in the deepest layers of human existence were emphasized. In session nine, to sum up, the words, readings and content of last meetings by treatment seekers during past sessions were reviewed for the post-test.

**Results**

Thirty breast cancer patients were interviewed. Thirty of the participants had undergone surgery by means of mastectomy or lumpectomy.

Table 1 shows that although the pre-test scores of variables such as life expectancy and resilience in control and experimental groups are almost identical, post-test scores of the experimental group have increased.
Group logo-therapy is effective in increasing the components of life expectancy and resilience in women with breast cancer. As can be seen in Table 2, the adjusted mean of dependent variables refers to a significant difference.

From data in the above table, it can be concluded that in general, there is a significant difference between the scores of life expectancy between the groups F= 485.012, p= 0.005. Therefore, it can be concluded that, with a 95% confidence interval, life expectancy scores are not identical in pre-test and post-test.

As it is shown in Table 2, there is a significant difference between the mean scores of resiliencies among groups (F= 2.051, P= 0.001). Therefore, it can be concluded that, with a 99% confidence interval, an increase of resilience is not identical in pre-test and post-test. Furthermore, about 36% of the scores related to increase of resilience have changed in pre-test and post-test.

The ETA level also refers to the fact that about 85% of life expectancy scores are affected by pre-test and post-test, and this rate of change is a function of difference between tests.

Table 1. Statistical description of scores for subjects in experimental and control groups for the scales of life expectancy and resilience in women with breast cancer

<table>
<thead>
<tr>
<th>Scale</th>
<th>Group</th>
<th>test</th>
<th>mean</th>
<th>standard deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Life expectancy</td>
<td>Intervention</td>
<td>Pre-test</td>
<td>18.04</td>
<td>1.416</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>Post-test</td>
<td>25.12</td>
<td>2.781</td>
</tr>
<tr>
<td></td>
<td>Intervention</td>
<td>Pre-test</td>
<td>16.13</td>
<td>1.503</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>Post-test</td>
<td>18.6</td>
<td>3.558</td>
</tr>
<tr>
<td>Resilience</td>
<td>Intervention</td>
<td>Pre-test</td>
<td>26.8</td>
<td>2.026</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>Post-test</td>
<td>35.4</td>
<td>2.01</td>
</tr>
<tr>
<td></td>
<td>Intervention</td>
<td>Pre-test</td>
<td>26.2</td>
<td>1.124</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>Post-test</td>
<td>28.54</td>
<td>1.56</td>
</tr>
</tbody>
</table>

Table 2. Significant test of effects between subjects of life expectancy and resilience

<table>
<thead>
<tr>
<th>Source of Changes</th>
<th>dependent variable</th>
<th>sum of squares</th>
<th>degree of freedom</th>
<th>mean of squares</th>
<th>F</th>
<th>significance level</th>
<th>square of Eta</th>
</tr>
</thead>
<tbody>
<tr>
<td>Life expectancy</td>
<td></td>
<td>2136.012</td>
<td>1</td>
<td>71.2</td>
<td>485.012</td>
<td>0.005</td>
<td>0.854</td>
</tr>
<tr>
<td>Resilience</td>
<td></td>
<td>28.12</td>
<td>1</td>
<td>15.047</td>
<td>2.051</td>
<td>0.001</td>
<td>0.875</td>
</tr>
</tbody>
</table>

Discussion

According to the findings of the study, training based on short-term group logo-therapy are effective on life expectancy of women with breast cancer.

According to the statistics of the World Health Organization, cancer is the second cause of death and mortality after cardiovascular disease in the world and every minute in the world, a person loses his or her life because of cancer. In Western countries, breast cancer incidence rates increase with age, unlike Iran, where the rate of incidence is different, with the highest female mortality rate occurring in those aged between 30 and 50.

About the role of meaning of life in logo-therapy, Jaarsma et al. noted that the experience of the meaning in life was positively related to feelings of psychological wellbeing and negatively to feelings of distress. To explain these findings, it can be said that logo-therapy, by creating the meaning in life, leads to compatibility, life satisfaction and psychological well-being in patients with breast cancer. In other words, group logo-therapy can help women with breast cancer by finding the meaning in life and the supports they receive from the group, adapt themselves with sadness, despair, and diseases.

When treatment-seekers based on behaviors, habits, or illness, describe themselves, their problems will be intensified, and conditions will be more disappointing. During the treatment, refraining from oneself gives power to treatment-seekers by accepting and releasing their fighting force. They can take a stand and confront problems. In logo-therapy it is recommended to create a distance between treatment-seekers and symptoms, to let them be free from neuroticism. Therefore, with continuous collaboration between patient and therapist, symptoms will be reduced.

Based on the results of the study, it can be concluded that training based on short-term group logo-therapy was effective in the resilience of women with breast cancer.

Many women with breast cancer are those who have experienced dark aspects of human nature, those who have faced profound questions related to the loss of meaning of life and the concept of the hope in life. In the other word, by redefining the concept of suffering and pain, individuals try to find the meaning of existence and they will be ready for confrontation in facing with difficulties and challenges of life. If the individual can be successful in finding out the meaning of better and unexpected and disappointing events of life, he or she will be able to withstand the tribulations of life. In logo-therapy, people talk about
freedom of human spirit, and that deterministic laws do not influence a human. A human has the right to choose an attitude about the existing situation. Decision-making is granted to humans. For humans, nothing has the power of determining how to think and behave about the unchanging destiny. Humans will always be responsible for their actions and words. As a result, the way of looking at the issues and difficulties is important, and logo-therapy intends to find a meaning-seeking attitude for people facing challenges. So, it is clear that the attitude of people in facing difficulties and pains of life can be affected by logo-therapy and their tolerance and resilience will be increased. According to the results obtained, it can be concluded that psychological interventions, such as group logo-therapy could reduce the amount of hopelessness and increase resilience in patients with breast cancer. Hence, it can be concluded that an explanation of comprehensive approaches in the treatment and management of cancer symptoms would be an important step in improving psychological components in the lives of breast cancer patients. In a study of Kaviani et al., the majority of participants (52.7%) declared that psychosocial care is necessary for all patients with breast complaints.

In conclusion, it can be said that group logo-therapy can help women with breast cancer to find meaning in their life, receive support from a group, and adapt themselves with diseases. Also, logo-therapy can be beneficial in the attitude of the breast cancer patients towards towards hardships and problems and can increase their strength and resilience.

Limitations of this study were problems in accessing the samples and receiving the consent of the doctor's patients. Second, the lack of follow-up periods. Third, variables such as marital status, occupation, and socioeconomic status of patients have not been controlled; hence, this intervention can be used to reduce hopelessness in breast cancer patients, in line with current medical treatments.

Conflict of Interest
The authors did not have any conflict of interest to do this research. Also, they did not receive any financial support to do the project.

References


ARTICLE INFO

Background: This study aimed to translate and validate the Fear of Cancer Recurrence Inventory (FCRI) questionnaire into Persian and to investigate its psychometric properties.

Methods: The FCRI was translated to Persian using a linguistic methodology according to WHO guidelines. A total of 450 breast cancer survivors who had the following inclusion criteria were included: time elapse of more than six months after the treatment prior to the study; absence of objective markers of recurrence, fluency in the Persian language, and signing the informed consent. Internal consistency was estimated with Cronbach’s α coefficient and test-retest reliability with Interclass correlation. Concurrent validity was estimated through Pearson’s correlation between the FCRI and Hospital Anxiety and Depression Scale (HADS). Principal component analysis (PCA) and confirmatory factor analysis (CFA) were employed to evaluate dimensionality.

Results: The Persian version was acceptable for patients. The content validity index (CVI) was 0.80. The instrument had good test-retest reliability (ICC= 0.96) and internal consistency (Cronbach’s α=0.86). PCA and CFA indicated that the factor structure of the Persian version was similar to the original questionnaire and had acceptable goodness of fit. Correlations between the FCRI and HADS was remarkable (r= 0.252 – 0.639), indicating acceptable concurrent validity.

Conclusions: The Persian version of FCRI could be considered a good cross-cultural equivalent for the original English version. The questionnaire was a reliable and valid instrument in terms of internal consistency, test-retest reliability, and dimensionality.

Key words: Breast Cancer, fear of cancer recurrence inventory, Persian, psychometric properties

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ABSTRACT

The Persian Version of the Fear of Cancer Recurrence Inventory (FCRI): Translation and Evaluation of Its Psychometric Properties

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Introduction

The number of cancer survivors has increased more than threefold over the last 30 years. Among patients with recently diagnosed cancer, nearly two-thirds are expected to survive five or more years. Psychosocial problems are common in cancer survivors. Fear of cancer recurrence (FCR) is one of
these problems, which is estimated to involve 50-89% of cancer survivors. Two main definitions have been used for FCR. The first is defined as the “fear that cancer could return or progress in the same place or in another part of the body” , which adopts a patient’s perspective of FCR and is relevant across the cancer trajectory. The second is “the degree of concern about the chances of cancer returning at a future time”; this definition emphasizes recurrence more than progression. These patients constantly express the need for help, which, unfortunately, is not addressed by cancer care systems, as reported by 20 to 40 percent of patients.

It is essential to screen for FCR using an appropriate measure. Several screening tools have been introduced in the literature, including subscales of more comprehensive psychosocial and quality-of-life assessment tools, brief FCR questionnaires, and longer FCR instruments. Lack of a widely-accepted definition for FCR and the use of measures with different cut-off scores may explain an alternative approach for the assessment of FCR as well as variability in its reported prevalence rate.

Fear of Cancer Recurrence Inventory (FCRI) is a 42-item multidimensional questionnaire that is appropriate for all cancer patients. Items were developed based on a cognitive-behavioral formulation of FCR , literature review, and DSM-IV diagnostic criteria. The FCRI was originally validated in a French-speaking sample of 600 patients with mixed cancers, and its English version was developed later. The instrument had very good psychometric properties in previous studies.

To our knowledge, scanty research has been conducted in the Iranian population regarding the fear of cancer recurrence, which might be tracked to the lack of appropriate measures. The purpose of this study was to develop a valid and reliable version of FCRI in Persian.

**Methods**

**Linguistic Validation**

The English version of FCRI was translated to Persian based on the standard guideline of the World Health Organization (WHO). Accordingly, the English questionnaire was translated to Persian by two bilingual translators. After reaching a consensus regarding the translated Persian version, ten patients filled out the questionnaire, and words with unclear meaning were replaced and the final version was provided. An independent bilingual translator back-translated the final Persian version to English.

The content validity and equivalence testing were performed by five independent academic psychiatrists and a clinical psychologist. They rated the degree of the content covered by each item of the instrument, which is supposed to measure as an index for content validity. A five-point Likert scale was used in the ascending order for “appropriateness” and “relevance” of the items.

**Psychometric Evaluation**

**Participants**

Participants in this study were recruited from a breast cancer clinic affiliated to Tehran University of Medical Sciences (TUMS), and a private breast cancer clinic located in Tehran, Iran. Patients meeting the following criteria were included: The acceptable time period after the breast cancer treatment including surgery, radiation therapy and chemotherapy being six months to 5 years; absence of the objective evidence of recurrence; being fluent in the Persian language, and signing the informed consent. The protocol of the study was approved by the ethics committee of the Faculty of Medicine, Tehran University of Medical Sciences.

**Measures**

Fear of Cancer Recurrence Inventory (FCRI): The English version of FCRI has 42 items. FCRI is a multidimensional inventory developed by Simard et al. for use in all cancer patients. The questionnaire was originally validated in French-speaking patients with different cancers, and the English version was developed later by the same authors. The inventory evaluates seven aspects associated with FCR: the potential stimuli activating FCR (triggers; sample item: “Conversations about cancer or illness in general”); the presence and severity of intrusive thoughts associated with FCR (severity; sample item: “I believe it is normal to be worried or anxious about the possibility of cancer recurrence”); the emotional disturbance associated with FCR (psychological distress; sample item: “When I think about the possibility of cancer recurrence, I feel frustration, anger or outrage”); the impact of FCR on important areas of functioning (functioning impairments; sample item: “My thoughts or fears about the possibility of cancer recurrence disrupt my work or everyday activities”); the self-criticism toward FCR intensity (insight; sample item: “I feel that I worry excessively about the possibility of cancer recurrence”); the behavioral reassurance such as self-examination or repeated medical consultations (reassurance; sample item: “I call my doctor or other health professional to reassure myself”); and other strategies to cope with FCR (coping strategies; sample item: “I pray, meditate or do relaxation”).

The Hospital Anxiety and Depression Scale (HADS): HADS is a brief and widely-used self-report questionnaire to determine the levels of anxiety and depression a person experiences. It is a fourteen-item scale. It has two subscales: HADS-A for anxiety and HADS-D for depression. Seven of the items are related to anxiety and seven are related to depression. It has been translated and validated in many languages and it is widely used in the Persian
population for clinical and research purposes. ¹

Reliability Study

The Persian version of FCRI was tested for internal consistency through Cronbach’s alpha coefficient for each domain and also for the whole questionnaire. A random sample of 60 patients was tested two weeks after the initial assessment. The intraclass correlation coefficient (ICC) was utilized for assessing the test-retest reliability of the questionnaire.

Validity Study

Concurrent Validity: In order to test the concurrent validity of the instrument, all participants completed the HADS questionnaire concurrent with the Persian version of FCRI, and the correlation of the scores of all questions was calculated.

Construct Validity: Factorial structure and dimensionality of the questionnaire were assessed through both principal component analysis (PCA) and confirmatory factor analysis (CFA).

Statistical analyses

For determining the degree of agreement between expert panel members in the second step of the translation process, a content validity index (CVI) was calculated. To assess the reliability of the Persian version of FCRI, Cronbach’s alpha coefficient was assessed for internal consistency. Cronbach’s alpha of greater than 0.7 was assumed satisfactory. For test-retest analysis, the intraclass correlation coefficient (ICC) was utilized. Principle component analysis (PCA) with oblique rotation was adopted for exploratory factor analysis. A Confirmatory factor analysis (CFA) with the parceling method was utilized as another way for assessing the dimensionality of the questionnaire.¹¹ Concurrent validity of FCRI was evaluated using correlations between the Persian version of FCRI subscale scores and HADS scores. A significance level of p ≤ .05 was assumed satisfactory. IBM SPSS-22 and AMOS-22 software were used for CFA.

Results

Linguistic Validation

The Persian version of FCRI was developed based thoroughly on the previously-mentioned translation process. Each step was designed to improve the comprehensibility and acceptability of the questionnaire. There was no major cultural discrepancy between English and Persian versions. A panel of experts examined content validity. The content validity index (CVI) for the seven subscales of the instrument (triggers, severity, psychological distress, functioning impairments, insight, reassurance and coping strategies) and total score of FCRI were 0.82, 0.84, 0.80, 0.85, 0.77, 0.79, 0.78 and 0.80 respectively. The Paucity of missing data in psychometric evaluation also confirmed the acceptability of the instrument.

Psychometric Evaluation

A total of 450 patients with breast cancer participated in this study. The demographic characteristics of the subjects are summarized in Table 1. The mean age of the patients was 50.50 years (SD=9.75). Regarding the marital status of participants, 9.1% were single, 78.8% were married, 6.1% were widowed, and 6.1% were divorced. The descriptive statistics of different measures are also presented in Table 2.

Reliability Study

Internal consistency was found to be acceptable with Cronbach’s alpha coefficient at 0.86. The interclass correlation coefficient for test-retest reliability was between 0.87 and 0.99 (Table 3).

Table 1. Demographic characteristics of participant with breast cancer

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Mean(SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number</td>
<td>450</td>
</tr>
<tr>
<td>Age (years)</td>
<td>50.50(9.75)</td>
</tr>
<tr>
<td>Education level (%)</td>
<td></td>
</tr>
<tr>
<td>Illiterate</td>
<td>4.5</td>
</tr>
<tr>
<td>Elementary and junior high school</td>
<td>15.2</td>
</tr>
<tr>
<td>High School and Diploma</td>
<td>47</td>
</tr>
<tr>
<td>Higher education</td>
<td>33.3</td>
</tr>
<tr>
<td>Employment status (%)</td>
<td></td>
</tr>
<tr>
<td>Housewife</td>
<td>57.6</td>
</tr>
<tr>
<td>Employed</td>
<td>21.2</td>
</tr>
<tr>
<td>Jobless</td>
<td>3</td>
</tr>
<tr>
<td>Retired</td>
<td>18.2</td>
</tr>
</tbody>
</table>

Table 2. Descriptive statistics of different measures in participants with breast cancer

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mean</th>
<th>Std. Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time passed from Diagnosis</td>
<td>29.16</td>
<td>14.15</td>
</tr>
<tr>
<td>Triggers</td>
<td>20.16</td>
<td>6.92</td>
</tr>
<tr>
<td>Severity</td>
<td>21.94</td>
<td>6.91</td>
</tr>
<tr>
<td>FCR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychological Distress</td>
<td>8.91</td>
<td>4.31</td>
</tr>
<tr>
<td>Functional Impairment</td>
<td>12.79</td>
<td>5.96</td>
</tr>
<tr>
<td>Insight</td>
<td>5.78</td>
<td>3.01</td>
</tr>
<tr>
<td>Reassurance</td>
<td>7.24</td>
<td>2.90</td>
</tr>
<tr>
<td>Coping Strategies</td>
<td>21.89</td>
<td>8.37</td>
</tr>
<tr>
<td>Total Score</td>
<td>104.90</td>
<td>27.16</td>
</tr>
<tr>
<td>HADS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HADS A</td>
<td>6.63</td>
<td>4.42</td>
</tr>
<tr>
<td>HADS D</td>
<td>4.92</td>
<td>3.64</td>
</tr>
</tbody>
</table>
Table 3. Interclass correlation coefficients (ICC) for test-retest of seven subscales and total scores of FCRI (N=60)

<table>
<thead>
<tr>
<th>Items</th>
<th>ICC for test-retest</th>
<th>Lower Bound</th>
<th>Upper Bound</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trigger</td>
<td>0.87</td>
<td>0.72</td>
<td>0.94</td>
<td>0.001</td>
</tr>
<tr>
<td>Severity</td>
<td>0.76</td>
<td>0.47</td>
<td>0.89</td>
<td>0.001</td>
</tr>
<tr>
<td>Functional impairment</td>
<td>0.93</td>
<td>0.85</td>
<td>0.97</td>
<td>0.001</td>
</tr>
<tr>
<td>Insight</td>
<td>0.99</td>
<td>0.97</td>
<td>0.99</td>
<td>0.001</td>
</tr>
<tr>
<td>Reassurance</td>
<td>0.96</td>
<td>0.93</td>
<td>0.98</td>
<td>0.001</td>
</tr>
<tr>
<td>Coping Strategies</td>
<td>0.99</td>
<td>0.98</td>
<td>0.99</td>
<td>0.001</td>
</tr>
<tr>
<td>Total Score</td>
<td>0.96</td>
<td>0.93</td>
<td>0.98</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Table 4. Pearson’s correlation coefficient of the FCRI subscales scores and HADS subscales scores

<table>
<thead>
<tr>
<th>Triggers</th>
<th>Severity</th>
<th>Psychological Distress</th>
<th>Functional Impairment</th>
<th>Insight</th>
<th>Reassurance</th>
<th>Coping Strategies</th>
<th>FCRI-total</th>
</tr>
</thead>
<tbody>
<tr>
<td>HADS-A</td>
<td>0.52*</td>
<td>0.59*</td>
<td>0.65*</td>
<td>0.55*</td>
<td>0.64*</td>
<td>0.24*</td>
<td>0.59*</td>
</tr>
<tr>
<td>HADS-D</td>
<td>0.43*</td>
<td>0.45*</td>
<td>0.52*</td>
<td>0.51*</td>
<td>0.57*</td>
<td>0.14*</td>
<td>0.45*</td>
</tr>
</tbody>
</table>

* P<0.05

Validity Study

Concurrent validity of FCRI was measured by Pearson’s correlation coefficient between FCRI domains and scores of HADS. As it is shown in Table 4, except for the domain of coping strategies, all other six domains of FCRI, HADS-A, and HADS-D subscales were well correlated.

The principal component analysis revealed seven factors with eigenvalues of 13.96, 5.26, 2.33, 1.71, 1.53, 1.26, and 1.07, which accounted for 64.60% of the variance observed (Figure 1). The factors extracted in this study were consistent with the domains of the original version of FCRI.

Based on the result of PCA, it is evident that the structure of the FCR could be explained better by a 7-factor solution. Also, to address sample size limitation to run CFA with 42 items, we ran a CFA with the parceling method. For a good model fit in CFA, sample size plays a notable role in the analysis. It gains more significance when researchers propose a complex model with a greater number of indicators of a specific latent variable. The parceling method reduces the complexity of the proposed model by reducing the number of indicators. It has some advantages for CFA, including more reliability, meeting normality assumptions, satisfying sample size requirements, and better model fit indices. In the parceling method, after computing item-scale correlation coefficients, two or three items would be summed creating a group under their subscale. Then, CFA would be run on these created groups rather than original items of the scale. The path diagram of CFA is presented in Figure 2. The goodness of fit measures is shown in Table 5 for CFA with 42 items and parceling methods. As illustrated in table 5, the goodness of fit measures was better in the parceling model than the original 42-item model. In the parceling model, RMSEA, CFI, IFI, PNFI, and PCFI showed acceptable goodness of fit, and GFI was nearly close to the acceptable value, i.e. 0.90. Meyers et al discussed the detailed information on the target values. As previously mentioned, the parceling
method can help researchers to reduce the complexity of the model and address sample size limitation. Then, the results of the parceling model might imply that the sample size limitation in the present study leads to weaker model fit indices in CFA and there is no need to modify the hypothesized model of FCR.

According to figure 2, the factor coefficients of the original hypothesized model (with 42 items) were assessed by AMOS 22 and the maximum likelihood estimation method. All of the factor coefficients were statistically significant at \( p < 0.05 \). The standardized regression weights (\( \beta \)) of the Item-Subscale level for the 7-factor solution changed from 0.21 (item 8- Triggers) to 0.89 (item 19- Distress). The standardized regression weights of the Subscale-method can help researchers to reduce the complexity of the model and address sample size limitation. Then, the results of the parceling model might imply that the sample size limitation in the present study leads to weaker model fit indices in CFA and there is no need to modify the hypothesized model of FCR.

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<table>
<thead>
<tr>
<th>Model</th>
<th>Chi-Square</th>
<th>DF, p-value</th>
<th>GFI</th>
<th>RMSEA</th>
<th>CFI</th>
<th>IFI</th>
<th>PNFI</th>
<th>PCFI</th>
</tr>
</thead>
<tbody>
<tr>
<td>42 items</td>
<td>2846.3</td>
<td>812, P&lt;0.001</td>
<td>0.73</td>
<td>0.08</td>
<td>0.82</td>
<td>0.83</td>
<td>0.73</td>
<td>0.78</td>
</tr>
<tr>
<td>parceling</td>
<td>641.4</td>
<td>182, P&lt;0.001</td>
<td>0.87</td>
<td>0.08</td>
<td>0.92</td>
<td>0.92</td>
<td>0.78</td>
<td>0.79</td>
</tr>
</tbody>
</table>

Note: GFI= goodness of fit index; RMSEA= root mean square error of approximation; CFI= comparative fit index; IFI= Incremental Fit Index; PNFI= parsimonious normed fit index; PCFI= parsimonious CFI.

Figure 2. Path diagram of confirmatory factor analysis for the Persian version of FCRI

FCR total Score level ranged from 0.14 (Coping) to 0.95 (Severity). The majority of standardized regression weights achieved meaningful significance (\( \beta > 0.3 \)). However, two Beta weights did not achieve meaningful significance criterion, including item 8 (0.21) and the Coping subscale (0.14). Then, it might be proposed to modify the hypothesized model to achieve a stronger model for the FCR. It is also notable to mention that the Beta weight of the subscale level in the parceling model ranged from 0.21 (coping) to 0.95 (severity). The Beta weight of the coping subscale increased from 0.14 to 0.21, respectively, in original and parceling models. It might be considered that sample size limitation could explain the weak results of the original model.

Table 5. Goodness of fit measures of the confirmatory factor analysis with a grouping method for the Persian version of FCRI

Figure 2. Path diagram of confirmatory factor analysis for the Persian version of FCRI
Discussion

This study aimed to develop a Persian version of FCRI and to assess its reliability and validity. It was accomplished through standard forward-backward guidelines. The final version of the questionnaire was obtained after face and content validation. The FCRI was comprehensible and easily applicable to the patients. Content validity indices of total and specific domains of the questionnaire were robust. According to Lynn, with six or more judges, the CVI should not be lower than 0.78 for an item to be judged acceptable. The Cronbach’s alpha for the whole questionnaire that provides an estimate of internal reliability was 0.86, which is high and satisfactory. Test-retest reliability was 0.96 over two weeks using ICC, which shows the high stability of FCRI over time. Correlations between the FCRI and HADS were remarkable (r= 0.252 to 0.639), indicating acceptable concurrent validity. As expected, there was a negative correlation between HADS subscale score and coping strategies subscale score of FCRI.

In other words, higher scores in coping strategies imply the fact that patients have better ways to deal with their fear of cancer recurrence and the lower possibility of depression and anxiety.

A similar value was found by Lebel et al. while assessing 350 English-speaking patients with different cancer types. In that study, the English version had high internal consistency (0.96 for the total scale and 0.71–0.94 for the subscales) and test-retest reliability (0.88 for the total scale and 0.56–0.87 for the subscales). In the original study conducted by Simard et al., they evaluated 600 French-Canadian patients who had been survivors of breast, prostate, lung, and colorectal cancer. Results supported the internal consistency (α=0.95) and the temporal stability (r=0.89) of FCRI, as well as its construct validity with other self-report scales assessing the fear of cancer recurrence (r=0.68 to 0.77) or related constructs such as psychological distress (r=0.43 to 0.77), and quality of life (r= 0.20 to 0.36).

Factor analysis using principal component analysis (PCA) revealed seven-factor solutions for this questionnaire. This finding is similar to seven dimensions of the original French questionnaire and the English version of FCRI. Confirmatory factor analysis, along with parceling method, illustrated an acceptable fit of the factor structure of the FCR. However, the sample size limitation could explain the weak goodness of fit measures for CFA with 42 items.

The current study has various limitations that should be considered in the interpretation of the results. First, the sample size of the study may not be ideal for confirmatory factor analysis. Second, due to the lack of another validated instrument for the evaluation of FCR, only the HADS questionnaire was used for the assessment of concurrent validity of the Persian version of FCRI.

In conclusion, the Persian version of FCRI is a reliable and valid measure and can be used for the assessment of the fear of cancer recurrence in patients with breast cancer. It can assist clinicians to have a multidimensional view of the fear of cancer recurrence and can be used for both clinical and research purposes. We recommend that the Persian version of FCRI is employed in populations with different types of cancer and that its sensitivity to change be assessed.

Conflict of Interests:

There is no conflict of interest to declare to do in this study.

Acknowledgment:

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References:

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