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Review Article

Breast Cancer and its Radiotherapeutic Methods

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Abstract

Breast cancer is the most common cancer in women after skin cancer. In Iran, the presentation age of this cancer is younger than the global average. There are different therapeutic methods for treatment of breast cancer and the choice of treatment depends on the stage of the disease as well as its type and characteristics. Therapeutic methods include surgery, radiotherapy, and systemic therapies, each consisting of a variety of techniques. The two main surgical techniques are lumpectomy and mastectomy. The main systemic methods are biological therapy (immunotherapy), hormone therapy, and chemotherapy. Radiotherapy is mainly categorized into external-beam radiotherapy and brachytherapy. In this paper, we present a brief review of the different types of breast cancer and their treatments using conventional and modern radiotherapy methods, as well as the treatment efficacy and side effects of breast radiotherapy.

Keywords: Breast Cancer, Radiotherapy, Review

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1. Introduction

On a global level, breast cancer continues to be a challenging disease. After skin cancer, breast cancer is the most common cancer among women, nearly 1 in 4 cancers diagnosed in the United States women. Age is one of the most important risk factors in breast cancer and as age increases, breast cancer incidence rate increases too. The incidence rate increases in 40-years old and older women and the most significant incidence rate is in 75- to 79-years old women [1]. Breast cancer occurrence in families may result from the interaction between lifestyle factors and low-risk variations in genetic factors that may be shared by women within a family [2-4].

There is no comprehensive statistics on breast cancer in Iran but it is evident that it is the most common cancer among women. Due to as yet unknown reasons, average age of breast cancer patients in Iran is lower than the global mean. A study which assessed the effects, risk factors, and prescribed medications on 277 breast cancer patients under the age of 40 years at our center revealed that more than 50% of the patients in southern Iran present with advanced stages of the disease (stages 3 and 4), which suggests that they may not be aware of the symptoms of this cancer to see a physician at an earlier stage [5-6].

Nowadays, the global belief is that postoperative adjuvant irradiation after breast-conserving or mastectomy surgery is necessary [7]. Post-mastectomy radiotherapy (PMRT) is often performed using megavoltage X-rays and electron beams. As with other types of computer-planned radiotherapy (RT), the differences between computed dose distribution and that delivered to the patient should be minimized [8].

This article is a brief review of different types of breast cancer and the progressive path of its radiotherapeutic methods. The search engine used in this study was Pubmed.

2. Different Types of Breast Cancer

Breast cancer can be benign or malignant. Breast cancer cells may arise from any breast tissues such as epithelial tissue, glands, lobules, areola, and nipple. The place where breast cancer results from determines the name of the breast cancer [9]. Cancerous cells usually arise from ductal or glandular cells and are, therefore, called ductal or lobular carcinomas, respectively [10].

Breast cancers are classified into invasive and non-invasive carcinomas. Invasive carcinomas may metastasize and transfer to surrounding tissues in contrast to non-invasive carcinomas, which are isolated at their origin. Breast tumors may be discovered at an early stage, when they are still small and remain in the site of origin. They are called in situ or non-invasive. Because of their small size, they are usually not detected during a physical exam but there is a good chance for them of being diagnosed by mammography. Metastatic cancers which penetrate to the surrounding tissues and spread to other sites are called infiltrating or invasive carcinoma. In addition to ductal and lobular carcinoma, three well-recognized types of invasive breast cancer are: tubular, medullary, and mucinous. There are also some other types of breast cancer such as inflammatory cancers and rare types of sarcomas [9].

3. Risk Factors

Age, family history, age at first full-term pregnancy (above 35 years old), early menarche, late menopause, and breast density are some of the most important risk factors for breast cancer. These factors are not under the patient's control. However, there are some controllable risk factors such as postmenopausal obesity, use of combined estrogen and progestin menopausal hormones, alcohol consumption, and physical inactivity [1, 3].

Seventy percent of breast cancer women may not have any of these risk factors. Because breast cancer is usually painless and asymptomatic, the patient may not recognize

the problem until it progresses to an advanced stage, therefore making treatment difficult [3].
Breast cancer mostly occurs in women but there is a possibility of its occurrence in men, too. The causes of breast cancer in men have not been fully understood, but researchers have found several factors that may increase the risk of getting it. As with female breast cancer, many of these factors are related to sex hormone levels in the body. Some other risk factors include aging, family history of breast cancer, inherited gene mutations, radiation exposure, alcohol, liver disease, estrogen treatment, obesity, conditions affecting the testicles, and certain occupations [11].

4. Methods of Breast Cancer Treatment

There are lots of influencing factors which determine treatment type such as tumor stage, type and characteristics, the person's general health, and also some medical conditions which can influence treatment [12]. One or several treatment modalities are used depending on these factors. There are three major treatment methods for breast cancer, namely, surgery (e.g. lumpectomy, radical mastectomy, segmental mastectomy, and skin sparing mastectomy), systemic therapy (e.g. biological therapy, chemotherapy, and hormone therapy), and RT (e.g. external-beam RT and brachytherapy) [7, 13,14].
In order to obtain local control in breast cancer, mastectomy was the standard treatment technique for years. In the 1970s, breast-conserving surgery changed the treatment to some extent. RT after breast-conserving surgery has been shown to reduce 5-year local recurrence rate from about 26% to 7% and the 15-years risk of breast cancer mortality from about 36% to 31%. Moreover, after PMRT to the chest wall and regional lymph nodes of node-positive patients, local recurrence rate has been decreased from 23% to 6% and breast cancer mortality from 60% to 55% [15].
Different kinds of breast cancer RT are described briefly below.

4.1. Radiotherapy

Radiotherapy can be used before or after surgery; before surgery to reduce tumor size and after it to destroy the remaining cells in the breast, chest wall, and axilla (underarm) regions. There are two types of RT, namely, external-beam RT and brachytherapy. Type, stage, and tumor location determine the method of RT. Chest wall irradiation is mostly recommended for patients with positive lymph nodes, positive pathologic margins, or very large tumors. In external-beam RT, the radiation-generating machine is located outside the body. Such machines include accelerators that produce high energy X-rays and electrons, cobalt-60 machines which emit high energy gamma rays, and much less frequently, kilovoltage X-ray tubes. Depending on the size and extent of the cancer, the treated region may include the whole breast with or without chest wall and axilla. Brachytherapy, on the other hand, usually uses radioisotope sources in the shape of seeds, needles, catheters, and wires which are directly located into the tumor or surrounding tissues [1].
Total dose in external radiotherapy is about 45-50 Gy, 5 days per week during 5 to 7 weeks. A boost dose can be delivered to the tumor site using external-beam RT (often with electrons) or brachytherapy. Deep tumors may be treated by an internal boost using electrons, kilovoltage X-rays, or radioactive sources given during the breast surgery session [12].
Breast cancer RT can also be divided into chest wall treatment and locoregional lymph node treatment [16]. There are different treatments for lymph nodes. For example, the axilla nodes can be treated by an anterior field using external-beam megavoltage photons. In order to boost the central dose, a posterior field can also be used. Internal mammary and supraclavicular nodes may be irradiated separately with the advantage of ensuring that sufficient dose is delivered to them, although this may increase heart and lung dose [17].
Tangential fields using photons, sometimes matched with an additional electron field to treat the internal mammary chain (IMC), are

often used for chest wall irradiation. This method can reduce the irradiated lung volume in comparison with the use of tangential fields alone and is particularly useful for irregular, sloping, or thick chest walls. However, regularly-shaped thin chest walls can be irradiated by electron fields [16]. At our center, post-mastectomy chest wall irradiation has been performed for many years using kilovoltage X-rays, giving a standard and acceptable local control rate [18,19].

There are some contraindications for breast RT such as patients with connective tissue diseases such as scleroderma or systemic lupus erythematosus, where severe reactions to radiation such as scars or non-healing ulcers may occur. Moreover, in case of tangential external-beam RT of a very large breast, insufficient photon energy of cobalt-60 gamma rays or low-energy megavoltage linear accelerator X-rays may cause inhomogeneous dose distributions and hot spots [12].

Breast RT, similar to other kinds of treatments, may cause some side effects. It can have some early and late side effects such as pulmonary, cardiac and skin toxicity. Feeling" pins and needles" or fatigue, reddening or peeling of skin, and loss of underarm hair are some examples of these side effects. To reduce them, the treatment dose distribution should be improved in order to reduce skin dose. Obviously, benefits of breast cancer RT should be greater than, or balanced against, the risk of these effects. Researches aimed at prevention of RT skin effects and improving their healing are ongoing [20,21]. Radiation-induced damages have mostly occurred after long latency periods (15-20 years), however, modern treatments seem to be less harmful, although long-term data are not yet available [22]. Greater use of adjuvant systemic chemotherapy and targeted therapies increase the risk of cardiac side effects. Possible cardiac toxicity from breast RT is discussed in more detail later.

4.1.1. Conventional 2D Radiotherapy

The conventional RT technique has been a 2D-planned method in which the patient is in a supine position with arms placed over the head to take them away from the radiation fields. Tangential fields are designed to cover the breast with some margin, defined on the patient's skin based on surface anatomy and normally with the help of a conventional, fluoroscopic RT simulator. In this method, in addition to the complicating problem of the inclusion of locoregional lymph nodes in the target volume, normally only the central breast contour is taken for treatment planning so it cannot consider all the variations and inhomogeneities in patient anatomy. As a result, when the target volume becomes more complex with thickness variations, dose inhomogeneities can occur which may cause side effects. Again, this is particularly evident in patients with pendulous breasts. Normally, wedged fields are used to improve dose uniformity in the target volume. Multiple fields have also been used but they usually lead to non-uniformity in dose distribution at the field junctions [23].

4.1.2. Modern Techniques in Breast Cancer Radiotherapy

In order to improve dose distribution, allow more accurate dose delivery, and reduce complications, various modern techniques have been developed, which will be briefly described in the following sections. These techniques have been employed to deliver whole-breast and/or partial-breast RT, which will be discussed consecutively.

4.1.2.1. Whole Breast Irradiation

Three-dimensional external-beam conformal RT is gaining increasing use in breast RT. Figure 1 shows an example of this technique. This technique employs CT data of the patient which is entered into a computerized 3D treatment planning system (TPS). Information including positions and densities of different tissues is used in a TPS in order to design the beams based on 3D anatomy. Beams are shaped to conform to the planning target volume, usually using a multileaf collimator (MLC). Individualized field shaping is carried out while taking account the positions of the glandular breast tissue, regional lymph nodes, and the heart as well as the chest wall contour [24,25]. When only the breast is included in the target volume, 3D conformal RT using tangential beams improves dose coverage of the breast tissue and reduction of the volume of irradiated lung and heart [26]. However, because of non-uniform dose distribution at the junctions of the tangential breast and lymph node fields in locoregional breast irradiation, 3D techniques are increasingly employed to solve this problem [27]. Accelerator-produced asymmetric collimation in one or both directions helps significantly in forming an acceptable (often vertical-plane) match between asymmetric half or quarter beams. Patient CT data can even help to customize the location of field boundaries in the TPS. Nonetheless, achieving an acceptable 3D conformal treatment plans for some patients with large breasts can be highly challenging [28].

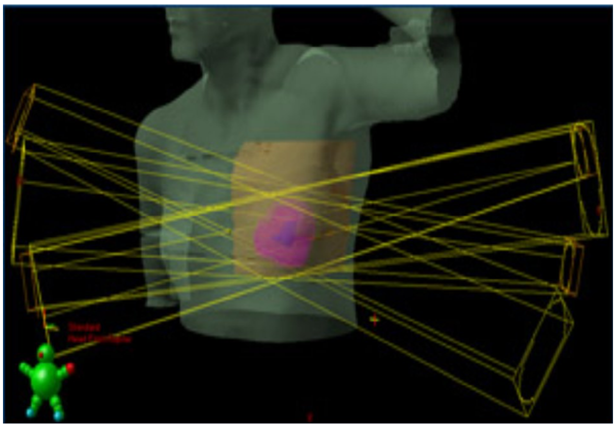

Figure 1. Example of external-beam 3D RT in breast cancer using multiple beams [29].

In cases when 3D conformal RT has shortcomings, intensity-modulated RT (IMRT) can often offer better solutions to improve the dose distribution. IMRT is an advanced treatment technique in which beam intensity is modulated within the treatment fields to offer flexibility to produce more conformal dose distributions, improve dose uniformity, and reduce heart and lung doses. For breast irradiation, IMRT can be used in plans with two tangential fields as well as more complex geometries with multiple fields and even to deliver a single-phase plan with concomitant boost treatment [28,30-31].Usually the option of two conventional tangential fields is preferred because multiple field plans have disadvantages including greater setup complexity and increased low doses to surrounding normal tissues. In the most frequently used method ("step-and-shoot"), most of the dose is given by conventional-style tangential beams and the remainder is delivered by several MLC-shaped field segments that create an intensity modulated beam [32].

In more complex multiple-beam IMRT techniques using low monitor unit efficiency delivery methods, considerably more leakage radiation and higher total-body dose can result compared with a simple tangential pair. The carcinogenic risk after IMRT is estimated to be almost double that of the standard 3D RT. The choice of the best technique must be patient-specific [33,34].

In modern techniques such as IMRT, which produce sharp dose gradients, patient set-up uncertainties (including breathing) can produce significant errors in the actual dose distribution delivered to the patient [35-37]. Image-guided RT (IGRT) comprises various image-based techniques and strategies to prevent (or at least reduce) errors resulting from patient organ motion and set-up deviations. Production of 2D and 3D anatomical images before or during treatment in the actual treatment position by linear accelerators coupled with imaging equipment such as a kilovoltage X-ray set or the megavoltage beam itself allow this technique to measure and correct positional errors of radiation fields [38-40].

Some examples of IGRT are methods which reduce the effects of patient breathing on the delivered dose distribution and are often referred to as respiratory correlation techniques which use respiratory gating. In this method, using sensors to monitor the patient's breathing pattern, the treatment is synchronized with the breathing cycle and the radiation beam is turned on during a pre-determined phase of the respiratory cycle. Figure 2 shows an example of transverse CT slices in both gated and non-gated methods. Inspiration is the best phase of the breathing cycle to use in breast RT because the distance between the breast and the heart is greatest in this phase and the lung density is also lowest. There is significant reduction in the dose to the heart and lungs by gating in the end-inspiration phase in comparison with gating in the end-expiration phase [41,42]. A moderate deep inspiration breath-hold strategy using tangential IMRT fields forms a useful respiratory gating technique for breast treatment and internal mammary nodes irradiation which has been shown to produce favorable dose distributions in terms of reduced dose to the heart and lungs [42,43].

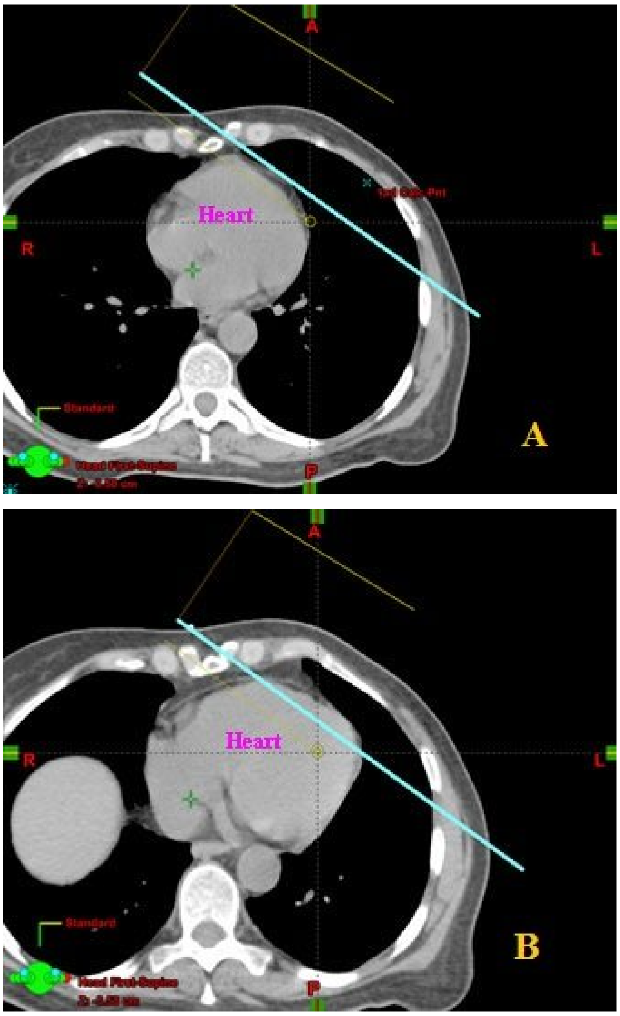

Figure 2. Transverse CT slices for the cases of respiratory gating (A) and regular breathing (B). The blue lines represent an example of a ray of radiation towards the medial border of the field in each case [44].

4.1.2.2. Partial Breast Irradiation

Irradiation of the whole breast may not always be necessary in early-stage breast cancer considering the fact that about 85% of local recurrences after breast conserving surgery and whole breast irradiation occur near the original tumor bed [45]. As a result, partial breast irradiation techniques have been developed that treat just the tissue in the region of the original tumor bed. For some patients with low risk of disease recurrence, reducing the treatment volume offers the possibility of prescribing higher doses for each treatment fraction and completing the course of treatment in a shorter time period (as short as 1 to 10 days). Therefore, this technique is called accelerated partial breast irradiation. Various treatment techniques have been developed for accelerated partial breast irradiation, most commonly used methods involving brachytherapy (intracavitary and interstitial) as well as intraoperative and external-beam RT [25, 46].

External-beam techniques such as 3D conformal RT and IMRT using multiple beams have been employed to give accelerated partial breast treatments, too. While target volume definition and localization can be challenging, the improved dose homogeneity and the non-invasive nature of these techniques are desirable [25].

Intraoperative radiotherapy (IORT) is also utilized as another accelerated partial breast technique in which a single dose is delivered to the tumor bed during breast surgery. Routinely, electrons or kilovoltage X-rays are used as the radiation [46]. Because of the types of radiation and the geometry of irradiation used, advantageous aspects of this method include its potentials for skin sparing and the practicability of shielding the thoracic wall using a metallic plate to spare the lungs and heart. The fact that the treatment is given in a single fraction together with surgery has both positive and negative consequences. While a separate multi-fraction treatment is obviated as an advantage, completion of RT before the final pathology report on the surgical specimen is known as a drawback in terms of patient selection [25].

Brachytherapy, in both its interstitial and intracavitary forms, is also applied to partial breast irradiation. The interstitial technique can be planned in the setting of low-dose-rate, pulsed-dose-rate, or high-dose-rate brachytherapy technique. In this technique, multiple catheters, separated by a distance of 1-2 cm, are placed in the breast tissue surrounding the tumor bed cavity. Figure 3 shows an example of interstitial multicatheter breast brachytherapy [47].

Figure 3. Example of bilateral interstitial multicatheter brachytherapy. The dose distribution, shown only for the right breast, demonstrates the localized nature of the high dose region sparing the organs at risk [48].

In intracavitary brachytherapy for partial breast irradiation, a balloon catheter (commercially marketed as MammoSite (Hologic, Bedford, MA, USA) is located inside the tumor bed cavity to fit its whole volume and treat a margin of 1 cm of tissue around the cavity as a high-dose-rate method. Figure 4 demonstrates an example of intracavitary balloon brachytherapy. The spherical dose distribution produce by this technique is an important disadvantage. If the tumor bed is near the surface of the breast, the skin will receive a high dose and, therefore, this technique is limited to cases where the source can be placed more than 1 to 1.5 cm from skin [47].

Figure 4. Example of intracavitary brachytherapy using a MammoSite balloon catheter [49].

5. Other Considerations

5.1. Cardiac Toxicity

Late events of breast cancer treatment such as cardiac toxicity mostly occur ten or more years after breast cancer [50]. Studies have revealed that patients with positive lymph nodes are at a higher risk of fatal myocardial infarction which results from excessive irradiation to peripheral lymph nodes. Lots of studies have been planned to find the causes of late mortality in irradiated patients. Some studies performed on left-sided stage 1-3 patients reveal that more than half of the patients suffered from local hypoperfusion, which probably resulted from irradiation to microcirculation. Other studies have confirmed an increased mortality due to cardiac disease in left-sided breast cancer patients. Irradiation of the IMC is the other risk factor for cardiac disease resulting from irradiation [51-54]. Some studies have been performed with the aim of reducing cardiac dose in IMC irradiation, for instance, a medial IMC electron field combined with photon IMRT can reduce the dose to the heart and lungs [55].

Several decades ago when information about radiation tolerance levels was limited, heart was taken into account as a radioresistant organ but in techniques which tried to deliver maximum dose to anterior mediastinal parts. Based on this idea, some complications such as pericardial effusion, constriction, and tamponade were seen [56]. Pericardial disease is found to be the most common cardiac complication. Cardiomyopathy and valve disease are seen as well [54].

Estimating the possibility of radiation-induced coronary artery disease is more challenging, because its symptoms are nearly the same as ischemic heart disease. The difference is that ischemic heart disease usually affects an older age group which have more risk factors for this disease. Although there are some case reports of cardiac effects following RT, making a conclusion is controversial because of insufficient histological information, usage of different treatment techniques, and the fact that lots of patients had at least one risk factor for heart disease.

Ignoring the older group of people, there were lots of young patients with right main coronary and left anterior descending coronary artery complications, thought to be attributed to the location of coronary arteries because they are located on the anterior part of mediastinum where they receive maximum doses. Tissue specimens of these patients had intimal fibrosis which is a sign of premature coronary artery disease. A study on coronary artery segments confirmed an increased chance of stenosis in irradiated patients especially in right main and left anterior descending coronary arteries [57]. In another study, cardiac disease was seen in 96% of the irradiated patients [54].

The most reliable evidence of radiation-induced coronary artery disease comes from long-term follow up with large number of early stage patients who needed postmastectomy chest wall irradiation. In an overview of ten trials, when follow up exceeded 10 years, a highly statistically significant increase in mortality was seen in the irradiated group [58]. In another study, the increased risk in cardiac mortality was confirmed to be a result of chest wall irradiation. It was also revealed that different modalities may lead to different amount of risks, for example, cardiac mortality risk was greatest when left-sided tumors were treated with orthovoltage X-rays [59] Another study reported that the number of deaths from myocardial infarction was significantly increased in stage 1 irradiated patients. Studies of delivered dose to the heart in RT of other cancers such as esophageal cancer also provide useful supplementary information [60,61].

5.2. Prone Positioning

Prone positioning is a solution for delivering maximum dose to thick or pendulous breasts as well as improving dose homogeneity and minimizing delivered dose to the underlying tissues such as lungs [62-63]. In this method, the patient lies in a prone position on a dedicated board which has a hole to place the breast in so that it can be away from the chest wall. It must be pointed out, however, that the heart in this position is pushed toward the anterior part of the mediastinum and gets closer to treated volume, so that the sparing effect of the heart is unclear. Another issue is that tumor coverage near medial and lateral borders of the breast may be reduced as a result of the patient's position [64]. Generally, the risk of epidermolysis is reduced because of the elimination of skin folds. Moreover, breathing motion is less pronounced, so intra-fraction motion is smaller. However, patient set-up variations can be significantly larger leading to an increased inter-fraction variation [63].

6. Conclusion

Using RT after breast surgery is increasing. Studies have shown that postoperative RT reduces the rate of local recurrence after treatment for early breast cancer. However, no significant improvement in survival rates has been shown after RT, and some critics have claimed that it even has a deleterious effect.

Increasing the dose homogeneity and conformity of the high-dose region with the target volume while decreasing the lung and heart doses are the main goals of breast RT. Modern RT techniques aim to achieve this goal. The developmental process of breast RT suggests that these treatments are going to be more effective and less harmful. For example, brachytherapy offers several advantages including preservation of the breast shape.

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