

Introduction

Breast cancer is the second most common cause of death in all cancer female patients. The American Cancer Society estimated that 235, 030 new cases of invasive breast cancer were diagnosed in the United States during 2014, of which approximately 40, 430 women were expected to die from it (*Siegel et al., 2014*).

In 2006 the estimated age adjusted annual incidence of breast cancer in the European Union (25 countries) was 110.3/100,000 and the mortality 25.0/100,000 (*Ferlay et al., 2007*).

In Egypt, breast cancer is the most common cancer in females, it represents 26.8% of all cancer cases in Minia female registry 2009 & 32.9% of all cancer female cases in Damietta cancer registry 2009 (*NCI, 2010*).

Radiotherapy reduces the risk of local relapse and breast cancer mortality and is offered to nearly all patients after conservative surgery (*Clarke et al., 2005*).

The international standard RT regimen after breast conservative surgery for early breast cancer delivers 25 daily fractions of 2 Gy to a total dose of 50 Gy over 5 weeks followed by 5-8 fractions of 2 Gy (10 -16 Gy) as a boost to the tumor bed . The high number of women with breast cancer, receiving postoperative RT, led to think that a shorter course of irradiation would result in improved quality of life for patients, in potentially better integration with systemic treatments and in reduced costs. Therefore, alternative schedules based on a lower total dose delivered in fewer, larger fractions (hypofractionation) were firstly introduced in Canada and the United Kingdom (UK). The Canadian randomized trial tested 42.5 Gy in 16 fractions against 50 Gy

in 25 fractions. Results suggested equivalence in terms of local control and breast cosmetic results for the 16-fractions regimen (*Owen et al., 2006*).

The two most recent randomized studies were conducted by the START Trials in order to test the effects of radiotherapy schedules using fraction size larger than 2.0 Gy. The START Trial A tested two dose levels of a 13-fractions regimen delivered over 5 weeks and the START Trial B compared 40 Gy in 15 fractions of 2.67 Gy in 3 weeks with a control group of 50 Gy in 25 fractions of 2.0 Gy over 5 weeks. These studies seem to offer rates of late adverse effects and local-regional tumor relapse at least as favorable as the standard schedule (*The Start Trailists's Group, 2008*).

Aim of the Work

The aim of the present study is to assess hypofractionated radiotherapy after conservative breast surgery in early breast carcinoma using a regimen of 2.25 Gy/fraction, 5 fractions / week, over 4 weeks to a total dose of 45 Gy to the whole breast followed by a boost of 9 Gy in 3 fractions versus conventional fractionation in terms of Local control, Acute and late toxicities, Breast cosmesis at 1 year as primary end points.

Epidemiology

Breast cancer is by far the most frequent cancer among women with an estimated 1.38 million new cancer cases diagnosed in 2008 (23 % of all cancers). And ranks second overall (10.9% of all cancers). It is now the most common cancer both in developed and developing regions with around 690 000 new cases estimated in each region, incidence rates vary from 19.3 per 100, 000 women in Eastern Africa to 89.7 per 100, 000 women in Western Europe, and are high (greater than 80 per 100.000) in developed regions of the world (except Japan) and low (less than 40 per 100, 000) in most of the developing regions (*Ferlay et al., 2008*).

Incidence rates in some of these countries, including the United States, United Kingdom, France, and Australia, sharply decreased from the beginning of the millennium. Partly due to lower use of combined postmenopausal hormone therapy. In contrast, breast cancer death rates have been decreasing in North America and several European countries over the past 25 years, largely as a result of early detection through mammography and improved treatment see Fig. (1) (*Jemal et al., 2011*).

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In Egypt cancer registry program and in Aswan profile in 2008 breast cancer, though mainly a cancer of women was still the most frequent for both genders together, it represented more than one-fifth of cases. Breast cancer was by far the most frequent cancer in females representing approximately 40% of cases. In Damitta profile 2009, also Breast cancer was the most common malignancy in female: it represented 32.9% of all females' cancer. In El-Minia profile 2009, Breast cancer

represented 26.8% of all females Cancer (**Ibrahim et al., 2010**).

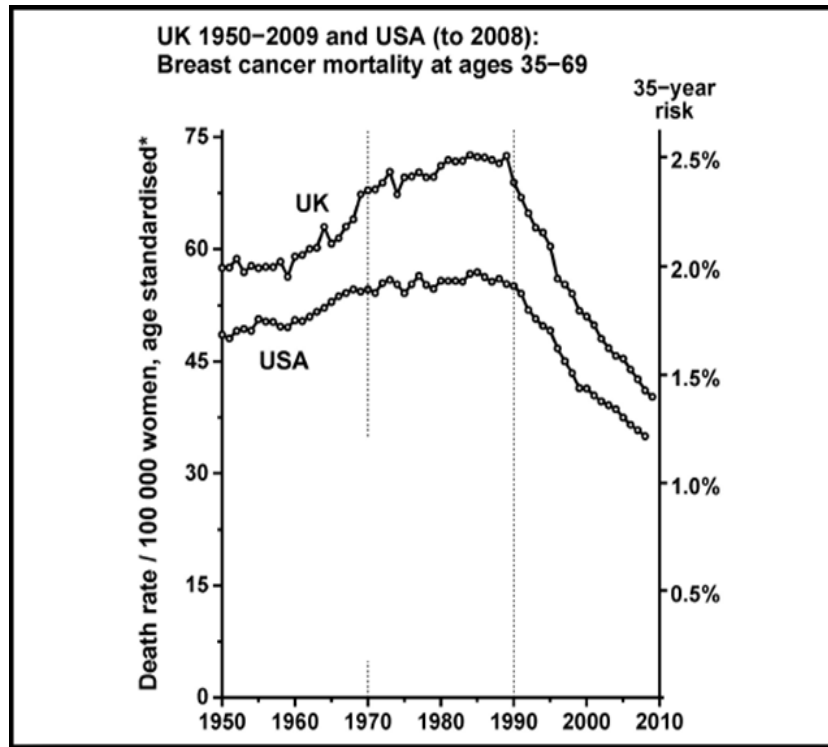


Fig. (1): Showed breast cancer mortality in USA and UK from 1950-2009 (Early Breast Cancer Trialists' Collaborative Group (EBCTCG), *Lancet* 2011)

In Egypt breast cancer constitutes 33% of all female Cancer at national cancer institute (NCI) and 50% in private series. The median age is 46 years (**El-Bolkainy et al., 2005**).

Breast Cancer in Egyptian patients is biologically more aggressive than in western population this may be due to earlier age at presentation and to a lesser extent the late presentation. In an epidemiological study national cancer institute (NCI) the breast cancer patients presented by T1 stage in 1.2%, T2 in 30%, T3 in 26.4% and T4 in 42.4% and the mean tumor diameter is 4.5 cm Positive lymph node metastasis is found in 75% of patients (**El-Bolkainy et al., 2005**).

In Ain shams university average in 4 years from 2006 - 2009 Breast cancer was by far the most frequent cancer in representing approximately 25.6% of cases.(Average 380 cases of cancer breast out of 1500 new cancer patient per year) ***(In Ain Shams University, from 2006 -2009).***

Breast Anatomy and Routes of Spread :

The mammary gland is composed of glandular tissue, subcutaneous fat, and dense fibrous stroma containing an intricate network of lymphatics, nerves, and blood vessels. The gland is supported between the superficial fascia attached to the dermis and the deep fascia overlying the chest wall muscles interconnected by the Cooper- ligament. The breast is mainly situated on the pectoralis muscle and extends craniocaudally between the second and sixth anterior ribs and mediolaterally from the sternum to the axillary midline with a portion of the breast reaching into the low axilla referred to as the tail of Spence see Fig. (2).

The glandular tissue of the breast is made up of between 4 and 18 milk ducts emanating, not always radially, from the nipple-areola complex. The ducts branch early on after leaving the nipple and form a highway of pathways, which terminate in ductal-lobular complexes. The lobules consist of specialized cells, which secrete milk products that travel down the ducts to the nipple predominantly during lactation. Most breast cancers originate from the interface of the ductal-labular complex.

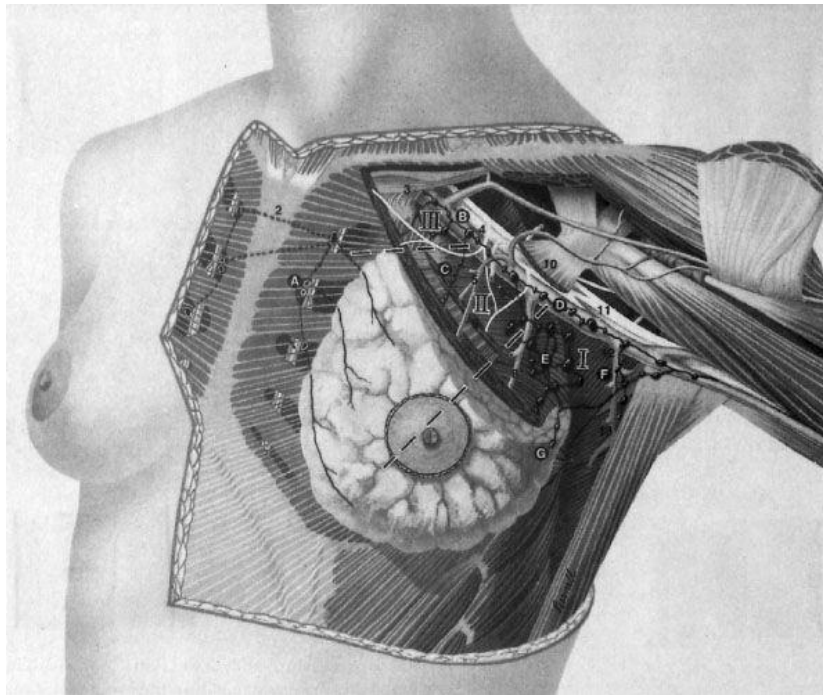


Fig. (2): Anatomy of the breast and lymphatic drainage (From Osborne MP. Breast development and anatomy. In: Harris JR, Hellman S, Henderson IC, et al., eds. Breast diseases. Philadelphia: JB Lippincott, 1987:1–14, with permission.)

The lymphatic channels are present in the subareolar skin and follow the duct lobular complexes and most frequently drain into the lymph node chains located in the axillary basin. Breast lymphatics can also directly communicate with the infraclavicular/supraclavicular or internal mammary lymph node chains. Intramammary nodes are located within the breast parenchyma and can contain the metastatic tumor from the primary site. The **axillary nodes** are divided into three levels (I-III) based on their relationship with the pectoralis minor muscle. **Level (I)** is located caudal and lateral, **level (II)** nodes are beneath the muscle, and **level (III)** (infraclavicular) nodes are located cranial and medial to the pectoralis minor see Fig. (3).

Orderly spread of tumor cells from the primary breast tumor most commonly starts at the level I axillary nodes and then proceeds to level II and level III lymph nodes.

Skip metastases that defy this order can occur but are less likely and a standard axillary dissection for sentinel positive disease requires pathologic analysis of level I and level II axillary nodes.

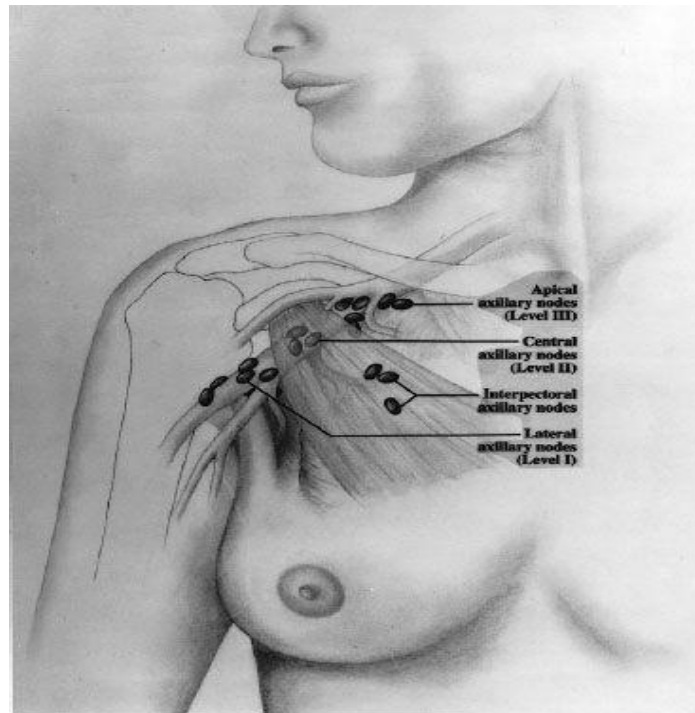


Fig (3): Location of the three levels of axillary lymph nodes (Redrawn from Morrow M. Axillary node dissection: what role in managing BCa? Contemp Oncol 1994; 8(4):16-27, copyright Medical Economics. Adapted from an illustration by John Daugherty, copyright 1994) .

The **Supraclavicular lymph nodes** (SCV) are located within the space defined by the omohyoid muscle and tendon (lateral and superior borders), the internal jugular vein (medial border), and the clavicle and subclavian vein (inferior border). The **Internal Mammary lymph node chain** (IMN) is encased within the endothoracic fascia in the parasternal space and runs

alongside the corresponding artery and vein. The nodes located in the first through third intercostal spaces (**Madu et al., 2001**).

Inner quadrant tumors had a higher incidence of hot spots in the IMN nodes with the highest frequency in tumors in the lower inner quadrant. Upper quadrant lesions are more commonly localized to the second, third, and fourth interspaces while central and lower quadrant lesions are more commonly localized to the second, third, fourth, and fifth interspaces. Drainage to the supraclavicular nodes occurred in less than 1% of the patient expect for those with a central primary tumor (**Chen et al., 2008**).

Risk Factors :

Risk factor for the breast cancer can be divided into those are modifiable and those that are not. Nonmodifiable risk factors include gender, age, family history, age at menarche, age at menopause, race, and history of prior benign breast biopsy. Modifiable factors include parity age at live birth, mammographic density, breast-feeding, obesity and weight gain, exogenous hormones, radiation, alcohol consumption, and diet. Aside from being female age is the single most important Breast cancer risk factor. According to the National Cancer Institute, the risk between ages 30 and 39 is 0.43% (1 in 233), 40 and 49 is 1.440% (1 in 69), 50 and 59 is 2.63% (1 in 38), and between 60 and 69 is 3.65% (1 in 27) based on probabilities for the whole population and not individual risk factors (**Bethesda, 2008**).

A family history of breast cancer particularly in a first degree relative is a significant risk factor, and the risk escalates with the number of relatives affected and younger age at diagnosis. This pattern suggests an inherited genetic mutation that predisposes to the development of the breast cancer.

Approximately 5% to 10% of breast cancer patient have a familial form of the disease (**Garber et al., 2005**).

Many of these cases contain an alteration in the breast cancer genes, BRAC1 and BRAC2. More than 100 distinct mutations have been identified in high-risk families and it is not clear if all carry an equal cancer risk. Some populations have a higher likelihood of carrying germline mutations such as family members of Ashkenazi Jewish (Eastern European) heritage and families with multiple cases of breast and /or ovarian cancers. The estimated lifetime risk of developing a breast cancer is up to 80% (36% to 85%), with a near 40% risk of developing a contralateral breast cancer. The risk of developing an ovarian cancer is 40% in BRCA1 carriers and 20% for BRAC2 carriers. Genetic counseling should be offered to these patients including those of young age at diagnosis, two primary breast cancers (ipsilateral or contralateral) or with breast and ovarian cancer and male breast cancer (**Gulati et al., 2008**).

The absolute risk of a contralateral breast cancer in women with a personal history is 0.5% to 1% per year or up to 10% during the 10 years following diagnosis. Biopsy-proven atypical proliferative disorders, including atypical laboular hyperplasia (ALH), lobular carcinoma in situ (LCIS), and atypical ductal hyperplasia (ADH), may increase the risk by a range of fourfold to tenfold with a further increase in a patient with a family history (**Li et al., 2006**).

Mammographic density is a strong independent risk factor with a fourfold to sixfold increase for postmenopausal women with high breast density compared with those with least dense breasts. Breast density refers to the amount of white area (fibrous and glandular tissue) on a black (primarily fat tissue) mammogram (**Chen et al., 2006**).

The risk of the developing breast cancer after exposure to ionizing radiation is dose and age dependent and has been demonstrated from data collected from the Japanese atomic bomb survivors and patients exposed to radiation for nonmalignant conditions, such as thymus enlargement, multiple chest fluoroscopies for tuberculosis, and mastitis examinations (**Land, 1995**).

Secondary breast cancer has been described in young women who underwent mantle irradiation for Hodgkin disease with doses ranging from 20 to 44 Gy (**Hoppe et al., 1997**).

A moderate relative risk is associated with factors which affect circulating hormone levels such as delayed childbirth, nulliparity, early or late menarche and exogenous hormones. Body mass index (BMI) or postmenopausal obesity, has clearly been associated with breast cancer risk likely due to higher estradiol levels, associated with aromatase in adipose tissue which converts androgens to estradiol (**Van Den Brandt et al., 2000**).

Alcohol consumption increases the risk of breast cancer. The relative risk of breast cancer was dose-dependent and increased with daily amount (**Lew et al., 2008**).

Environmental factors pollutants; tobacco, nutrition and physical activity have not clearly been linked with breast cancer risk to date. Diet, nutrition, and physical activity are clearly interrelated with obesity and BMI but are difficult to dissect apart.

Screening and early detection:

Screening Mammography:

A **Screening mammogram** is a mammogram that consists of two standard views of each breast that are obtained on asymptomatic women. Screening mammography's efficacy in reducing breast cancer mortality is well established,

especially in women aged 50 to 69 years. Trials comparing screening mammography with or without clinical breast examination to usual care (with little or no screening mammography) demonstrated remarkably consistent beneficial results for women older than 50 years. Meta-analyses that included all trials demonstrated statistically significant reductions of 20% to 35% in mortality from breast cancer for women aged 50 to 69 years (*Fletcher and Elmore, 2003*).

The goal of a screening mammography program is to detect small (<1 cm) tumors, typically through identification of characteristic masses and/or microcalcification. Mammographic screening is generally suggested to the asymptomatic 40–45 years old female population at 2-year intervals, while the American Cancer Society and the American College of Radiology recommend yearly mammograms beginning at the age of 40 years (*Elmore et al., 2005*).

The current evidence is insufficient to assess the additional benefits and harms of clinical breast examination (CBE). A randomized controlled trial comparing high-quality CBE to screening mammography showed equivalent benefit for both. It was also used in conjunction with mammography in one Canadian trial. Thus, it is not possible to assess the efficacy of CBE as a screening modality when it is used alone versus usual care (*Semiglazov et al., 2003*). Breast self-examination (BSE) has been compared to usual care (no screening activity) but has not been shown to reduce breast cancer mortality (*Thomas et al., 2002*).

Magnetic Resonance Imaging Screening:

The role of MRI screening is rapidly evolving. MRI is unlikely to replace mammography for screening of the general population and is not recommended by the USPSTF in their statement on breast cancer screening (*Nelson et al., 2009*).

However, its use in screening high-risk populations has recently been supported in several studies. For women at high risk for breast cancer due to strong family history or positive BRCA1/BRCA2 status, the standard screening techniques of breast self-examination, clinical breast examination, and mammography may be suboptimal. Nearly half of the cancers in this population are detected by physical examination between routine radiographic surveillance. In this population, increased breast density and rapid proliferative rates likely contribute to the relative insensitivity of mammography. Although MRI has not yet been shown to impact mortality, the sensitivity of MRI over mammography, clinical examination, and ultrasound in this high-risk population has been demonstrated in several studies (*Kriege et al., 2004*).

In a surveillance study, 236 women with BRCA1/BRCA2 mutations underwent one to three annual screenings with breast examination, mammography, MRI, and ultrasound. Of 22 cancers detected, 17 (77%) were detected by MRI, 8 (36%) by mammography, 7 (33%) by ultrasound, and 2 (9.1%) by breast examination. All four screening modalities combined had a sensitivity of 95%, which compared favorably to the 45% sensitivity for mammography and breast examination alone (*Warner E et al., 2004*).

Clinical Presentation and Diagnosis:

The most frequent presentation of early stage breast cancer is an asymptomatic, nonpalpable mass, which is detected as an abnormality on screening mammogram. The most common physical sign is a nonpainful mobile mass (*Osteen et al., 2001*). A detailed physical examination includes evaluation of the ipsilateral and contralateral breast tissue and regional lymph nodes (bilateral axillae, supraclavicular, infraclavicular, anterior cervical/neck, and submental and submandibular lymph nodes chain). The treatment approach is determined, in part, by the clinical

presentation such as tumor size, location, and skin involvement. A large tumor can be contraindication to breast conservation; inner quadrant tumors require lymphoscintigraphy to identify sentinel nodes located in the internal mammary chain.

Diagnostic mammography:

A Diagnostic mammogram is the evaluation of a woman who has a diagnosed abnormality. A diagnostic mammographic examination usually consists of standard screening views and additional views using spot compression and/or magnification of a specific area (*William et al., 2002*).

Diagnostic mammogram may have superior performance over screening mammogram, because noticeable symptoms or clinical findings may indicate a more advanced tumor that is easier to locate and identify. Tumors detected by diagnostic mammogram are often larger than those detected by screening mammogram (*Dee and Sickles 2001*).

Mammographic signs of cancer consist of two primary finding: (1) a mass with ill-defined, irregular, or speculated edges and/or (2) irregular, pleomorphic calcifications.

The imaging reports should include size and location of the primary tumor and a description of the findings in accordance with the American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) guidelines (*BIRADS, RestonVA, 2003*).

BIRADS classification of the mammography findings:

Category 1: Negative

There's no significant abnormality to report. The breasts look the same (they are symmetrical) with no masses (lumps), distorted structures, or suspicious calcifications.

Category 2: Benign (non-cancerous) finding

This is also a negative mammogram result but the reporting doctor chooses to describe a finding known to be benign (e.g: benign calcifications or calcified fibroadenomas).

Category 3: Probably benign finding

Follow-up in a short time frame is suggested. The findings in this category have a very good chance (greater than 98%) of being benign. The findings are not expected to change over time. But since it's not proven benign, it's helpful to see if an area of concern changes over time. Follow-up with repeat imaging is usually done in 6 months and regularly thereafter until the finding is known to be stable (usually at least 2 years).

Category 4: Suspicious abnormality

Biopsy should be considered findings do not definitely look like cancer but could be cancer. The radiologist is concerned enough to recommend a biopsy.

Category 5: Highly suggestive of malignancy

Appropriate action should be taken the findings look like cancer and have a high chance (at least 95%) of being cancer. Biopsy is very strongly recommended.

Category 6: Known biopsy-proven malignancy

Appropriate action should be taken. This category is only used for findings on a mammogram that have already been shown to be cancer by a previous biopsy. Mammograms may be used in this way to see how well the cancer is responding to treatment (*Taplin et al., 2002*)