INTRODUCTION

The major change in the surgical treatment of primary breast cancer has been the shift towards breast conservation surgery that started over 30 years ago. Currently in western Europe about two-thirds of newly diagnosed cancers are amenable to breast conservation therapy (wide local excision and radiotherapy) but in the remaining third, mastectomy is still recommended because of presence of either absolute or relative contraindications to breast conserving therapy ***(Aebi et al., 2011).***

Approximately 95% of patients receiving radiotherapy will experience radiodermatitis and 87% will experience moderate to severe radiodermatitis during or after their radiotherapy. In a study done by RTOG , acute skin toxicity in patients who received radiation therapy for breast cancer without chemotherapy showed the following pattern: 7-9% grade 0, 50-58% grade 1, 32-41% grade 2, and 0-3% grade 3 ***(Fisher et al., 2000).***

Although relatively short lived, skin reactions are uncomfortable and itchy, can be painful and are some-times dose-limitingand has been associated with decreased quality of life. Furthermore, severe radiodermatitis necessitates treatment modifications or delays, which may compromise the efficacy of radiotherapy ***(McQuestion, 2006).***

Moist desquamation, evidenced by red, exposed dermis and serous oozing, occurs after four to five weeks of therapy as the basal cells are depleted. Moist desquamation is characterized by epidermal necrosis, fibrinous exudates and often considerable pain. Bullae, if present, may rupture or become infected. Histologically, arterioles are obstructed by fibrin thrombi and edema is prominent ***(Archambeau et al., 1995).***

In a study evaluating the effect of treatment interruption in cases of breast cancer,the authors reported that they have not found adverse effects resulting from less than-seven-day interruptions; on the other hand, in cases where the interruption duration was longer, they have found about 5% decrease in the local management of the disease ***(Bese et al., 2005).***

Although the prolongation of the overall treatment time allows the repopulation of cells in normal tissues, repopulation of surviving tumor cells also occurs, thereby increasing the number of tumor cells that must be eradicated. Furthermore, as cellular damage and cell death occur during the course of the treatment the tumor cells may respond with an increased rate of cell proliferation. There is evidence that this accelerated repopulation of tumor cells limits the effectiveness of radiation therapy ***(Schmidt et al., 1999).***

Local recurrences occurring in the breast can theoretically be divided into true local recurrence(at the lumpectomy site) or an “elsewhere” recurrence (away from the lumpectomy site) .In

general, the majority of in-breast local recurrences occur in the region of the prior lumpectomy site and index quadrant, whether the patient undergoes postoperative breast irradiation or not. On average, only 3% of patients treated with breast-conserving surgery will have an in-breast local recurrence away from the original lumpectomy site with or without postoperative standard whole-breast irradiation ***(Smith et al., 2000).***

Mark et al., 2010 conducted a study evaluating the ability of use of intercurrent boost(IB) during whole breast irradiation (WBI) to decrease the of grade 2/3 dermatitis and the treatment breaks needed to relief it. The idea of IB is to stop the WBI during the 4^{th} week of irradiation to give a time period for the dermatitis to be improve while irradiating the area of the tumor bed which is well known to the most susceptible for local recuurence.

AIM OF THE WORK

The present study aims to evaluate the ability of planned intrercuurent boost method to decrease occurrence of radiodermatitis in the breast in comparison to the conventional method of giving the boost after finishing whole breast irradiation.Our primary end point is to comparetheplanned intrercuurent boost method with the conventional WBRT method regarding the rate of radiodermatitis, treatment breaks and the average overall treatment time.Our secondary end point is to comparetheplanned intrercuurent boost method with the conventional WBRT method regarding the rate of ipsilateral breast local recurrence(IBLR).

REVIEW OF LITERATURE

EPIDEMIOLOGY AND DIAGNOSIS

Incidence:

In 2013, an estimated 232,340new cases of invasive breast cancer were expected to be diagnosed in women in the U.S., along with 64, 640 new cases of non-invasive (in situ) breast cancer, and an estimated39,620 deaths per year are reported. The lifetime risk of an American female developing breast cancer is 13% ***(Jemal et al.,2013).***

Although breast cancer incidence rates in Egypt are substantially lower than the rates in the United States and other developed countries, it is the most common cancer among women in Egypt. In Egypt, the median age at diagnosis for breast cancer is ten years younger than in the United states and Europe. It is the leading cancer-related cause of death among women.The disease accounts for 37% of women's cancer with an incidence rate of 49.6/100, 000 ***(Rennert, 2006).***

The overall breast cancer incidence rates increased in Gharbiah, Egypt, from 1999 to 2008 by an average annual percent change (AAPC) of 2.3%.Women aged 50–59 years had the highest overall breast cancer incidence rates through this period

with AAPC of 5.1%. They expected a significant increase in the breast cancer caseloads from 2009 to 2015 among women aged 30–39 years (AAPC = 1.0%)and among women aged 40–49 years (AAPC = 1.8%) ***(Kelly et al., 2013).***

Etiology:

Risk factors for breast cancer in women can be categorized according to their relative risk for causing breast cancer. Factors with a higher level of relative risk (RR)>2.0 includes past history of breast cancer, selected precursor lesions of breast cancer including atypical ductal carcinoma, lobular carcinoma in situ and ductal carcinoma in situ and increased breast density ***(Tamimi et al., 2007).***

Other factors appear to have a moderate level of increased risk (RR : 1.5-2.0) such as heavy alcohol intake,delayed childbirth and exogenous hormones. Some risk factors appear to have modest levels of increased risk (RR: 1.0-1.5) such as post menopausal obesity, hormone replacement therapy. Finally, for some risk factors the level of increased risk was difficult to determine such as early menarche (likely to be relatively modest), xenoestrogens and phytoestrogens ***(Rehm et al., 2003).***

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 1.44% (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 (***Ries et al., 2005).***

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. Approximately 5% to 10% of breast cancer patients have a familial form of the disease ***(Garber and Offit, 2005).***

The most common cause of hereditary breast cancer is an inherited mutation in the *BRCA1* and *BRCA2* genes. These cancers tend to occur in younger women and often affect both breasts .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***(Malone et al., 1998).***

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 ***(Clarke et al., 2005).***

The risk of developing breast cancer after exposure to ionizing radiation is dose and age dependent. Secondary breast cancer has been described in young women who underwent

mantle irradiation for Hodgkin lymphoma with doses ranging from 20 to 44 Gy. The risk of breast cancer significantly increases 15 to 30 years after treatment for those women exposed between the ages of 10 to 30 years. Current practice using lower doses of radiation and limited fields for Hodgkin lymphoma may decrease the risk of breast cancer for these patients ***(Travis et al., 2005).***

A pooled analysis of prospective studies demonstrated a 30% higher risk in postmenopausal woman with a BMI more than 31 kg/m2 compared with a BMI of less or equal to 20 kg/m2 ***(Van et al., 2000).***

Screening and early detection:

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-year-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).***

Diagnosis:

Symptoms and Signs:

Early breast cancer usually does not cause symptoms. As the mass grows, symptoms start to appear and include breast lumpthat is often hard, has uneven edges, and usually painless. Symptoms may also include change in the size, shape, or consistency of the breast or nipple (e.g: redness, dimpling, or puckering) discharge coming from the nipple that may be bloody, clear to yellow, green, and may be purulent ***(Warner, 2011).***

Diagnostic mammography:

A screening mammogram is a mammogram that consists of two standard views of each breast that are obtained on asymptomatic women while 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).***

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)***

Ultrasound, either hand-held or automated, has gained acceptance as supplemental screening, aimed primarily for high-risk women and those with dense breasts inadequately visualized with mammography. Pathological diagnosis should be based on core needle biopsy obtained by manual, or preferably by ultrasound or stereotactic guidance. A core needle biopsy, or if that is not possible, at least a fine needle aspiration indicating carcinoma should be obtained before any surgical operation ***(Berg et al., 2012).***

Women with breast cancer gene (*BRCA*) mutations are at higher risk for breast cancer at an earlier age, and experts recommend surveillance by self-examination and healthcare professionals at younger ages. ***Warner et al., 2004*** concluded that, in *BRCA* mutation carriers, MRI is more sensitive than mammography, ultrasound and clinical breast examination alone.

Some studies have shown that MRI is better at identifying multifocal and multicentric lesions than triple assessment (clinical

examination, fine-needle aspiration cytology and mammography) (***Drew et al., 1999).***

MRI is also useful in patients with axillary lymphadenopathy due to occult breast cancer. Some studies have shown that MRI can detect a suspicious lesion in 76% of stage II patients ***(Buchanan et al., 2005)***. MRI is also useful in detecting cancer in contralateral breast in women with newly diagnosed breast cancer ***(Lee et al., 2003).***

PATHOLOGY AND STAGING

Pathology

The American Joint Committee on Cancerclassifies breast cancers into the following histopathologic categories: in situ cancers and invasive cancers. Carcinoma in situ represents malignant epithelial cells are limited to the basal membrane of ductus and acinus.Invasive carcinoma (infiltrative cancer)means that neoplastic cells invaded the basal membrane and show stromal invasion; therefore, invasive cancers may invade lymphovascular spaces, and they have the ability to metastasize to regional lymph nodes and distant organs ***(Stephen and Carolyn 2010).***

The in situ cancers include those that are not otherwise specified (NOS),lobular carcinoma in situ, ductal carcinoma in situ (DCIS, intraductal cancer), and Paget disease with DCIS. The invasive cancers include those that are not otherwise specified, ductal, lobular, medullary NOS, or medullary with lymphoid stroma, mucinous, tubular, papillary (predominantly micropapillary pattern), Paget disease with invasive cancer, inflammatory, undifferentiated, squamous cell and adenoid cystic***(Greene et al., 2002).***

Ductal carcinoma in situ (DCIS) is a premalignant lesion in which there is proliferation of malignant epithelial cells

completely within the breast ducts. The average age at diagnosis is 55 years It occurs more commonly than lobular carcinoma in situ (LCIS), .Approximately 80% of DCIS lesions are nonpalpable and detected by screening mammography ***(Abeloff et al., 2000).***

Invasive ductal carcinoma(IDC) is the most common form of invasive breast cancer. It accounts for 80% of breast cancer incidence upon diagnosis. On a mammogram, it is usually visualized as a mass with fine spikes radiating from the edges***(Eheman et al., 2009).***

Invasive lobular carcinoma (ILC) of the breast is the second most common histological type of breast cancer next to invasive ductal carcinoma (IDC). It accounts for 5–15% of newly diagnosed invasive breast cancers. They are often characterized by multifocality and a higher incidence of bilaterality ***(Pestalozzi et al., 2008).***

The ***International Breast Cancer Study Group*** (IBCSG) has shown that the presence of perivascular invasion (PVI) predicts the presence of occult lymph node metastases on serial sectioning and predicts the presence of positive sentinel nodes ***(Viale et al., 2005).***

Determining the status of estrogen and progesterone receptors, HER2 amplification and Ki-67 antigen expression is practical and valuable for estimating the patient prognosis and for determination of the treatment strategy ***(Raica et al., 2009).***