بسم الله الرحمن الرحيم

﴿قَالُواْ سُبْحَانَكَ لاَ عِلْمَ لَنَا

إِلاَّ مَا عَلَّمْتَنَا إِنَّكَ أَنتَ

الْعَلِيمُ الْحَكِيمُ﴾

صدق الله العظيم

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INTRODUCTION

Excluding skin cancers, breast cancer is the most common cancer diagnosed among women in the United States, accounting for nearly 1 in 3 cancers. It is also the second leading cause of cancer death among women after lung cancer. Approximately 232,340 new cases of invasive breast cancer and 39,620 deaths are expected among US women in 2013. Approximately 79% of new cases and 88% of breast cancer deaths in 2013 will occur among women aged 50 years and older. In addition to invasive breast cancers, about 64,640 new diagnoses of in situ breast cancer are expected among US women in 2013 ***(Siegel and Jemal, 2013)***.

Age, family history, early menarche, late menopause, nulliparity, late age at first full-term pregnancy and use of hormone replacement therapy (HRT) are well-established risk factors for the development of breast cancer ***(McPherson et al., 2000)***.

Early detection of breast cancer is important to reduce mortality and morbidity. Traditionally, three methods of breast screening were recommended: mammography, clinical breast examination (CBE), and breast self-examination (BSE). At present, BSE and CBE are no longer widely recommended, while mammography is still broadly promoted in the Western world. It is argued that it is premature to caution women against BSE and CBE because the current evidence is inconclusive or

incomplete. Moreover, women should be better informed about the potential harms associated with mammography screening ***(Kearney and Murray, 2009)***.

It has been estimated that a 70% participation of the target population is necessary to effectively reduce mortality from breast cancer through screening ***(WHO, 2007)***. It is generally agreed that mammography may not be an appropriate screening test for low- and middle-income countries. Mammography is expensive, requires skilled manpower and stringent quality control, and is on the whole a complex screening test. In addition, since the median age at diagnosis of breast cancer is approximately ten years younger in low- and middle-income countries than that in the developed world, and since mammography is less effective in women below the age of fifty, this test may not significantly affect mortality in these populations ***(Harford, 2011)***. In countries where breast cancer is diagnosed at an advanced stage, screening by CBE with the teaching of BSE as an integral component will probably be effective in reducing breast cancer mortality ***(Miller and Baines, 2011)***.

The 'Gold Standard' treatment for breast cancer is a complete surgical excision of the tumour and staging of the axillary lymph nodes, followed by appropriate combinations of adjuvant therapies ***(Wyld and Reed, 2007)***.

These treatments are individualized for each patient, often with the treatment plan developed through the input of a

multidisciplinary team ***(NBCC 2006)***. Ideally, choices between treatment options should be informed by extensive evidence, based mainly on evidence from randomised trials and encapsulated in published treatment guidelines ***(NBCC 2001)***.

Prognostic factors are frequently helpful in the clinical management of breast cancer patients and have the potential to improve the quality of individual care for these patients. Lymph node status and tumor size are the most important prognostic factors of breast cancer recurrence and survival ***(Axelson et al., 2005)***. In recent years, many tumor biomarkers have been investigated for patient survival, such as p21 ***(Somlo et al., 2008)***, cyclin E ***(Potemski et al., 2009)***, and MMP-9 ***(Zhang et al., 2012)***.

Breast care specialists rank the detection of treatment related morbidity the most important reason for follow-up care for women with breast cancer ***(Khatcheressian et al., 2006)***.

The breast cancer survivor may have undergone multiple treatment modalities, including surgery, radiation, chemotherapy, biologic or targeted therapies, and/or endocrine therapy. Not all patients receive all breast cancer therapies, but side effects for all the breast cancer treatment modalities can appear and persist ***(Zalewski et al., 2010)***.

There are several problems in identifying and estimating the frequency of treatment-related side effects. Information about side effects is often derived from retrospective case-

control and registry studies that have been subject to several biases ***(Shapiro and Recht, 1994)***.

AIM OF THE WORK

The aim of this work is to review the treatment related late side effects noticed in female breast cancer long after completing their cancer treatment and their effects on quality of life.

EPIDEMIOLOGY, DIAGNOSIS AND STAGING

A) Epidemiology:

Excluding skin cancers, breast cancer is the most common cancer diagnosed among women in the United States, accounting for nearly 1 in 3 cancers. It is also the second leading cause of cancer death among women after lung cancer. Approximately 232,340 new cases of invasive breast cancer and 39,620 deaths are expected among US women in 2013. Approximately 79% of new cases and 88% of breast cancer deaths in 2013 will occur among women aged 50 years and older. In addition to invasive breast cancers, about 64,640 new diagnoses of in situ breast cancer are expected among US women in 2013 ***(Siegel and Jemal, 2013)***.

An estimated 232,340 new cases of invasive breast cancer are expected to be diagnosed among women in the US during 2013; about 2,240 new cases are expected in men. Excluding cancers of the skin, breast cancer is the most frequently diagnosed cancer in women. In addition to invasive breast cancer, 64,640 new cases of in situ breast cancer are expected to occur among women in 2013. Of these, approximately 85% will be ductal carcinoma in situ (DCIS) ***(Cancer Facts & Figures, ACS. 2013)***.

An estimated 40,030 breast cancer deaths (39,620 women, 410 men) are expected in 2013. Breast cancer ranks second as a cause of cancer death in women (after lung cancer). Death rates for breast cancer have steadily decreased in women since 1989, with larger decreases in younger women; from 2005 to 2009, rates decreased 3.0% per year in women younger than 50 and 2.0% per year in women 50 and older. The decrease in breast cancer death rates represents progress in earlier detection, improved treatment, and possibly decreased incidence as a result of declining use of MHT ***(Cancer Facts & Figures, ACS. 2013)***.

Leading New Cancer Cases and Deaths – 2013 Estimates

Estimated New Cases*		Estimated Deaths	
Male	**Female**	**Male**	**Female**
Prostate 238,590 (28%)	Breast 232,340 (29%)	Lung & bronchus 87,260 (28%)	Lung & bronchus 72,220 (26%)
Lung & bronchus 118,080 (14%)	Lung & bronchus 110,110 (14%)	Prostate 29,720 (10%)	Breast 39,620 (14%)
Colon & rectum 73,680 (9%)	Colon & rectum 69,140 (9%)	Colon & rectum 26,300 (9%)	Colon & rectum 24,530 (9%)
Urinary bladder 54,610 (6%)	Uterine corpus 49,560 (6%)	Pancreas 19,480 (6%)	Pancreas 18,980 (7%)
Melanoma of the skin 45,060 (5%)	Thyroid 45,310 (6%)	Liver & intrahepatic bile duct 14,890 (5%)	Ovary 14,030 (5%)
Kidney & renal pelvis 40,430 (5%)	Non-Hodgkin lymphoma 32,140 (4%)	Leukemia 13,660 (4%)	Leukemia 10,060 (4%)
Non-Hodgkin lymphoma 37,600 (4%)	Melanoma of the skin 31,630 (4%)	Esophagus 12,220 (4%)	Non-Hodgkin lymphoma 8,430 (3%)
Oral cavity & pharynx 29,620 (3%)	Kidney & renal pelvis 24,720 (3%)	Urinary bladder 10,820 (4%)	Uterine corpus 8,190 (3%)
Leukemia 27,880 (3%)	Pancreas 22,480 (3%)	Non-Hodgkin lymphoma 10,590 (3%)	Liver & intrahepatic bile duct 6,780 (2%)
Pancreas 22,740 (3%)	Ovary 22,240 (3%)	Kidney & renal pelvis 8,780 (3%)	Brain & other nervous system 6,150 (2%)
All sites 854,790 (100%)	All sites 805,500 (100%)	All sites 306,920 (100%)	All sites 273,430 (100%)

*Excludes basal and squamous cell skin cancers and in situ carcinoma except urinary bladder.

Figure (1): Leading New Cancer Cases and Deaths - 2013 Estimates, American Cancer Society, "Cancer Facts & Figures", 2013

In Egypt, It is the most frequent occurring cancer according to Aswan Governorate Statistics in 2008, with 247 cases 21.5% of all cancers, more in females above 50 years old. And the second most frequent occurring according to Damietta statistics in 2009 (231 cases 15.8% of all cancers) after liver cancer (417 cases 28.5% of all cancers) more in females above 55 years old. But the most frequent in females ***(NCRPE, 2009)***.

B) Diagnosis:

The diagnosis of breast cancer is based on clinical examination in combination with imaging, and confirmed by pathological assessment (Table 1).

Clinical examination includes bimanual palpation of the breasts and loco regional lymph nodes and assessment for distant metastases (bones, liver, lungs and neurological examination in the case of symptoms) ***(Senkus et al., 2013)***.

Table (1): Diagnostic work up for early breast cancer ***(Senkus et al., 2013).***

Assessment of general health status	History Menopausal status Physical examination Full blood count Liver and renal function tests, alkaline phosphatase and calcium
Assessment of primary tumor	Physical examination Mammography Breast ultrasound Breast MRI[a] Biopsy

Assessment of regional lymph nodes	Physical examination Ultrasound Ultrasound-guided biopsy if suspicious
Assessment of metastatic disease	Physical examination Other tests are not routinely recommended, unless locally advanced or when symptoms suggestive of metastases are present

[a]Not routinely recommended, but may be considered in cases of familial breast cancer associated with BRCA mutations, breast implants, for lobular cancers, before neoadjuvant chemotherapy or when the findings of conventional imaging are inconclusive

Pathological diagnosis should be based on a core needle biopsy obtained manually 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) must be obtained before any type of treatment. If preoperative systemic therapy is planned, a core needle biopsy is mandatory to ensure a diagnosis of invasive disease and assess biomarkers, and a marker (e.g. surgical clip, carbon) should be placed into the tumour at biopsy to facilitate evaluation of tumour response during treatment and to ensure surgical resection of the correct site [V, A]. As a minimum, ultrasound-guided fine needle aspiration or core biopsy of suspicious lymph nodes should be carried out. In patients with clinically and imaging negative axilla, the best timing to carry out sentinel lymph node biopsy (SLNB), before or after preoperative systemic therapy, remains controversial ***(Senkus et al., 2013)***.

Final pathological diagnosis should be made according to the World Health Organization (WHO) classification ***(Lakhani et al., 2012)*** and the tumour-node-metastases (TNM) staging system analyzing all tissue removed. The pathological report should include the histological type, grade, immuno-histochemical (IHC) evaluation of estrogen receptor (ER) status using a standardized assessment methodology (e.g. Allred or H-score), and, for invasive cancer, IHC evaluation of PgR and HER2 receptor expression. HER2 gene amplification status may be determined directly from all tumours using in situ hybridization (fluorescent or chromogenic or silver in situ hybridisation), replacing IHC or only for tumours with an ambiguous (2+) IHC score [II, B] ***(Hammond, 2011)***. Proliferation markers such as the Ki67 labelling index may supply additional useful information, particularly if the assay can be standardised [V, A] ***(Dowsett et al., 2011; Guiu et al., 2012)***. Alternatively, these biological markers can be assessed in the definitive surgical specimen if primary systemic therapy is not planned, although fixation is better controlled for core biopsies, allowing safer antigen preservation for IHC ***(Mann et al., 2005)***. In case of negativity of ER/PgR and HER2 in the biopsy specimen, it is advisable to retest them in the surgical specimen, to account for the putative tumour heterogeneity ***(Chen et al., 2012)***. For the purpose of prognostication and treatment decisionmaking, tumours are grouped into surrogate intrinsic subtypes defined by routine histology and IHC data (Table 2) ***(Goldhirsch et al., 2013)***.

Table (2): Surrogate definitions of intrinsic subtypes of breast cancer according to the 2013 St Gallen Consensus Conference and also recommended by the ESMO Clinical Practice Guidelines ***(Goldhirsch et al., 2013)***.

Intrinsic subtype	Clinicopathologic surrogate definition	Notes
Luminal A	'Luminal A-like' • ER-positive • HER2-negative • Ki67 low* • PgR high**	*The cut-off point between high and low values for Ki67 varies between laboratories. **Suggested values are 20% for both PgR and Ki67, but laboratory specific cut-off points can be used to distinguish between low and high values for Ki67 and PgR; quality assurance programmes are essential for laboratories reporting these results.
Luminal B	'Luminal B-like (HER2-negative)' • ER-positive • HER2-negative • and either • Ki67 high or • PgR low	
	'Luminal B-like (HER2-positive)' • ER-positive • HER2-positive • any Ki67 • any PgR	
HER2 overexpression	'HER2-positive (nonluminal)' • HER2-positive • ER and PgR absent	
'Basal-like'	'Triple-negative (ductal)' • ER and PgR absent • HER2-negative	There is 80% overlap between 'triple-negative' and intrinsic 'basal-like' subtype, but 'triple-negative' Also includes some special histological types such as (typical) medullary and adenoid cystic carcinoma with low risks of distant recurrence.

C) Staging and Risk Assessment:

Disease stage should be assessed according to the TNM system (Figs. 2&3). The postoperative pathological assessment of the surgical specimen should be made according to the primary TNM (pTNM) system to include number, location and maximum diameter of tumours removed, the total number of removed and number of positive lymph nodes, and the extent of metastases in the lymph nodes [isolated tumour cells, micrometastases (0.2-2 mm), macrometastases]. The report should also include the histological type and grade of the tumour(s) (using a standard grading system), evaluation of the resection margins, including the location and minimum distance of the margin, vascular and lymphovascular invasion and biomarker analysis, as described above ***(Senkus et al., 2013)***.

Primary tumour (T)[a,b,c,d]	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma *in situ*
Tis (DCIS)	Ductal carcinoma *in situ*
Tis (LCIS)	Lobular carcinoma *in situ*
Tis (Paget's)	Paget's disease (Paget disease) of the nipple NOT associated with invasive carcinoma and/or carcinoma *in situ* (DCIS and/or LCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget's disease are categorised based on the size and characteristics of the parenchymal disease, although the presence of Paget's disease should still be noted.
T1	Tumour ≤20 mm in greatest dimension
T1mi	Tumour ≤1 mm in greatest dimension
T1a	Tumour >1 mm but ≤5 mm in greatest dimension
T1b	Tumour >5 mm but ≤10 mm in greatest dimension
T1c	Tumour >10 mm but ≤20 mm in greatest dimension
T2	Tumour >20 mm but ≤50 mm in greatest dimension
T3	Tumour >50 mm in greatest dimension
T4	Tumour of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules)[e]
T4a	Extension to the chest wall, not including only pectoralis muscle adherence/invasion
T4b	Ulceration and/or ipsilateral satellite nodules and/or oedema (including peau d'orange) of the skin, which do not meet the criteria for inflammatory carcinoma
T4c	Both T4a and T4b
T4d	Inflammatory carcinoma[f]

Regional lymph nodes (N)	
Clinical (cN)[g, h, i, j, k]	
NX	Regional lymph nodes cannot be assessed (e.g. previously removed)
N0	No regional lymph node metastases
N1	Metastases to movable ipsilateral level I, II axillary lymph node(s)
N2	Metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted; or in clinically detected[k] ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node metastases
N2a	Metastases in ipsilateral level I, II axillary lymph nodes fixed to one another (matted) or to other structures
N2b	Metastases only in clinically detected[k] ipsilateral internal mammary nodes and in the absence of clinically evident level I, II axillary lymph node metastases
N3	Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph node involvement; or in clinically detected[k] ipsilateral internal mammary lymph node(s) with clinically evident level I, II axillary lymph node metastases; or metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
N3a	Metastases in ipsilateral infraclavicular lymph node(s)
N3b	Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
N3c	Metastases in ipsilateral supraclavicular lymph node(s)
Regional lymph nodes (N)	
Pathological (pN)[h, i, j, k]	
pNX	Regional lymph nodes cannot be assessed (e.g. previously removed or not removed for pathological study)
pN0	No regional lymph node metastasis identified histologically
pN0(i–)	No regional lymph node metastases histologically, negative immunohistochemistry (IHC)
pN0(i+)	Malignant cells in regional lymph node(s) not >0.2 mm [detected by haematoxylin and eosin (H&E) staining or IHC including isolated tumour cell clusters (ITCs)]
pN0(mol–)	No regional lymph node metastases histologically, negative molecular findings (RT–PCR)[l]
pN0(mol+)	Positive molecular findings (RT–PCR)[l], but no regional lymph node metastases detected by histology or IHC
pN1	Micrometastases; or metastases in 1–3 axillary lymph nodes; and/or in internal mammary nodes with metastases detected by SLNB but not clinically detected[m]
pN1mi	Micrometastases (>0.2 mm and/or >200 cells, but none >2.0 mm)
pN1a	Metastases in 1–3 axillary lymph nodes, at least one metastasis >2.0 mm
pN1b	Metastases in internal mammary nodes with micrometastases or macrometastases detected by SLNB but not clinically detected[m]
pN1c	Metastases in 1–3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by SLNB but not clinically detected[m]
pN2	Metastases in 4–9 axillary lymph nodes; or in clinically detected[k] internal mammary lymph nodes in the absence of axillary lymph node metastases
pN2a	Metastases in 4–9 axillary lymph nodes (at least one tumour deposit >2.0 mm)
pN2b	Metastases in clinically detected[k] internal mammary lymph nodes in the absence of axillary lymph node metastases
pN3	Metastases in ≥10 axillary lymph nodes; or in infraclavicular (level III axillary) lymph nodes; or in clinically detected[k] ipsilateral internal mammary lymph nodes in the presence of one or more positive level I, II axillary lymph nodes; or in more than three axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by SLNB but not clinically detected[m]; or in ipsilateral supraclavicular lymph nodes
pN3a	Metastases in ≥10 axillary lymph nodes (at least one tumour deposit >2.0 mm); or metastases to the infraclavicular (level III axillary lymph) nodes
pN3b	Metastases in clinically detected[k] ipsilateral internal mammary lymph nodes in the presence of one or more positive axillary lymph nodes; or in more than three axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by SLNB but not clinically detected[m]
pN3c	Metastases in ipsilateral supraclavicular lymph nodes
Distant metastasis (M)	
M0	No clinical or radiographic evidence of distant metastases
cM0(i+)	No clinical or radiographic evidence of distant metastases, but deposits of molecularly or microscopically detected tumour cells in circulating blood, bone marrow or other non-regional nodal tissue that are not >0.2 mm in a patient without symptoms or signs of metastases
M1	Distant detectable metastases as determined by classic clinical and radiographic means and/or histologically proven >0.2 mm

Figure (2): Tumour-node-metastases (TNM) staging system for carcinoma of the breast ***(NCI, 2013)***.

Anatomic stage/prognostic groups[a]		
0		
Tis	N0	M0
IA		
T1[b]	N0	M0
IB		
T0	N1mi	M0
T1[b]	N1mi	M0
IIA		
T0	N1[c]	M0
T1[b]	N1[c]	M0
T2	N0	M0
IIB		
T2	N1	M0
T3	N0	M0
IIIA		
T0	N2	M0
T1[b]	N2	M0
T2	N2	M0
T3	N1	M0
T3	N2	M0
IIIB		
T4	N0	M0
T4	N1	M0
T4	N2	M0
IIIC		
Any T	N3	M0
IV		
Any T	Any N	M1

Figure (3): Stage grouping system for carcinoma of the breast ***(NCI, 2013).***