VALUE OF HORMONE RECEPTOR STATUS IN PATIENTS WITH LOCALLY ADVANCED BREAST CANCER AS REGARD THE RESPONSE TO NEOADJUVANT CHEMOTHERAPY

Thesis submitted for partial fulfillment of master degree in general surgery

Presented by

Omnia Mohammed Mohammed Essawy

MBBCh

Supervised by:

Prof. Dr. Samy Ahmed Abdel Rahman

Professor of general surgery

Faculty of medicine

Ain Shams University

Dr. Sherif Morad Gerges

Lecturer of general surgery

Faculty of medicine

Ain Shams University

Dr. Sherif Hassanien Ahmed

Lecturer of oncologynuclear medicine

Faculty of medicine

Ain Shams University

2019

Acknowledgement

First and for all, thanks to ALLAH "The Most Merciful ".

I extend my most sincere thanks to **Prof. Dr. Samy Ahmed Abdel Rahman,** Professor of general surgery, Faculty of medicine, Ain-Shams University, for honoring me with the supervision of this thesis and for his help, support, great effort and guidance throughout the work and in writing the thesis. Sincere appreciation and magnificence thanks to **Dr. SherifMoradGerges**, Lecturer of general surgery, Faculty of medicine, Ain Shams University And **Dr. SherifHassanien Ahmed**, Lecturer of oncology nuclear medicine, Faculty of medicine, Ain Shams University, , for their great support, precious advices, great encouragement and help throughout this work and in writing the thesis.

Many thanks to my lovable father may God mercy his soul.
I wish to express my thanks and appreciation to my adorable mother, lovely sisters for their endless love, care and support.

Table of Contents

List of figures:

List of tables:

List of Abbreviations:

AAL:	Anterior axillary Line
ADH:	Atypical ductal hyperplasia
ACC:	Adenoid cystic carcinoma
BCIS:	Breast cancer in situ
BCS:	Breast conservation surgery
BMI:	Body mass index
BRCA1/2:	Breast Cancer gene1/2
CR:	Complete response
DCIS:	Ductal Carcinoma in situ
DFS:	Disease free survival
ER:	Estrogen receptor
FEA:	Flat epithelial atypia
GIT:	gastrointestinal tract
HER2:	Human epidermal growth factor receptor 2
HR:	Hormone receptor
IBC:	Inflammatory breast cancer
IHC:	Immunohistochemistry
ILC:	Invasive lobular carcinoma
LABC:	Locally advanced breast cancer
LCIS:	Lobular carcinoma in situ
LN:	Lymph node
MAL:	Mid axillary line
MDT:	multidisciplinary team
MRI:	Magnetic resonance imaging
MRM:	modified radical mastectomy
NAC/ NACT:	Neoadjuvant chemotherapy
NAT:	Neoadjuvant therapy
NST:	Neoadjuvant systemic therapy
OC:	oral contraceptives
OS:	Overall survival
pCR:	pathologic complete response
PD:	progressive disease
PR:	Partial response
SD:	Stable disease
SHBG:	Sex hormone binding globulin
TNBC	Triple negative breast cancer

Introduction

Breast cancer is the commonest malignancy in women internationally, with nearly 2 million new patients diagnosed in 2018 (it ranks second in most common malignancy overall).***(Bray, et al., 2018).***

Locally advanced breast cancer; are the most advanced and aggressive breast tumors in the absence of distant metastasis. It has been recognized that multimodality approach of treatment (surgery, chemotherapy, radiotherapy and hormonal and targeted therapy if required) can significantly improve the prognosis in these group of patients.***(Kumar, 2015)***

LABC has been described by the U.S. National Comprehensive Cancer Network as stage III breast cancer; the definition includes breast cancer with the following criteria in the absence of distant metastasis:

- Tumors mass ≥5 cm in size (T 3) +/-pathological enlarged lymph nodes (N1–3)
- Tumors of any size that infiltrate the chest wall and/or the skin (T4), regardless the regional lymph nodes status.

- Tumors of any size with the presence of regional pathologically enlarged lymph nodes (clinically fixed or amalgamated axillary lymph nodes, or any of; infraclavicular, supraclavicular, or internal mammary LNs).***(Kumar, 2015)***

Immunohistochemistry (IHC) testing of cancer cells collected with a core needle biopsy or surgery will be done to evaluate the estrogen and progesterone receptors status. When the hormones estrogen and progesterone attach to these receptors, this reaction promotes the growth of the cancer. Information about the hormone receptor status is critical to decide the optimal treatment

options. Women with hormone receptor positive (HR +ve) cancers tend to have a better outcomes in the short-term, but these subtype of breast cancer can sometimes presents with recurrence after years following completion of treatment. This subtype of breast cancer is more common in menopausal females. Hormone receptor negative (HR -ve) breast cancers have neither estrogen nor progesterone receptors. These cancers tend to grow faster than HR +ve cancers. If they recurrent after treatment, it's often in the first few years. They are more common in premenopausal females.***(Alteri, et al., 2017).***

Hormone receptor positive breast cancer is the commonest type of breast cancer, which represents 70-80 % of all breast carcinomas.***(Bardia, et al., 2017).***

Neoadjuvanttherapy; is the administration of chemotherapy before surgery and has been used for over twenty years for the aim of down staging locally advanced and inoperable breast cancers to make them operable ***(Bardia, et al., 2017).***

The selection of neoadjuvant chemotherapy are based on the same algorithm for adjuvant therapy. Recently, breast cancer was recognized as a heterogeneous disease in which the thought of that one treatment program will beneficial to all cases is not realistic and tailored therapies are more acceptable.***(Colleoni and Montagna 2012)***

Neoadjuvant chemotherapy (NAC) has traditionally been the standard management of LABC for the aim of downstaging and facilitating conservative breast surgery (CBS). The selection of the neoadjuvant therapy drug combinations depends on testing the tumor core needle biopsy for hormonal receptors (ER, PR) and human epidermal growth factor receptor 2 (HER2) status**.**

(Gahlaut et al. 2016)

Aim of work

The aim is to study the Value of hormone receptor status in patients with locally advanced cancer breast as regard response to neoadjuvant therapy.

Anatomy of breast

Embryological development:

During the 5th or 6th gestational week, two thickened ectodermal bands develop at the ventral surface of the embryo which are called mammary ridges or milk lines. ***(Brunicardi, et al. 2015)***

Milk lines; extend from the axilla to the groin. Paired breast buds develop along these lines, but at the time of birth only one pair persists in the chest while the others involute. ***(Allan, et al., 2012).***

The breast forms a secondary sexual character of females and a source of feeding for neonates. The female breast vary in size and shape (hemispherical, conical, variably pendulous, piriform or thin and flattened) which is decided according to many factors; genetic, racial, dietary, age, parity and menopausal status. ***(Standring, et al., 2016).***

Variations of breast size depend on the amount of the adipose tissue rather than the glandular tissue. ***(Prendergast, 2013).***

Surface anatomy:

The breast lies on the anterior chest wall within the superficial fascia.

It extends from the level of the 2nd- 6th ribvirtically. And extends medially from the sternal border and laterally to the anterior axillary line and sometimes to the mid axillary line***. (Macéa & Fregnani 2006)***

The nipple position may correlates to the 4thintercostals space in non-pendulous breast.The areola; is a circular area of pigmented skinlies at the nipple's base. However, according to the skin type;

nipple and areola complexmay appear pink or brown.***(Prendergast 2013)***

The breast tail extends towards the axilla along the inferolateral border of pectoralis major muscle***. (Standring, et at. 2016)***

Clinically, the breast is divided by horizontal and vertical lines crossing the nipple into 4 quadrants. Moreover, lesions can also be localized as the time on a clock and the distance in centimeters from the nipple (e.g., 5 o'clock 3 cm from nipple). ***(Bickley, et al., 2013).***

Functional Anatomy

The breast is a modified apocrine sweat gland, thatdistributed within adipose "fatty" tissue.

The breast consists of pyramidal shaped lobes ranging from 15 to 20 lobes. Its apex directed towards the nippleand radially arranged within the supporting fibrous stroma and fat. Breast lobes consist of several smaller lobules which contain several blind-endingacini that are potentially milksecreting. Each lobule drains into a solitary lactiferous duct. Each lobe has a single lactiferous ductthat opens into the nipple.***(Prendergast 2013)***

The structural support of the breast obtained from "Cooper's ligaments" which arefibrous bands of connective tissue that travel through the breast, and then insert perpendicularly into the dermis. ***(Brunicardi, et al. 2015)***

The "retromammary space" is a thin loose areolar tissue that lies between the breast and pectoralis major muscle and includes lymphatics and small vessels. The pectoralis minor muscle lies deep to the

pectoralis major muscle in the clavipectoral fascia, whichmeet the axillary fascialaterally . ***(Hunt, et al., 2017)***

Blood supply:

The arterial supply:

The arterial supply of the breast comes from three main sources:

1- The axillary artery by giving:
   a. the highest thoracic.
   b. lateral thoracic.
   c. pectoral branches of the thoracoacromial artery**.**
   (Brunicardi, et al. 2015)

2- The internal thoracic (the internal mammary) artery by giving perforating branches which pierces the 1^{st}-4^{th} intercostal spaces and then reaching the medial border of the breast by passing through the pectoralis major muscle. The largest of these branches are the first and second perforators ***(Ellis 2006)*****.**

3- Lateral perforating branches from the intercostal arteries.**(Ellis 2006)**

Some people do not classically get their arterial blood supply to the breast as previously discussed and there are some variations exist, as following;

- In 18% arterial blood supply is from the all the three sources that previously mentioned.
- In 30% the axillary artery gives minimal or no blood to the breast.

- In 50% there is little or no blood supply is provided by the intercostal arteries.
  (Prendergast 2013)

The venous drainage:

The breast drains to veins corresponds to its arterial supply, which are:

1- The axillary vein.
2- Internal thoracic vein.
3- Intercostal veins.

(Ellis 2006)

Innervation:

Lateral cutaneous branches from the third to sixth (3^{rd},4^{th}, 5^{th}, 6^{th}) intercostal nerves which gives sensory fibers to the breast (lateral mammary branches). It also gives sensations to the anterolateral part of the chest wall. These branches leaves the intercostal spaces between the heads of the serratus anterior muscle. Cutaneous branches from the cervical plexus, small area of skin at the upper part of the breast is supplied mainly by the anterior branches of the supraclavicular nerve.

The intercostobrachial nerve; is the lateral cutaneous branch of the second intercostal nerve .It is usually seen during axillary lymph node dissection surgery, its injury causes loss of sensations at the medial aspect of the upper arm. . ***(Brunicardi, et al. 2015)***

Lymphatic drainage:

Understanding the lymphatic drainage of the breast has a great clinical importance in breast cancer. Lymphatics are principally the primary route of metastasis of the breast carcinomas. The axillary and the internal mammary lymph nodes are the main sites for lymphatic drainage of the breast; at least 75% of the total lymphatic drainage of the breast is into the axillary nodes. ***(Prendergast, 2013).***

The lymphatic vessels of the breast are arranged in four main lymphatic plexuses that are intercommunicating with each other, which are:

- The cutaneous plexus; which is located at the dermis layer of the skin.
- The subcutaneous plexus that is at in the superficial subcutaneous layer.
- The fascial plexus which lies within the pectoralis major muscle fascia.
- The glandular plexus which lies within the mammary gland, involving the lobes and ducts.

(Macéa & Fregnani 2006)

Abundant lymphatic channels lie in the breast parenchyma and dermis. Sappey's plexus is formed by the collection of specialized lymphatic channels under the nipple and areola complex which was first described in 1885 by an anatomist and named after him. The lymph flows from the skin to the subareolar plexus and then runs to the interlobular lymphatics of the breast parenchyma. Understanding the direction of the lymphatic flow is important for performing sentinel lymph node surgery successfully.

(Hunt, et al., 2017)

The lymph drainage of the breast, as withother organs, follows thepathway of its blood supply so it runs accompanying:

1. The tributaries of the axillary vessels to axillary lymph nodes.
2. The tributaries of the internal thoracic vessels, piercing the pectoralis major muscle then to each intercostal space to drain into lymph nodes that is located along the mammary chain, which also receive lymphatics penetrating accompanying with the lateral perforating branches of the intercostal blood vessels. ***(Ellis, 2006)***

However, there is a superficial lymphatics that drain skin over the breast except for the nipple and areola complex. In addition, the deep lymphatics drain parenchyma and the nipple and areola complex.

- 75% of the total lymphatic drainage of the breast is received by the axillary lymph nodes.
- 20% drains into internal mammary nodes.
- 5% drains into posterior intercostal nodes.

  (Bhat,et.al, 2014)

The axilla contains 20–40 axillary lymph nodes ***(Standring, et at. 2016),***which receive lymphatics from the breast, the pectoral region, the upper abdominal wall and the upper limb.***(Ellis, 2006)***

The axillary lymph nodes can be classified into six groups:

1. Anterior (pectoral) group: this group consists of 5-6 lymph nodes, where it is located along the lower border of pectoralis minor muscle near to the lateral thoracic vessels. Most of the lymphics from the lateral aspect of the breast drain into this group.
2. Posterior (scapular) group: this group consists of 5-7 lymph nodes which can be found along the posterior axillary wall at the lateral border of the