INTRODUCTION

Breast carcinoma is the commonest cancer in females through out the world. During the mid 1980, mortality from cancer of the breast overtook that, of every other female cancer, to become the commonest cause of cancer death ***(Anderson, 2004)***.

In Egypt it consists 27% of all female cancers ***(Abul Nasr and Botrous, 2004)***.

In the early half of this century, prevailing currents of medical opinion had led to the imposition of surgery, even more aggressive than the radical mastectomy proposed by Halsted to treat breast cancer. More recently breast conserving surgery has become established, but it is always flanked by addition of local treatment, and often by systemic therapy ***(Veronesi and Urrida , 2004)***.

Conservative treatment of breast cancer is now an accepted oncological procedure. It further allows good functional and cosmetic results. This treatment needs more skills and time than mastectomy, as it doesn't only include a surgical excision but also a postoperative local radiotherapy and sometimes a difficult follow-up for many years. The contraindication for conservative breast cancer therapy are numerous and depend on many factors as tumors, patient and radiotherapy ***(Dupont and Lampart , 2004)***.

Locoregional recurrence is a major concern in conservative breast cancer surgery, and many studies have attempted to identify risk factors for these events, yet these risk factors are not fully clarified ***(Veronesi and Urrida., 2004)***.

The success of conservative surgery and radiotherapy dependent on minimizing the possible microscopic residual tumor burden in the breast. Histological margin status is one measure of the extent of residual tumor ***(Kearney and Morrow, 2005)***.

Therefore breast conserving surgery can be offered as an alternative to mastectomy to the majority of women with early stage of the disease ***(Cuzick and Stewart, 2005)***.

Most centers agree that the indication of conservation are tumor less than 3 cm and mobile one group of axillary lymph nodes ***(Veronesi and Urrida , 2004)***.

However Fisher, 1989 passes up to the diameter of 4 cm and more than one group **of** lymph nodes. This was represented on gratifying results ***(Fischer , 2005)***.

According to the TNM and Manchester classification, Early stage of the disease is known to be:

- Tis Non palpable tumor

- T1 tumor less than 2 cm
- N0 Non palpable lymph nodes and no nodal metastasis
- N1 Mobile one group of axillary lymph nodes
- M0 No distant metastasis ***(Powles , 2005)***.

It is known that the mutations that activate or inactivate selected/normal genes are responsible for loss of cell growth control, and the acquisition of invasive and metastatic properties ***(Roberts , 2005)***.

The most important genes inactivated in a proportion of breast cancer include the Retinoblastoma, NM23, and P53 tumor suppressor genes ***(Marx, 2003)***.

The p53 gene is a (guardian of the genome). It regulates multiple components of the DNA damage control response and promotes cellular senescence. P53 deficient cancers are often unstable, aggressive and resistant to therapy ***(Carson and Louis , 2003)***.

The screen for P53 abnormalities, both immunohistochemistry (IHC) and the polymerase chain reaction single strand confirmation polymorphism (PCR-SSCP) methods are commonly used, ***(Fujino , 2003)***.

Therefore loss of tumor suppressor P53 function is a frequent phenomenon in breast carcinoma ***(Hietanen, 2003)***.

AIM OF THE WORK

The aim of this thesis is to evaluate the value of determination of the P53 in early breast cancer cases treated conservatively, aiming for better choice of the conservative surgery that secure microscopic removal of the tumor, and hence, minimizing the incidence of loco-regional recurrence.

BREAST DEVELOPMENT AND PHYSIOLOGY

During the fifth week of gestation, a milk streak develops and extends from the axilla to the groin. It progresses through the milk-ridge and milk-hill stages to form the early breast buds. During this time, mesenchymal cells form the smooth muscle of the nipple and areola while epithelial elements form buds that ultimately give rise to 15 to 25 future ducts and lobules. It is thought that phylogenetically the breast arises as a modified apocrine sweat gland. These early phases of breast development are independent of hormones and occur in fetuses of both sexes. During the third trimester of pregnancy, placental sex hormones cause the previously formed epithelial buds to be converted into hollow ducts. It is these structures that produce the colostrum or "witch's milk" of the newborn that may be observed 4 to 7 days after birth. These secretions cease over subsequent weeks as the effects of placental hormones wane ***(Allred , 2003)***.

The nipple itself protrudes from the center of the pigmented areola and contains 10 to 15 terminal duct openings. Within the areola are Montgomery's glands, the slightly raised, nodular apocrine glands ***(Powles , 2005)***.

As many as 2% to 6% of adult women have accessory nipples (polythelia) along the milk ridge, most commonly in the axilla or just inferior to the breast. Some have breast ductal tissue beneath the accessory nipple (polymastia). This breast tissue may enlarge and even lactate as the result of pregnancy, and must be distinguished from a breast mass appearing during pregnancy. In general, however, there is no need to remove this accessory nipple or breast tissue except for cosmetic purposes or if palpable abnormalities arise ***(Appleton and Lee , 2006)***.

Asymmetry of the breasts is common'and can range from slight asymmetry to dramatic hypoplasia on one side. Complete amastia is rare and is often accompanied by chest wall deformities. Poland syndrome produces absence of the breast with defects of varying severity in the underlying pectoralis major muscle and bony chest wall and is often associated with hand abnormalities ***(Appleton and Lee, 2006)***.

Abnormalities of breast structure may also have iatrogenic sources. **Overly** extensive excision of the breast bud underneath the nipple and areola during biopsy of a subareolar lesion in a young child can result in removal of tissue critical for breast development and in gross asymmetry after puberty ***(Apple et al., 2006)***.

Microscopic anatomy of the breast:

The mature breast is composed of three principal tissue types: (1) glandular epithelium, (2) fibrous stroma and supporting structures, and (3) fat. Infiltrating cells, including lymphocytes and macrophages, are also found within the breast. In youth, the predominant tissues are epithelium and stroma, which may be replaced by fat in the breasts of older women ***(Gallager, 1995)***.

However, there is great variability among individual women of any age. Mammography in women younger than 30 years of age, whose breast tissue is dense with stroma and epithelium, may produce an image without much definition. This has led to the impression that mammograms in young wo.men are rarely useful, an impression which may not always be true. In contrast, fat absorbs relatively little radiation and provides a contrasting-background that favors detection of small-density lesions in the older patient ***(Goldhirsch et al., 1998)***.

Throughout the fat of the breast, coursing from the overlying skin, to the underlying deep fascia, strands of dense connective tissue provide shape and hold the breast upward. These strands, devoid of epithelial elements, are called Cooper ligaments (Fig. 1). Because they are anchored into the skin, tethering of these ligaments by a small scirrhous carcinoma commonly produces a dimple or subtle deformity on the otherwise smooth surface of the breast ***(Haagensen, 1995)***.

The glandular apparatus of the breast is composed of a branching system of ducts, roughly organized in a radial pattern, which spread outward and downward from the nipple-areolar complex (Fig. 1). These lactiferous ducts are so named because they carry the milk produced in the more distal lobular groupings. At the summit of the arborizing ductal system, the subareolar ducts widen to form the lactiferous sinuses, which then exit through 10 to 15 orifices on the nipple. These large ducts close to the nipple are lined with a low columnar or cuboidal epithelium that abruptly meets the squamous epithelium of the nipple surface, which invades the duct for a short distance ***(Harris et al., 1996)***.

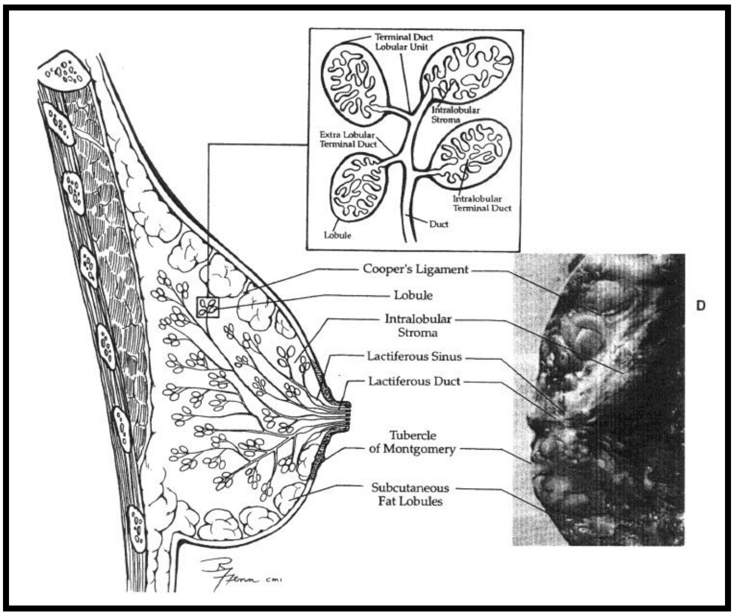

Fig (1): Diagrams and corresponding gross photograph illustrate the location of the terminal lobule, ductules, and fusion of the lactiferous ducts ***(Harris et al., 1996).***

and after progressive generations of branching, the ducts end blindly in clusters of spaces that are called terminal ductules or acini. These are the milk-forming glands of the lactating breast, and together with their small efferent ducts or ductules, are known as the lobular units or lobules ***(Hartmann et al., 1999)***.

The terminal ductules are invested in a specialized loose connective tissue that contains capillaries, lymphocytes, and other migratory mononuclear cells. This intralobular stroma is clearly distinguished from the denser and less cellular interlobular stroma and from the fat within the breast ***(Hartmann et al., 1999)***.

Under the luminal epithelium, the entire ductal system is surrounded by a specialized myoepithelial cell of ductal epithelial origin that has contractile properties and serves to propel secretion of milk toward the nipple. Outside the epithelial and myoepithelial layers, the ducts of the breast are surrounded by a continuous basement membrane containing laminin, type IV collagen, and proteoglycans. The basement membrane layer is extremely important in differentiating in situ from invasive breast cancer. Continuity of this layer around proliferations of ductal cells identifies ductal carcinoma in situ, or noninvasive breast cancer ***(Hortbagyi, 1994)***.

Blood supply of the breast:

The breast receives its blood supply from perforating branches of internal mammary artery, lateral branches of the posterior intercostal arteries, and several branches of the axillary artery. The latter vessels include the highest thoracic, lateral thoracic and pectoral branches of the thoracoacromial artery. Branches from the 2^{nd}, 3^{rd}, 4^{th} anterior perforating arteries pass to the breast as medial mammary arteries, (Fig. 2) ***(Cunningham, 1995)***.

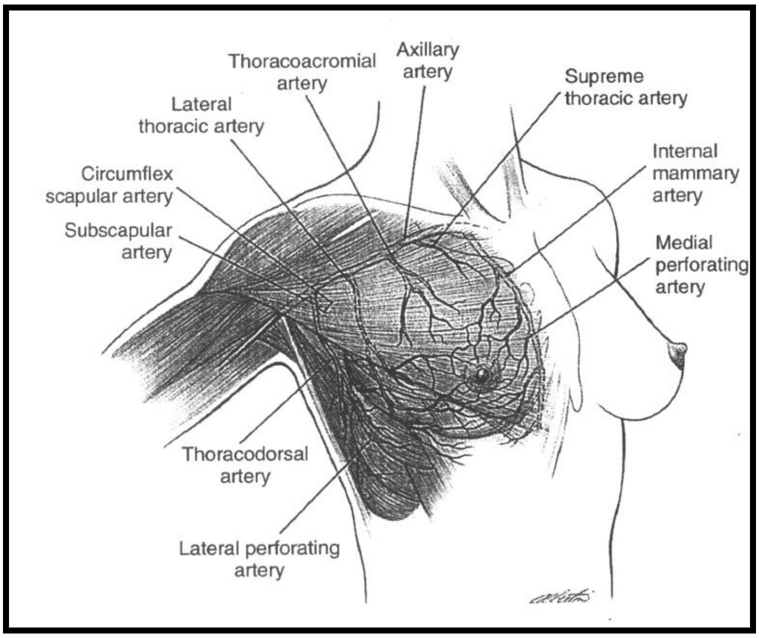

Fig (2): Arteries of the breast. The arteries have their origin from the interanal mammary and axillary arteries ***(Cunningham, 1995)***.

Although the thoracodorsal branch of the subscapular artery doesn't intimately associated within the central and scapular node groups of the axilla, this fact should be taken into consideration during axillary node dissection as bleeding that is difficult to control can result when penetrating branches of this vessel served.

The three principal groups of veins essential to provide venous drainage at breast and the thoracic wall include(a) perforating branches of the internal mammary vein (b) tributaries of the axillary vein. (c) perforating branches of the posterior intercostal veins (Fig3).

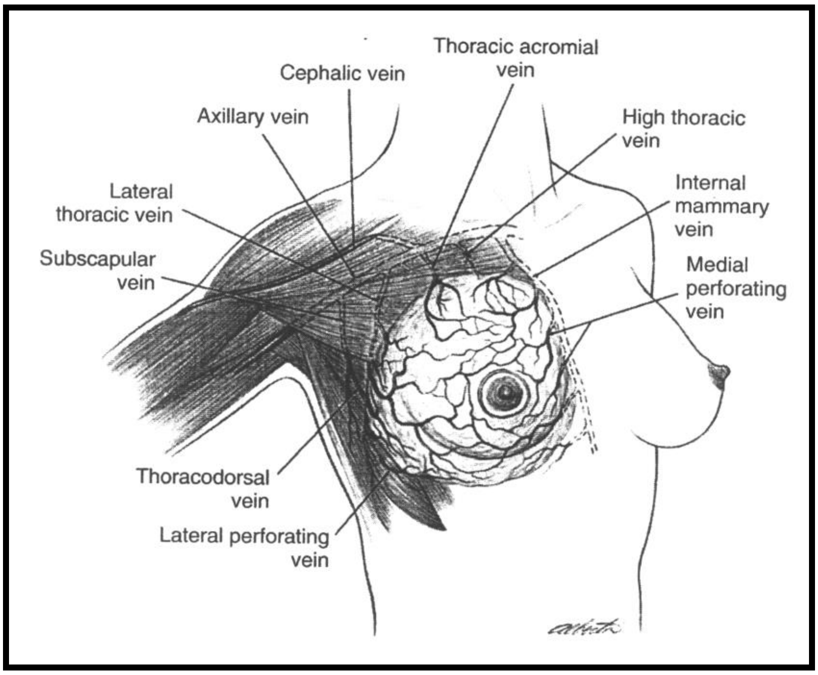

Fig (3): A schematic of the venous drainage of the breast ***(Cunningham, 1995)***.

The posterior intercostal veins lie in direct continuity with the vertebral plexus of veins (Batson's plexus) that surround the vertebrae and extend from base of skull to the sacrum, clinically this plexus may provide an important pathway for hematogenus dissemination of breast cancer and physiologically account for metastases to the skull vertebrae, pelvic bones ***(Gray, 1995)***.

Lymphatic drainage of the breast

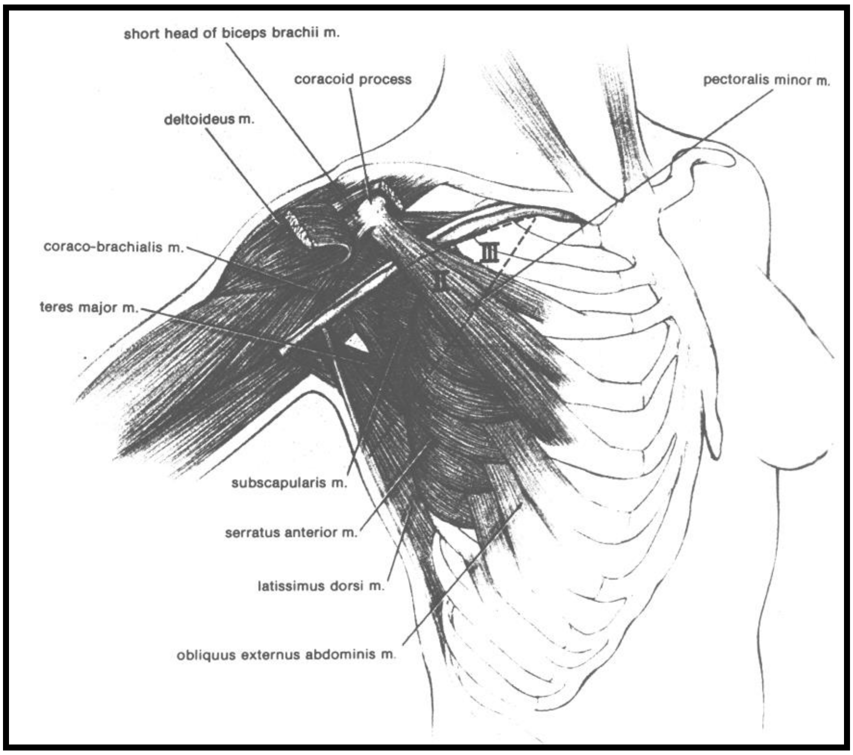

Fig (4): Standardized description of axillary nodal contents. The axillary nodes are divided into three groups defined by their position relative to the pectoralis minor muscle***(Gray, 1995***)

The lymphatic drainage of the breast is rich, and appreciation of the major pathways allows one to predict the sites most commonly containing lymph-borne metastases.

Lymphatic channels within the breast follow centrifugal pathways from the subareolar plexus along major lactiferous ducts and then along efferent veins to draining nodal beds. Three principal pathways are identified in (Fig4) ***(Moore and Harge , 1998)***.

The major site of drainage is the central axillary nodes. The internal mammary and interpectoral nodes, although primary routes of lymph flow, are rarely the sites of nodal metastasis from breast cancer in the absence of simultaneous axillary disease. In locally advanced cases of breast cancer, disease may be found in the high axillary nodes under the clavicle and in supraclavicular nodes in the neck ***(Fischer et al., 1995).***

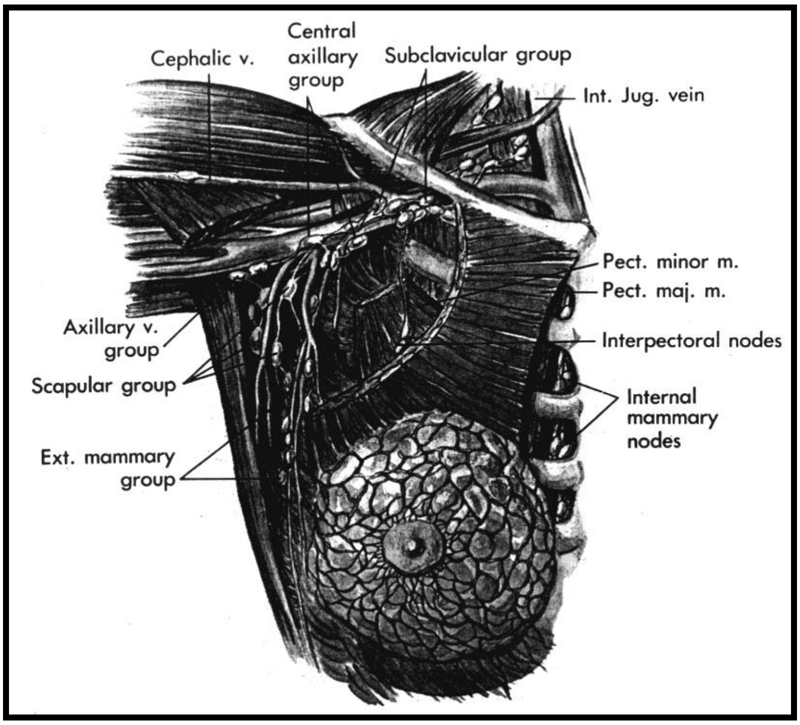

Fig (5): Contents of the axilla. Five named groups of lymph nodes are generally contained within a complete dissection of the axillary contents (***Gray , 1995)***.

The number of lymph nodes found in the axilla depends on the extent of dissection and the diligence of methods used to identify these nodes. An upper limit is established by the work of Durkin and Haagensen using ethanol clearing. These investigators found an average of 50 nodes in 100 specimens obtained "in the course of a Halsted-type radical mastectomy. The current approach to less radical procedures has, reduced the number of nodes retrieved ***(Andersen and Nielsen , 1995)***.