Management of Locally Advanced Breast Cancer

Essay
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Introduction

Breast cancer is the commonest malignant disease among women in the western world accounting for 1/5 (18%) of all cancers in women. Every year about one million and several thousand men are diagnosed with breast cancer worldwide and approximately 60.000 die from it. It is also rapidly emerging as a very common cancer in the devolving countries as well. In India it is the second most common cancer in females with 75.000 new cases occurring every year as per the cancer registries in the country ***(Rustogi, 2005)***.

Locally advanced breast cancer account for 10% - 15% of new breast cancer cases in the United States . In under developed countries , the rate of locally advanced breast cancer (LABC) at the first diagnosis is estimated to be as high as 25% - 30% ***(Wingo et al., 1995)*** .

The definition of a locally advanced breast tumour has changed over time as the staging system has evolved , but in general, it includes patients with tumour larger than 5 cm (T3), tumours with skin or chest wall involvement (T4) or matted axillary nodal metastasis (N2) in addition to inflammatory breast cancer (IBC) ***(Chopra, 2001)***.


During the first half of the twentieth centaury patients with LABC underwent extensive surgical procedures and aggressive radiotherapy. The radical mastectomy was developed by William Halsted, and modified radical mastectomy had been used ***(Haagensen et al., 1998)***.

Studies revealed that the local management alone for LABC was inadequante. So systemic treatment was introduced by several research group in Europe and North America . Two types of systemic therapy were used either chemotherapy or hormonal therapy. Chemotherapy used either adjuvant or neoadjuvant therapy ***(Zatuski and Szoszkiewicz, 2003)***.

Many authors have reported improved survival and freedom from distant relapse in patients who received adjuvant chemotherapy after local treatment with surgery or radiation therapy ***(Kelly et al., 2000)***.

Neoadjuvant Chemotherapy was used initially to convert unresectable tumours to smaller tumours more amenable to local control with either surgery or radiation therapy . In addition to improve the disease free survival ***(Darut – Jouve et al., 2003)***.

The use of hormonal therapy in estrogen receptor (ER) positive patients together with adjuvant chemotherapy was found to decrease recurrence and improved survival rates ***(Cancer research UK, 2004)***.


Aim of work

Evaluation of different modalities in management of locally advanced breast cancer .

Surgical pathology of locally advanced breast cancer

Pathogenesis:

Histogenetically, breast carcinoma, ductal or lobular type, arises from the terminal duct – lobular unit. A typical ductal hyperplasia (epitheliosis) and atypical lobular hyperplasia are the only two lesions of fibroadenosis that are considered precancerous (8% risk in 10 years).

Breast carcinoma in situ (CIS) either lobular (LCIS) or ductal (DCIS) then invades the basement membrane and reaches the stroma where it becomes vascularized and is capable of producing metastases . DCIS is more common than LCIS .

Estrogen plays a minor role in breast carcinogenesis. The underlying hormonal imbalance is a predominance of estrogen over progesterone, either as a result of pathophysiology (ovarian origin) or iatrogenic (estrogen therapy). The production of growth factors such as TGF (mediated by estrogen) is necessary for tumor promotion and progression ***(Edward N.,2004)***.


Macroscopy:

The outer breast hemisphere is more commonly affected (60%) than the inner hemisphere (20%) with about one half of cases arising in the upper outer quadrant. In the 3% of cases the disease is diffuse or multifocal.

Bilaterality is observed in 4% of invasive duct carcinoma and 25% of invasive lobular carcinoma, often at different time intervals (metachronous). The gross appearance varies according to the histologic type ***(El Bolkainy, 2000)***.

Histopathology:

Breast carcinoma includes a heterogeneous group of malignant tumors of variable natural history. It is customary to divide them into non-invasive (favourable) and invasive categories. It is important to recognize in the invasive category, special types of tumors associated with favourable prognosis.

Table 1: Histologic Classification of Breast Cancer

Noninvasive (5%)*
DCIS 4%
LCIS 1%
Invasive (95%)
Duct carcinoma (NOS) 70%
Lobular carcinoma 10%
Special types 14%
Tubular
Medullary
Mucinous
Papillary
Rare unfavorable 1%

(El Bolkainy, 2000)

Noninvasive Carcinoma:

The enthusiasm for screening has led to the increasing detection of breast cancer at early carcinoma in situ (CIS) stage. Before mammography, the incidence of noninvasive carcinoma was only 5%, but increased to 15% and more in screening series. By definition, the carcinoma is confined by the basement membrane within the duct or lobules, and it is classified into ductal carcinoma in situ (DCIS) and lobular


carcinoma insitu (LCIS) with an incidence ratio of 4:1 respectively. Three mammographic growth pattern are described namely: the microfocal, tumor forming, and diffuse.

DCIS is divided into comedo and noncomedo types with marked biologic differences. Comedo carcinoma shows solid tumor in the ducts with central necrosis. The comedo type is the most common (about 40% of CIS) and most aggressive. Noncomedo group includes 5 subtypes: 1) solid, 2) cribriform, 3) micropapillary, 4) papillary and 5) clinging. The solid type may precede the comedo variant and is biologically similar. The micropapillary type is most likely to be multicentric ***(Ravdin, 1997)***.

Most cases of Paget's disease (70%) are typical intraduct carcinoma involving the main excretory ducts with infiltration of the epidermins of nipple and areola. This subset of Paget's disease is associated with excellent prognosis. But if the ductal component is invasive to the stroma (30%), the carcinoma will behave as conventional invasive duct carcinoma.

LCIS is an incidental and uncommon lesion (1% of breast biopsies). It is often multicentric (50%) and bilateral (40%). Histologically, the acini of the lobular unit are


distended by uniform cells with obliteration of the lumen. Lobular carcinoma may extended to proximal ducts in pagetoid fashion. LCIS has low risk to progress into an invasive carcinoma with an annual cumulative risk of 1% only, hence, prophylatic mastectomy for tumors is not justified. The developing invasive tumors are commonly ductal rather than lobular carcinomas ***(Edward N., 2004)***.

Invasive Carcinomas:

1- Invasive duct carcinoma (IDC) is the most common (70%) and rather aggressive tumor. Grossly, it appears as a firm (scirrhous) tumor, whitish gray in colour with irregular stellate shape. Histologically, it is composed of a pleomorphic cell population with central nuclei and evidence of ductal differentiation. It is usually graded into-3 grades according to tubule formation, analapsia and mitosis. The relative frequency of grades in Western series is Grade I (18%), Grade II (37%) and Grade III (45%). Lymphatic invasion by tumor is found in 10% of node negative patients and is a prediction of recurrence and metastatic spread. Invasive duct carcinoma associated with extensive intraduct component (EIC), comprising at least 25% of tumor area, is associated with high risk of local

recurrence (24% in 5 years) after conservative surgery especially in premenopausal women. This combination is encountered in about 15% of IDC either within the tumor or in adjacent breast tissue, and inspite of recurrence, may offer better long-term survival ***(Edward N., 2004).***

2- Invasive lobular carcinoma (ILC) constitutes 10% of breast carcinomas and is characterized by the high risk of bilaterality (25%) (Dixon et al., 1983) and equals in aggression to IDC. Grossly, it presents as an indistinct mass with fine multifocal areas of indurtion. ILC is classified into classical (75%) and variant subtypes, including solid, alveolar, pleomorphic and mixed. The cells of lobular carcinoma are small, uniform, with eccentric nuclei and scanty vaculated cytoplasm. The classic type shows a characteristic single – cells pattern of invasion (Indian file) or concentric pattern of invasion around ducts and vessels (targetoid pattern). A mixed lobular – ductal carcinoma is encountered in 5% of cases of breast cancer and are best classified according to the predominant cell component.

3- Special Types: the following four subtypes of invasive carinomas are associated with a favourable prognosis,


provided they represented more than 90% of tumor area. They are usually not graded.

a- Tubular carcinoma is the most favourable tumor, but with high risk of bilaterality (20%). It is composed of tubules oval in shape with angular end (tear drop) and dense fibrous stroma. It is lined by a single layer of cuboidal or columnar epithelium. Invasive cribriform carcinoma is cytologically and biologically related to tubular carcinoma ***(Mc Boyle et al., 1997)***.

b- Medullary carcinoma is also a favourable tumor which appears grossly as rounded, mobile, well – circumscribed mass of soft consistency. Histologically, the tumor has a pushing rather than invasive margin. The cells are pleomorphic with syncytial cytoplasm and stroma rich in lymphocytes ***(Fisher et al., 1990)***.

c- Mucinous carcinoma is common in older women. Grossly, it shows a glistening gelatinous appearance. Microscopically, it is composed of small islands of tumor cells suspended in abundant mucin in the stroma ***(Fentiman et al., 1997)***.