Comparison Between Lymph Node Status& Tumor Marker Levels in Evaluation of II& III Stage Breast Cancer

Thesis
Submitted For Partial Fulfillment of M.D Degree In
General Surgery
By

Mahrous Fathy Mahrous Abou Zaid

M.B.B.Ch, M.Sc.

Supervised By

Prof. Dr/ Mohammed Emad Saleh
Professor of General Surgery
Faculty of Medicine
Ain Shams University

Prof. Dr/Abd El-Wahab Mohammed Ezzat
Professor of General Surgery
Faculty of Medicine
Ain Shams University

Prof. Dr/ Osama Mahmoud El-Sayed
Assistant Professor of General Surgery
Faculty of Medicine
Ain Shams University

Faculty of Medicine
Ain Shams University
2012

PROGNOSTIC FACTORS IN BREAST CANCER

A prognostic factor is defined as a biologic or clinical measurement associated with disease-free or overall survival, which can be used to estimate the prognosis of the patient. A predictive factor is any measurement associated with response or lack of response to a particular therapy, which can be used to guide the use of the particular therapy. Some markers may be both prognostic and predictive. Moreover, a positive prognostic factor may have a negative predictive value and vice versa ***(Cianfrocca& Goldstein, 2004).***

Prognosis of patients with breast carcinoma strongly depends on a number of clinical and histological factors at the time of diagnosis, a few prognostic factors are currently well established and routinely utilized in risk assessment providing more accurate prognosis than tumor-node-metastases (TNM) staging alone ***(Masood, 2005).***

The most commonly used prognostic factors in breast cancer are: the number of positive axillary lymph nodes, tumor size, lymphatic and vascular invasion, histological tumor type and c-erbB2 and sex steroid receptors. It is particularly important to establish a prognosis in patients whose outcome could be so favorable that adjuvant treatment is unnecessary ***(Denley et al., 2001).***

1- Patient related prognostic factors:

a- Patient age:

In older women, the risk of local recurrence after partial mastectomy declines and the prevalence of metastases increase. The tumors in older patients have more indolent clinical course due to lesser support of tumor growth by the older tumor host ***(Krtolica and Campisi, 2002).***

In addition, the 5-year relative survival rate is slightly lower among women diagnosed with breast cancer before age 40 compared to women diagnosed at ages 40 and older ***(American Cancer Society, 2008).***

Tumors diagnosed in younger women may be more aggressive and less responsive to treatment than older patients ***(Ana et al., 2000).***

b- Ethnicity and socioeconomic factors:

African American women with breast cancer are less likely than white women to survive 5 years: 77% versus 90%, respectively. This difference can be attributed to later stage at detection with aggressive tumor characteristics in African American women. Also, a lack of health insurance is associated with more advanced stage at diagnosis. Moreover, the presence of additional illnesses, lower socioeconomic status, unequal access to medical care and disparities in treatment may contribute to the observed differences in survival between lower- and higher-income breast cancer patients and between African American and white women ***(American Cancer Society, 2008).***

c- Premorbid weight and obesity:

Obese patients with breast cancer had an unfavorable prognosis. Obesity was associated with a higher recurrence rate particularly in postmenopausal patients ***(Rowan, 2005).***

It was explained by obesity can act by increasing conversion of the precursor androstenedione to estrone by aromatase (which is found in adipose tissue) and hence stimulation of estrogen dependent breast cancer ***(Dignam and Mamounas, 2004).***

d- Pregnancy and lactation:

Carcinoma of breast manifesting during pregnancy and lactation is associated with an overall poorer prognosis ***(Gwyn and Theriault, 2001).***

The increased vascularity may be considered as a factor that possibly increases the risk of dissemination ***(Raina et al., 2005).***

e- Family history:

It is an important prognostic factor. First degree female relatives (i.e. mothers, daughters and sisters) of women with breast cancer are subjected to greater risk than the general population. The highest risk occurs in women whose mothers had bilateral breast cancer prior to menopause ***(Margolin et al., 2006).***

f- Delay in treatment:

It will lead to progression of the disease to higher clinical stages. Both tumor size and axillary nodal involvement increase with delay. Longer delay intervals were associated with more frequent involvement of the internal mammary nodes ***(Ben Ahmed et al., 2002).***

h- Psychological factors:

It was proposed that "fighters" have a better chance of survival than do "compilers". Also there is an important factor which is the "will to live". Finally, it has been also reported that increased emotional stress contributes to short-term survival ***(Goldstein, 2006).***

2- Tumor related prognostic factors:

1- Tumor size and stage:

It is an important prognostic factor. Its significance is greater in node positive

patients than in node negative patients. Tumors less than 2 cm in diameter are associated with a favorable course, the larger the tumor the worse the prognosis and the 5-year survival rate increases dramatically when breast cancer can be diagnosed at an early stage. No adjuvant therapy if the tumor is less than 1 cm ***(Michaelson et al., 2003).***

It shows a good correlation with the incidence of nodal metastasis survival rate. The majority of women with cancers larger than 2cm will have lymph nodes metastasis ***(Markopoulos et al., 2001).***

It should be noted that in tumors having both an in situ and an invasive component, the size of the latter is a better predictor than the total tumor size**.** It correlates with the number of histological involved lymph nodes, but has independent prognostic importance. In node-negative patients, with tumor size of <2 cm is typically considered low risk ***(Tabar et al., 2000).***

Breast cancer prognosis based on stage ***(Sugg and Donegan, 2002***):

Stage I 93% 5-years survival rate

Stage II 72% 5-years survival rate

Stage III 41% 5-years survival rate

Stage IV 18% 5-years survival rate

2-Tumor Location:

High-risk medial tumors are associated with significantly greater risk of relapse and death than high risk lateral tumors (two folds), there is reason to suspect that this increased risk may be due to metastases originating from involved, but untreated internal mammary nodes (IMNs) ***(Caroline et al., 2000).***

3- Tumor grade:

Grading is recommended for all invasive carcinomas of the breast. The most widely accepted grading system being the Scarff-Bloom-Richardson (SBR) classification. Mitotic index, cell differentiation and pleomorphism are scored from 1 to 3 and the scores from each category are totaled. Tumors with scores from 3 to 5 are well differentiated (grade 1), from 6 to 7 are moderately differentiated (grade 2) and 8 to 9 are poorly differentiated (grade 3) ***(D'Eredita et al., 2001).***

The combination of histological type and grade provides a more accurate assessment of prognosis than does histological type alone. Grading is not appropriate for the special histological types such as invasive tubular, invasive cribriform, mucinous, medullary and invasive lobular carcinoma ***(Tavassoli & Devilee, 2003).***

Patients with an SBR score of 3 had a relative risk of recurrence compared with those with an SBR of 1. The prognostic significance of tumor grade is primarily used to make decisions for lymph node-negative patients with borderline tumor sizes ***(Simpson et al., 2000).***

Both architecture (extent of tubular formation) and cytology (degree of nuclear atypia) has been found to correlate with prognosis. It has confirmed the association between high-grade undifferentiated tumor and poorer outcome compared with low-grade differentiated tumors ***(Lundin et al., 2001)*.**

Three tumor characteristics are evaluated; tubule formation as an expression of glandular differentiation, nuclear pleomorphism and mitotic counts.The degree of differentiations evaluated according to the ability of the tumor to form tubules and glandular structures. Nuclear pleomorphism is assessed by reference to the

regularity of nuclear size and shape of normal epithelial cells in adjacent breast tissue. Evaluation of mitotic figures requires care; hyperchromatic and pycknotic nuclei are ignored since they are more likely to represent apoptosis than proliferation ***(Lundin et al., 2001).***

The Nottingham /Tenovus Prognostic Index (NPI):

This index was formulated as follows:

NPI= 0.2 x Tumor size (cm) + tumor grade + lymph node stage.

The lower the NPI value, the better the prognosis ***(Anderson, 2002).***

It allocates patients to five different groups with variable 10 years survival rates.

Grade: G1 = 1

G2 = 2

G3 = 3

Nodal status: no lymph nodes = 1

1-3lymph nodes = 2

>3 lymph nodes = 3

The following describes 10 years survival data in 5 prognostic groups according to NPI for patients treated by surgery alone (table 7):

NPI	10 year's survival (%)	Prognostic group
< 2.4	95	Excellent
2.41-3.4	85	Good
3.41-4.4	70	Moderate 1
4.41-5.4	50	Moderate 2
>5.4	20	Poor

4- Fixation of the primary:

There are three degrees of fixation; the first (where there is no fixation) and second degree (fixed to overlying skin) were not considered as sign of advanced disease, while the third degree (solid fixation to the chest wall) was considered a sign of advanced disease and of bad prognosis (***Yildirim et al., 2000).***

5-Lymph node status:

In the absence of the distant metastasis; lymph node status is the most important prognostic factor. The commonest sites of regional node involvement are the axillary, supraclavicular and internal mammary nodes ***(Buchholz et al., 2002).***

One of the most significant discriminates in predicting prognosis is the presence or absence of axillary node metastases especially with early stage breast cancer and to determine the best course of treatment ***(De Mascarel et al., 2002).***

The tumor status of IMC nodes does have a prognostic value, which is comparable to that of the status of the axillary lymph nodes ***(Cranenbroek et al., 2005).***

Not only is the involvement important, but also the determination of the number of nodes involved, as there is a direct relationship between the number of involved axillary nodes and the risk for distant recurrence ***(Truong et al., 2005).***

Risk of recurrence rates ranged between 30 to 35% in patients with axillary lymph node negative, 50 to 55% for patients with one to three positive nodes and up to 80 to 90% for patients with four or more positive nodes ***(Cheng et al., 2002).***

An adequate axillary dissection usually contains at least ten lymph nodes. If the

nodes are free of carcinoma, about 10 yr disease free survival rate 70 to 80%, but it falls to 35 to 40% with 1-3 +ve nodes and to 10-15% with more than 10+ve nodes, so disease free and overall survival rates decrease as the numbers of positive nodes increase ***(Weir et al., 2002).***

In addition, it is important to know the levels at which they are involved, the 5-years survival rate for patients with level I involvement is 65.2%, for level II 44.9% and for level III is 28.4%. In general terms, the mortality for patients with level III involvement was twice that for level II which in turn was twice that for level I ***(Iyer et al., 2000).***

Extension of tumor through the capsule has been associated with short term failure. There were 47% and 30% recurrence rates for patients with and without capsular invasion, respectively. Extranodal extension has been found to be an adverse prognostic factor in patients with one to three positive lymph nodes. However, this finding has lost its significance in patients with equal or greater than four positive lymph nodes**.** Capsular invasion and rupture of lymph nodes by tumor cells were strongly related to the number of invaded lymph nodes, hence, it was of no prognostic value by itself ***(Hetelekidis et al., 2000).***

The prognosis was much better if metastatic node involvement was microscopic rather than macroscopic ***(Susnik et al., 2004).***

Micrometastases were defined as smaller than 2 mm and macrometastases being larger than this and generally visible grossly. The evaluation of axillary nodal status should be based on histological examination ***(Mokbel and Kirkpatrick, 2002)***.

Thus a single micrometastasis would not add much more to the patient overall tumor burdens, because the difference in overall survival between patient with

negative axillary lymph nodes results versus those with one positive axillary lymph nodes result is small approximately 3% at 5 years ***(Liberman, 2000).***

It is recommended that lymph nodes be examined by cutting at 2 mm intervals to find evidence of macrometastasis, which is reported to negatively impact the prognosis of patients. Breast cancer patients with micrometastasis in lymph nodes are diagnosed as metastasis positive ***(Edge et al., 2010).***

By clinical evaluation, if nodes are felt, the 10 years survival rate is 60% and if movable nodes are felt, the 10 years survival rate is 50%. This rate drops to 20% if fixed nodes are felt ***(Chua et al., 2001)***.

Analysis of a score based on four pathobiologic parameters (tumor size, grading, laminin receptor and HER2 overexpression), previously shown to have the same value as nodal status in breast cancer prognosis, indicated that this score was predictive of axillary node relapses as well as distant relapses in the patient ***(Fitzgibbons et al., 2000).***

In a series of patients with mainly T1c clinically node-negative tumors, the rate of axillary relapse was only 3% at 5 years. Such omission of axillary staging is unlikely to impair local control in these patients ***(Greco et al., 2000 b).***

ALND, axillary irradiation or observation only, have failed to reveal any survival benefit from removal of axillary nodes with long term follow up (whatever their pathological status) ***(Cady, 2007).***

6- Lymphatic and vascular invasion:

Lymphatic vessel invasion is an important and independent prognostic factor particularly in patients with T1, node negative breast cancer. The presence of tumor emboli in lymphatic vessels within the breast is associated with increased risk of tumor recurrence. Blood vessel invasion (emboli) shows a higher

correlation with tumor size, histologic grade, tumor type, lymph node status, development of distant metastases and poor prognosis. The recurrence rate for women with LVI-positive stage I disease was 38% compared to 22% for those with LVI-negative disease ***(Schoppmann et al., 2004).***

7- Stromal reaction and inflammatory carcinoma:

Tumors with an absence of inflammatory reaction at the periphery have lesser degree of nodal metastasis and a better prognosis. Women presenting with an enlarged swollen erythematous breast due to carcinoma plugging vascular space in the skin have a very poor prognosis, with 3-yr. survival rate of only 3 to 10 % ***(Carton et al., 2006).***

8- Pathological type:

The pathologic characteristics of the tumor have prognostic significance.

In general, a special type of breast carcinoma (tubular, colloid, medullary, lobular and papillary) has a better prognosis than those of no special type with exception is metaplastic carcinoma, which has a worse prognosis

For invasive carcinoma the 10 years survival rate were as follow (papillary 65%, medullary 58%, colloid 57% and lastly ductal 29%). Moreover, marked atypia and high mitotic index are associated with poor prognosis ***(Mirza et al., 2002).***

9-Extent of carcinoma in situ *(Fitzgibbons et al., 2000)*:

The following histologic features should be included

I- Nuclear grade:

Grade 1: Monotonous nuclei, equal to 1.5-2 RBC diameter, with finely

dispersed chromatin and only occasional nucleoli.

Grade 2: Neither nuclear grade (1) nor nuclear grade (3).

Grade 3: Markedly pleomorphic nuclei, usually >2.5 RBC diameters, with coarse chromatin and multiple nucleoli.

II- Presence or absence of necrosis.

III- Architectural pattern(s):

(1) High grade carcinoma in situ: The growth patterns of this group are comedo necrosis.

(2) Low grade carcinoma in situ: The growth patterns of this group are true cribriform, micropapillary, clinging or less frequently solid.

10- Steroid Hormonal Receptors (ER & PR):

Estrogen has been thought to be a promoter in breast carcinogenesis, possibly by its influence on autocrine growth factor production by cancer cells ***(Gruber et al., 2002).***

The number of estrogen receptors in breast cancer cells may be high, intermediate or absent. Synthesis of Progesterone receptor was depending on the activity of ER. Estrogen receptors (ERs) level is proportional to the degree of cell differentiation and to the potential response to hormonal therapy, oophorectomy or tamoxifen. In general, tumors with high ERs levels have a better prognosis than do those with intermediate to low ERs levels. Moreover, 70% of ER - positive tumors regresses after hormonal therapy as compared with 5% of those who are ER-negative. Furthermore, tumors positive for both ERs and progesterone receptors (PRs) are associated with a better response to hormonal therapy ***(Grann et al., 2005).***

Because the growth of breast cancer is often regulated by the female sex steroids, determinations of cellular concentrations of ER and PR in the tumor continue to be used to predict which patients are of good prognosis and may also benefit from anti-hormonal therapy ***(Bundred, 2001).***

The use of adjuvant chemotherapy showed that its effectiveness was somewhat greater in ER-poor cancer than in ER-positive cancer, thus establishing ER as a weak predictive factor for adjuvant chemotherapy ***(Berry et al., 2006).***

Hormone receptors are more commonly found in postmenopausal patients than in premenopausal patients. In estrogen receptor –positive patients with recurrent disease, a change in the hormonal environment usually affects the tumor size, in premenopausal patients; this change can be accomplished by oophorectomy, antiestrogen therapy or both. In postmenopausal patients, antiestrogen therapy is used ***(Morimoto et al., 2006).***

11-Oncogen products (c-erbB-2 HER2/neu)

C-erbB-2 oncogene has appeared to be a useful tool to evaluate the degree of malignancy of breast carcinomas**.** Membrane staining of c-erbB-2 was demonstrated more in invasive ductal carcinoma than in non invasive tumors with absence of staining in normal breast tissue. It was reported that c-erbB-2 oncogene was expressed in about 50% of DCIS and 14% of IDC. It has correlated with tumor recurrence and shorter survival ***(Mylonas et al., 2005)***

Overexpression of c-erbB-2 did not correlate with Ki67 immunostaining. C-erbB-2 immunostaining in moderately EGFR positive tumors has been associated with worsening of the prognosis of the patient but with highly positive EGFR staining, there was no further contribution to the already poor prognosis. Membranous staining has been shown to be prognostically relevant than

cytoplasmic staining. C-erbB-2 overexpression has been associated with poor prognosis in node positive breast cancer ***(Wilking et al., 2007).***

12- P53 tumor suppressor gene:

P53 positivity is an independent factor of poor prognosis for overall and disease-free hormonal receptor status and high grade lymph node ***(Kai et al., 2006).***

13- Tumor proliferative activity:

Tumors with high proliferation rates have a worse prognosis. Several methods have been developed to estimate the proliferative rate of tumor cells ***(Van Diest et al., 2004).***

1) Mitotic activity is assessed by one of two methods namely

(a) Mitotic index expressed as number of mitoses per 1000 cells.

(b) Mitotic count in 10 microscopic HPF.

The prognostic significance of mitotic count as a radical of tumor grading has been strongly emphasized. Tumor with high mitotic index had a high probability for recurrence within 5 years ***(Groenendijk et al., 2003).***

2) DNA content analysis consists of 2 parts:

(a) DNA ploidy: it measures the average amount of DNA per cell. Diploid tumors have normal DNA content and a better prognosis than aneuploid tumors, which have abnormal DNA content and a worse prognosis ***(Bracko et al., 2001).***

(b) S-phase fraction: refers to the percentage of cells preparing for mitosis by their active synthesis of DNA as measured by flow cytometry; the higher the S-phase fraction, the worse the prognosis. It was correlated with ploidy; where

diploid carcinomas usually have a lower SPF than aneuploid lesions. Tumors with a high SPF tend to be ER negative. Also, ploidy and SPF have been found to correlate with the histologic differentiation of duct carcinomas and with nuclear or cytology differentiation ***(Moureau-Zabotto et al., 2005).***

14- Prognosis after local recurrence:

Local relapse doesn't always herald distant metastasis. A prolonged interval between the initial treatment and local recurrence is the most important prognostic factor ***(Montagna et al., 2011).***

15- Prognosis after systemic recurrence:

Patients with breast cancer who suffer systemic spread of their disease often present with bone metastasis ***(James et al., 2003).***

Those who suffer bone metastasis as their first site of recurrence are known to have a longer survival than those who present first with visceral metastasis ***(Solomayer et al., 2005).***

Survival for those with solitary bone metastasis is known to be better than those who present with multiple bone metastases ***(Jacobson et al., 2001).***