Gamma Interferon in Radical Versus Conservative Breast Surgery

A Thesis submitted in partial fullfilment of a M. D. degree in general surgery

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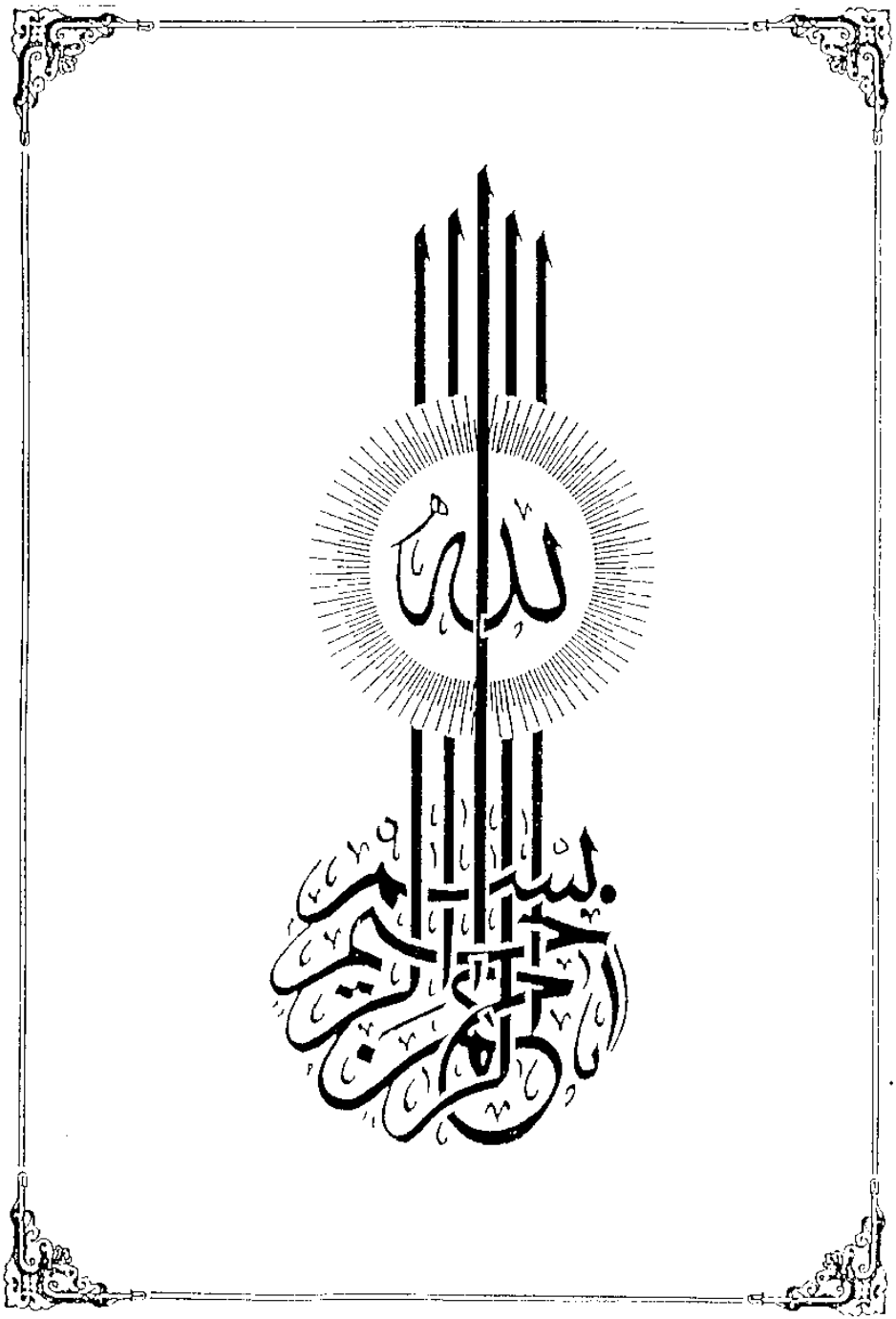

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Introduction

Twenty years ago the selection of therapy for primary breast cancer was simple, breast cancer equalled mastectomy. Currently however there is a wide variety of options for treatment of the primary cancer in the breast, the regional lymphnodes in the axilla and the distant preclinical micrometastases. There are many options available in the current therapy, thus the actual selection for therapy for an individual patient is complex confusing and controversial. [1]

For an individual patient's breast cancer the course is still largely unpredictable. Some women die of metastatic disease within a year whereas others survive several decades.

Despite the prognostic strength of the TNM staging system, women with ostensibly equivalent disease stage often exhibit vastly differing courses and periods of survival. This fact obviously implies the need to differentiate further between clinically agressive and clinically indolent disease.[2]

Gamma interferon is an endogenously produced substance that have antiviral and anti tumor activity.[44] The study will try to compare the differences between the patients with cancer and the normal controls. The study will also compare the gamma interferon levels to the established prognostic factors for breat cancer (tumor size, lymphnode status, hormone receptor status, hitologic grading and DNA analysis). Finally the study will compare the changes occuring in gamma interferon levels in the perioperative period in the radical and the conservative surgery group to evaluate the extent of immune suppression caused by either type of surgery on the breast cancer patients.

Staging and Prognostic Indicators in Breast Cancer

Chapter I

Staging and Prognostic Indicators in Breast Cancer

A major question in the biology of breast cancer can be formulated as follows: Is early stage breast cancer "early" because it has been detected at a potentially curable time in its course of growth, or is it's intrinsic biologic nature such that it permits detection at a favorable point in time?

Fisher[3] has put forth a framework for approaching the answer.

Fisher hypothesis of tumor biology:

1.There is no orderly pattern of tumor cell dissimination.

2.The positive lymph node is an indicator of possible disseminated disease.

3.Lymph nodes are not barrier to spread of disease.

4.The blood stream is an important factor in tumor cell spread.

5.Complex host-tumor relationships govern disease growth and spread.

6.Operable breast cancer is a systemic disease.

A.Staging:

The problem of comparing the results of treatment from different institutions and among different surgeons has been impaired for years by a lack of adequate classification or by a varying standards of classification. At present TNM for breast cancer is the preferable staging system.[4] Table 1-1 shows the American Joint Committee on Cancer (AJC) version of the TNM staging system. Several improvement over this version were made to ensure a uniform staging world wide. These include the addition of T4d for inflammatory carcinoma and adding stage O (TisNoMo) to the staging section. Stage II has been divided into IIa and IIb recognizing the better prognosis T2N0 patient when compared with node positive patient (T2N1).[4]

B.prognostic indicators in invasive breast cancer:

Clinical trials have demonstrated statistical relation between certain prognostic factors and two important intervals in the progression of breast cancer. The time from the initial diagnosis to the first disease recurrence and the time until death from breast cancer.[3] Besides predicting survival time after diagnosis, prognostic factors also help the clinician by providing information on likely site(s) of initial

Table 1-1

STAGING OF BREAST CARCINOMA

Definitions for all time periods

Primary tumor (T)

☐ TX Tumor cannot be assessed.
☐ TO No evidence of primary tumor.
☐ TIS Paget's disease of the nipple with no demonstrable tumor.

NOTE: Paget's disease with a demonstrable tumor is classified according to the size of the tumor.

T1* Tumor 2 cm or less in greatest dimension.
☐ T1a No fixation to underlying pectoral fascia or muscle.
☐ T1b Fixation to underlying pectoral fascia and/or muscle.
(Check below in addition to T1a or T1b)
☐ I tumor ≤ 0.5 cm.
☐ II tumor > 0.5 ≤ 1.0 cm.
☐ III tumor > 1.0 ≤ 2.0 cm.

T2* Tumor more than 2 cm but not more than 5 cm in its greatest dimension.
☐ T2a No fixation to underlying pectoral fascia or muscle.
☐ T2b Fixation to underlying pectoral fascia and/or muscle.

T3* Tumor more than 5 cm in its greatest dimension.
☐ T3a No fixation to underlying pectoral fascia or muscle.
☐ T3b Fixation to underlying pectoral fascia and/or muscle.

T4 Tumor of any size with direct extension to chest wall or skin.

NOTE: Chest wall includes ribs, intercostal muscles, and serratus anterior muscle, but not pectoral muscle.

☐ T4a Fixation to chest wall.
☐ T4b Edema (including peau d'orange), ulceration of the skin of the breast, or satellite skin nodules confined to the same breast.
☐ T4c Both of the above.

Lymph nodes (N)

Definitions for clinical-diagnostic stage

☐ NX Regional lymph nodes cannot be assessed clinically.
☐ N0 Homolateral axillary lymph nodes not considered to contain growth.
☐ N1 Movable homolateral axillary nodes considered to contain growth.
☐ N2 Homolateral axillary nodes considered to contain growth and fixed to one another or to other structures.
☐ N3 Homolateral supraclavicular or infraclavicular nodes considered to contain growth, or edema of the arm.†

Lymph nodes (N)

Definitions for surgical evaluative and postsurgical treatment-pathologic

☐ NX Regional lymph nodes cannot be assessed (not removed for study or previously removed).
☐ N0 No evidence of homolateral axillary lymph node metastasis.
☐ N1 Metastasis to movable homolateral axillary nodes not fixed to one another or to other structure.
☐ N1a Micrometastasis ≤ 0.2 cm in lymph node(s).
☐ N1b Gross metastasis in lymph node(s).
☐ I Metastasis more than 0.2 cm, but less than 2.0 cm in one to three lymph nodes.
☐ II Metastasis more than 0.2 cm, but less than 2.0 cm in four or more lymph nodes.
☐ III Extension of metastasis beyond the lymph node capsule (less than 2.0 cm in dimension).
☐ IV Metastasis in lymph node 2.0 cm or more in dimension.

☐ N2 Metastasis to homolateral axillary lymph nodes that are fixed to one another or to other structures.

☐ N3 Metastasis to homolateral supraclavicular or infraclavicular lymph node(s).

Distant metastases (M)—All time periods

☐ MX Not assessed.
☐ M0 No (known) distant metastasis.
☐ M1 Distant metastasis present.
Specify: _____

Tumor size: _____ × _____ × _____ cm.
Predominate lesion Measured on: ☐ Patient ☐ Pathological specimen ☐ Mammogram
Location (Multiple when necessary) ☐ OUQ ☐ OLQ ☐ IUQ ☐ Nipple/areola ☐ ILQ

Lymph nodes: Total No. _____ No. with met. _____

Performance status _____ (see reverse side.)

Examination by _____ M.D.

Date _____

STAGE:

☐ Clinical-diagnostic

☐ Stage TIS—In situ				
☐ Stage X—Cannot stage (unstageable)				
☐ Stage I	☐ T1ai	N0	M0 ☐	
	☐ T1aii	N0	M0 ☐	
	☐ T1aiii	N0	M0 ☐	
	☐ T1bi	N0	M0 ☐	
	☐ T1bii	N0	M0 ☐	
	☐ T1biii	N0	M0 ☐	
☐ Stage II	☐ T0	N1a or 1b	M0 ☐	
	☐ T1a or T1b	N1a or 1b	M0 ☐	
	☐ T2a or T2b	N0	M0 ☐	
	☐ T2a or T2b	N1a or 1b	M0 ☐	
☐ Stage IIIa	☐ T0	N2	M0 ☐	
	☐ T1a or T1b	N2	M0 ☐	
	☐ T2a or T2b	N2	M0 ☐	
	☐ T3a or T3b	N0	M0 ☐	
	☐ T3a or T3b	N1	M0 ☐	
	☐ T3a or T3b	N2	M0 ☐	
☐ Stage IIIb	☐ Any T	N3	M0 ☐	
	☐ Any T4	Any N	M0 ☐	
☐ Stage IV	☐ Any T	Any N	M1 ☐	

☐ Postsurgical treatment-pathologic
Stage TIS ☐
Stage X ☐
Stage I ☐
Stage II ☐
Stage IIIa ☐
Stage IIIb ☐
Stage IV ☐

* Dimpling of the skin, nipple retraction, or any other skin changes except those in T4b may occur in T1, T2, or T3 without affecting the classification.

NOTE: Cases of inflammatory carcinoma should be reported separately.

† Edema of the arm may be caused by lymphatic obstruction and lymph nodes may not then be palpable.

SOURCE: American Joint Committee on Cancer—1982.

recurrence and the expected response to medical therapy.[2] Because of the marked variability of the clinical course, identifying the people at higher risk is important due to the advent of promising stratigies for adjuvant therapy in patients without involved lymphnodes. Patients with tumor free lymphnodes who are at high risk for early disease recurrence may benefit from this adjuvant therapy, whereas if they could be identified reliably, patients at low risk of disease recurrence could be spared the toxicity of systemic therapy.[2]

1-Tumor size:

many studies have documented the relation between the tumor size and survival expectations. Larger tumors are associated with shorter interval before disease recurrence or death. In a representative sample consisting of 24,740 patients, survival data collected by the surveillance, epidemiology and end result(SEER) program of the U.S. National Cancer Institute have confirmed the importance of tumor size.[5] The relation between tumor size and survival at five years was linear regardless of nodal status, although for node negative patients, the adverse effect of size on survival was less than for node positive patients.[2] Five year survival rates adjusted for age expected mortality ranged from 45% for tumors more than 5 cm in size with involved lymphnodes to 96% for tumors

smaller than 2 cm with no involved lymphnodes.[6] Tumor size was more important in predicting tumor recurrence than was nodal status or histologic grading. A very favorable prognosis was implied for patients with tumors less than 1 cm for whom the probability of relapse was 12% compared with 28% for patients with tumors of 1-2 cm. When analysed by decade however tumor size was not found to be of significance in disease recurrence after 10 years.[6]

In a recent publication studying the relevance of tumor size on the survival of breast cancer patients, the study concluded that tumor size was a significant predictor of disease free and overall survival when the number of positive nodes, estrogen receptor status, menopausal status, and race were considered.135

2-Axillary node metastasis:

Evidence continues to affirm that the single most significant indicator of prognosis in women with invasive breast cancer is the presence or absence of metastatic carcinoma in axillary lymphnodes.[7] The presence of axillary lymphnode metastasis is an indicator of distant metastasis[8], and as the number of axillary lymphnode metastases increase the survival rate decreases. Historically, patients have been categorised as those with no lymphnode metastasis, those with

one to three nodes involved, those with four or more. The five year survival for patients with no axillary metastasis was 83%, for those with one to three nodal metastases was 73% and for those with four or more was 46%.[8] However the current data show that "four or more" is too broad a characterization because the hazard rate for patients with 4-6 involved lymphnodes(54%) is quite different from those with 13 or more (24%). Therefore when an axillary dissection is done it is prudent to try to remove at least ten and preferably 13 or more nodes.[8]

Despite the prognostic strength of the traditional TNM staging system women with ostensibly equivalent disease stages often exhibit vastely differing courses and periods of survival. This fact obviously implies the need to differentiate between clinically agressive and clinically indolent disease.

3-Hormone receptor status:

Numerous studies supported the value of estrogen and progesteone receptors as prognostic factors.[9,10] Low estrogen receptor value or estrogen receptor negative status is associated with earlier recurrence and shorter overall survival than in patients with an estrogen receptor positive tumor regardless of the nodal status.[2] For node negative patients, estrogen receptor status assumes a more important role as a prognostic factor. A multivarient analysis of 1647 patients

with stage I breast cancer found estrogen receptor status along with tumor size to be an independent prognostic factor.[11,12] The rationale for the use of receptor assays as prognostic factors is summerized in table 1-2.

Table 1- 2:
Rationale for estrogen receptor as a prognostic factor in primary breast cancer:[13]

Variable	ER+	ER-
Degree of differentiation	High	Low
Proliferative potential	Low	High
Visceral recurrence	Low	High
Hormone dependence	High	Low

Both estrogen and progesteron receptor status are predictive of recurrence, and several studies suggest that the progesterone receptor status has more prognostic value than the estrogen receptor status, especially in node positive patients.[14] For node negative patients, estrogen receptor status assumes a more important role as a prognostic factor.[12] The above data concludes that estrogen receptor status is important as a prognostic factor in stage I disease, progesterone receptor

status appears to be a more significant indicator for predicting survival in stage II disease.[15]

In addition to their usefulness in predicting survival in primary breast cancer and recurrent disease, the benefitial effect of positive estrogen receptor and progesterone receptor status has been demonstrated in numerous trials investigating disease response to hormonal therapy.[16] Table 1-3 demonstrates the response to endocrine therapy as a function of receptor status.

Table 1-3:[17]
Response to endocrine therapy as a function of receptor status:

Receptor status	Responses/patients(%)
ER+/PR+	87/113(77)
ER-/PR+	6/13 (46)
ER+/PR-	33/121(27)
ER-/PR-	12/111(11)

4.Histopathology and nuclear grade:

Several histopathological features are associated with a more aggressive cancer. A high mitotic rate, nuclear anaplasia, and a poor degree of celluler differentiation have been recognized for many years as predictors of a worse clinical outcome.[2,134] However, the cellular features that define the histologic