

# PROGNOSTIC MARKERS IN CANCER 2004

## ESTROGEN AND PROGESTERONE RECEPTORS

Measured by immunohistochemistry and was determined as positive if  $\geq 10\%$  of the tumor cells were stained in the nucleus. Patients whose tumors express 10% to 20% are positive but considered borderline for staining activity. Patients with positive receptors respond better to hormone therapy (1) and in some reports have a better prognosis (2). These results are primarily for breast cancer patients but there are similar reports in the literature for uterine cancer (3).

## Her2 EXPRESSION

This oncogene has a similar sequence to the epidermal growth factor receptor. Using immunohistochemistry, membrane specific expression is observed in 15 to 30% of all breast cancer tumors. Expression of Her2 is significantly related to positive lymph nodes, poor nuclear grade, lack of steroid receptors and high proliferative activity (4,5). Patients expressing this antigen have a poor prognosis (4,5). High dose adjuvant therapy is more beneficial to patients expressing this antigen (5).

## PLOIDY STATUS

DNA content per cell was measured by flow cytometry. A DNA index was defined as the ratio of DNA content of tumor to normal cells. Cells that have a ratio between 1 and 1.3 are considered more normal (diploid-like) and have been reported to have a better prognosis. Cells that are not in this range are defined as aneuploid-like and are usually of a poorly differentiated nature (6). Aneuploid tumors also have a higher percent of proliferating cells compared to the diploid-like cells (7). Tumors that contain more than one population of aneuploid clones are defined as multiploid tumors. Image analysis will also be performed and reported in cases where the flow cytometry data might be considered in error due to sampling artifact. Candidate tissues for sampling artifacts are tumors with low number of cancer cells or diploid only tumors.

## PROLIFERATIVE ACTIVITY

Measurement of tumor cell proliferation was performed by flow cytometry. High proliferation as expressed by %S (synthesis phase) activity is an indicator of poor prognosis (7,8). Since diploid tumors have considerably lower proliferative activity compared to aneuploid tumors, the distribution of the two groups was analyzed separately. This distribution of low, middle and high activity was determined from our laboratory results, which is determined annually. This follows the guidelines from the NIH CONSENSUS CONFERENCE ON FLOW CYTOMETRY for defining the degree of proliferative activity (9). These distribution ranges are given below:

<u>Tumor type</u>	<u>Range for low activity</u>	<u>Range for moderate activity</u>	<u>Range for high activity</u>
Diploid tumors	0% to 0.8%	0.9% to 1.7%	>1.7%
Aneuploid tumors	0% to 5.3%	5.4% to 10.3%	>10.3%

A second method to measure proliferation is through immunohistochemistry. In this procedure, the % of tumors that stain for the nuclear antigen called Ki-67 (also called **Mib-1**) is determined. Cells that stain positive are in the proliferative cycle. Tumors that have high levels of this antigen have a worse prognosis but may respond better to high dose chemotherapy (10,11). Tumors that are less than 5% (Group 1 and 2) are considered low, 5% to 20% are considered moderate (Group 3), and those tumors with greater than 20% are considered high (Group 4 and 5). Groups are used here because it is hard to define the actual percentage values.

## REFERENCES:

1. Pertschuk L.P. et. al. Estrogen receptor immunocytochemistry in paraffin embedded tissues with ER1D5 predicts breast cancer endocrine response Amer. Cancer Soc. 77:2514-2519, 1996
2. McGuire W. L. et. al. How to use prognostic factors in axillary node-negative breast cancer patients JNCI 82:1006-1015, 1990
3. Creasman W.T. et. al. Influence of cytoplasmic steroid receptor content on prognosis of early stage endometrial carcinoma Am J Obstet Gynecol 151: 922-932, 1985
4. Tetu B. et. al. Prognostic significance of HER-2/neu oncoprotein expression in node positive breast cancer. Cancer 73, 2359-2365, 1993
5. Muss H.B. et. al. c-erbB-2 expression and response to adjuvant therapy in women with node positive early breast cancer New Eng. J of Med. 330, 1260-1266, 1994
6. Kallioniemi O.P. et. al. Tumor DNA ploidy as an independent prognostic factor in breast cancer. Br. J cancer 56:637-642, 1987
7. Fisher B. et. al. DNA cytometric analysis of primary operable breast cancer Cancer 68:1465-1475, 1991
8. Kute T. E. et. al. Flow cytometry in node positive breast cancer: Cytometry 22:297-306, 1995
9. Hedley D. W. et. al. Consensus review of the clinical utility of DNA cytometry in carcinoma of the breast Can. Res. Treat 28:55-59, 1993
10. Sahin AA, Jungsil R, Jae R, et al. Ki-67 immunostaining in node-negative stage I/II breast carcinoma. Cancer 68: 549-557, 1991
11. Wintzer HO, Irmgard Z, Schulet-Monting J. et al Ki-67 immunostaining in human breast tumors and its relationship to prognosis Cancer 67: 421-428, 1991