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Tumor grade in prognosis of breast cancer

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TUMOR GRADE IN THE PROGNOSIS OF BREAST CANCER

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Six percent of American women will one day have breast cancer, the disease which is the leading cause of death in women from 40-44 years of age in this country. Little can be said for the treatment of breast cancer, the death rate from which has remained essentially unchanged over the last thirty years.[1] Perhaps it is for this reason that the topic of treatment of mammary carcinoma remains so controversial.

There is no general agreement as to the most suitable plan for the management of most cases of breast cancer. Difficulty arises from the fact that similar results are often achieved from different modes of treatment, and again the same measures, even in the hands of well-known authorities, have produced a wide variation of results. There are some patients with advanced tumors and symptoms extending over twelve months, or more, who live for a surprising number of years, while others, with growth apparently confined to the breast, seek advice from a physician, yet die in a few months from widespread metastases. Sometimes results are obtained with limited treatment even when only palliation is hoped for. But on the other hand, tragedy frequently results after radical treatment, even where success had been anticipated.

Therefore it is evident that the behavior of carcinoma of the breast is extremely variable. This makes it necessary that strictly comparable groups of patients be obtained in order to assess different methods of treatment. For this one needs a reliable system of classifying patients with mammary carcinoma. In order to determine the outlook for a patient, one must first somehow be able to determine the degree of malignancy of that patient's tumor as well as the extent of the tumor.[2]

The purpose of this paper shall be to review the controversy existing concerning attempts to group breast carcinomas as to the degree of their malignancy, and subsequently relate these groups to prognosis or survival time.

Further, an attempt is made to compare two such methods of grouping, and to illustrate their value in prognosis, by evaluating a series of tumors. It is hoped that such information might become useful in assessing the kinds of treatment most beneficial for particular groups of cases.

Historical literature indicates that though physicians have long recognized the variability of certain types of malignancies, little attention was directed to the grading of tumors until 1920. At this time Broders[3] published a paper which expressed numerically the malignancy of a large series of cancers, this numerical malignancy being based solely on the microscopic study of the cancer cells themselves without foreknowledge of the clinical history or the ultimate results.

His grading was based on the principle of cell differentiation, with division of cancerous tumors into four grades. He later revised his system to include consideration of mitotic figures and cells with prominent nucleoli. According to Broders' system, a Grade 1 tumor is one in which about three fourths of the cells are differentiated and one fourth are undifferentiated. In a Grade 2 tumor differentiation ranges from 75% down to 50%. In Grade 3 the differentiation ranges from 50% to 25%, and in Grade 4, which is considered the most malignant, differentiation ranges from 25% to practically nothing.

Broders felt that the grades of malignancy are in direct proportion to the proliferative, infiltrative, metastasizing, and death-dealing capacities of a tumor. He also maintained that the chief difference in the malignancy of

tumors depends on the cellular activity of that particular tumor.

Broders indicated in 1941 that though the grading of cancer would be valuable for prognosis, it would also be of considerable assistance in determining the most effective therapeutic procedure to be employed in a given case of cancer. He illustrated the prognostic value of his method of grading for carcinoma of the breast by separating four groups of patients with ten year survivals ranging from 14.9% for the most malignant group to 83.6% for the least malignant group.[3]

In 1925, long before Broders used his method for classifying breast tumors, Greenough[4] devised a similar method for grouping mammary carcinomas. He was, in fact, the first to grade cancer of the breast according to the principle of anaplasia, or lack of differentiation. He studied a series of breast cancer cases collected at the Massachusetts General Hospital during the years 1918-1920. This series had been presented at the meeting of the Southern Medical Association in New Orleans, with a discussion of the value of pre-operative and post-operative X-ray treatment.

In the hope of finding a factor of importance in this discussion, Greenough collected the microscopic specimens and reviewed their pathological characteristics. He gave

special attention to the loss of the adenomatous arrangement of tumor cells, to the evidence of secretory activity in the cell protoplasm, to nuclear changes, hyperchromatism, number of mitoses, especially irregular mitoses, and to variations in the size and shape of the cells and nuclei, which he called pleomorphism. He found that grouping the cases according to these characteristics permitted a suitable correlation with the number of cures obtained.[4]

It is difficult to evaluate Greenough's success because of his small series and his failure to define a "cure". But he did establish some criteria for grading of breast carcinoma which were later verified by other workers.

Greenough also realized the inadequacy of the only accepted method at that time for estimating the extent of disease in patients with cancer of the breast. This method was the grouping of patients into those in which lymph nodes were found to be free from disease, and those in which cancer was found to be present in the axillary lymph nodes. He stated that the inaccuracy in this method arises from the fact that tumors in the upper or inner hemispheres of the breast may extend through the lymphatics to involve the nodes above the clavicle or in the anterior mediastinum before the axillary nodes are affected. The possibility also exists that blood stream metastases may arise before

disease can be recognized in the axilla.

Greenough went further to state that the common classification of breast carcinomas according to whether they are medullary, scirrhous, or adenocarcinoma is somewhat arbitrary because the same tumor specimen often takes on different appearances in different locations, making an exact classification quite impossible.

One of the criteria which Greenough felt to be significant in classification of mammary carcinoma was the amount of adenomatous arrangement of the cells of the tumor. He felt that the arrangement of the cells around an open gland-lumen indicated a high degree of differentiation of the tumor. A second criterion for differentiation involved the presence, in the epithelial cells of the tumor, of droplets of mucoid secretion, retained in the cells as vacuoles. He found that the presence of marked secretory activity was an indication of low malignancy. A factor which Greenough's work showed to be quite important was the size and shape of the nuclei of the tumor cells. In each of his cases high degrees of variation in both size and shape of nuclei carried with them a serious prognostic influence. Greenough considered the conditions of hyperchromatism and the presence of numerous and irregular mitoses in his method of classification, large numbers of such figures again indi-

cating a high degree of malignancy.

Many observers at that time maintained that the tissues of the body were able in some way to resist the growth of cancer. Such a protective phenomenon in experimental animals was found to consist chiefly in a dense round-cell infiltration around the tumor. For this reason the presence of round-cell infiltrates, frequently observed in human cancer tissue, was also held to be an indication of the resistance of the individual to the tumor. Though Greenough believed that resistance of the individual to cancer was a fact of great importance, he was not able to show that such a resistance made itself evident by round-cell infiltration. In summary, the factors which Greenough found to be of importance in estimating the degree of malignancy of a given breast tumor were: (1) degree of gland formation; (2) degree of secretory activity of the tumor cells; (3) uniformity of size and shape of cells and nuclei; and (4) presence of hyperchromatic changes and mitotic figures.[4]

Following Greenough's work, many other workers attempted to pick out prognostic characteristics from the histological study of breast tumors. Many other features were alluded to as having prognostic significance. Some workers went so far as to devise histological "malignograms" and a "malignancy index". Yet other workers were

not able to find even one factor of prognostic value, with conclusions that attempts at precise histological grading of breast tumors was unscientific and a wasted effort. But in general, broad grouping methods such as that of Greenough were considered to be of value.[5]

The success of such a method might be explained by a study by Caspersson and Santesson[6] on the metabolism of tumor cells. In reviewing the chemical differences between normal cells and tumor cells, they found that the tumor cells contained an increased amount of nucleic acids and diamino acids. Cytologically, they found that tumor cells contained an increased number of mitoses, especially abnormal mitoses, an increase in size of nuclei, and an increase in nucleolar substance, the latter characteristics being the most constant change.

These workers went on to define two specific types of tumor cells. The Type A cells formed small infiltrating strands. These cells contained high amounts of cytoplasmic protein and RNA, and were especially high in nuclear RNA. Type B cells were found in inner areas of cell complexes. These were poor in both cytoplasmic and nuclear protein and RNA but showed prominent nucleoli rich in RNA. They felt that the Type A cell was a more rapidly growing and thus more malignant cell than the non-growing Type B cell.

The only explanation they offered for the difference was a possible difference in nutritional conditions.[6]

The first recent work of significance in the field of breast tumor grading was published by Bloom[5] in 1950. His method will be described in some detail, because it is the one used in the study related later in this paper.

His method of grading was based on the principles laid down by Greenough in 1925, with chief importance being given to three factors:

(1) Tubule formation. A high degree of differentiation was thought to be indicated by well marked tubular, acinar arrangement, with cells grouped more or less regularly around a central space. Actual tubules must be distinguished from clefts in the tissue probably caused by shrinkage during processing. In the actual tubules a rim of cytoplasm can usually be seen, separating the nuclei from the lumen. Points were awarded to the specimen according to the amount of tubule formation present. If a large part of the section showed well marked tubule formation, one point was awarded. If there was only slight or no attempt at differentiation, three points were assigned. If there was a moderate attempt at tubule formation, two points were given.

(2) Pleomorphism. This factor concerned irregularity

of nuclei insofar as size, shape and staining were concerned. Pleomorphism was judged by the nuclei, rather than the whole cells, because the cell outline was usually found to be indistinct in the histological preparation. If the tumor showed uniformity in the size, shape and staining of the nuclei, one point was awarded. If this factor was moderate in degree, two points were given. However, if there was a great degree of pleomorphism or irregularity, three points were awarded.

(3) Hyperchromatic and mitotic nuclei. Prognosis was felt to be worse, the greater the number of such nuclei present. Again the factor was divided into three degrees. If only an occasional hyperchromatic or mitotic figure was seen per high power field, one point was assigned. If two or three such figures were seen in most fields examined, this factor was felt to be present in moderate severity, and was awarded two points. Any greater number of such figures present warranted three points. In making use of this factor, one must allow for the degree of cellularity of each microscope field, because in the case of a very fibrous area with few cells, few mitoses will be seen in each field.

Both the degree of mitotic activity and pleomorphism of nuclei must be assessed from the growing edge of a tumor, rather than from a necrotic or fibrous center.

To assign a final grade to a particular tumor, the points allotted to each of the three histological factors are added together, making a possible total of three to nine. The smallest total represents the lowest degree of malignancy. Bloom arbitrarily cut the malignant scale into three grades, placing those tumors with three, four and five points into Grade 1; those with six or seven points into an intermediate Grade 2; and those with eight or nine points into Grade 3, the latter being the one showing the greatest degree of malignancy.

For his study published in 1957, Bloom made use of a series of 1,544 female patients with breast cancer seen at the Middlesex Hospital in London between the years of 1936 and 1949, all of which were followed at least five years after being first seen. Eighty-four per cent of these patients were treated either by radical or modified radical mastectomy, with or without ancillary irradiation. In the remainder of the cases, at least a biopsy was taken, in order to provide histological material for grading. Though treatment was not uniform, variation in treatment did not appear to materially influence the conclusions reached from this experiment. One hundred thirty-five cases were excluded from the series for the following reasons: post-operative deaths; air raid casualties; lack of follow-up at five years;

no evidence of frank carcinoma in the available section; bilateral carcinoma of the breast; sections were impossible to grade; the tumor consisted of a sarcoma or a squamous cell carcinoma. This left a total of 1,409 cases for final consideration. Preparations were parafin-embedded sections stained with hematoxylin and eosin. It was found, in general, that frozen sections were too thick and the nuclear detail was not definite enough. The clinical records were not consulted until after the grading was performed.

The correlation between the histological scale of malignancy and the five year survival rate for these patients is shown in Table 1. It is evident that there is a marked difference in prognosis between the various groups.

Table 1.--Relationship between Grade of Malignancy and 5-Yr. Survival.[5]

Grade of Malignancy:	1 Favorable	2 Intermediate	3 Unfavorable
Number of Cases:	362	640	407
5-Yr. Survivors:	272	298	130
5-Yr. Survivors %:	75%	47%	32%

Bloom points out that the three classes of tumors are not distinct pathological entities, but that the classes fall on a continuous scale of malignancy. Nor does he ascribe mathematical accuracy to his numerical point system for grading.

The first objection usually raised by the opponents of grading of breast cancer is that the histological appear-

ance varies in different parts of the primary tumor. Bloom readily agrees that though the histology may vary insofar as the type of tumor is concerned, a definite total individual pattern can be recognized if one takes into account the cytological features of the tumor. He states that in order for this to be possible, grading should be carried out on a section of reasonable size, perhaps 1½-2 cm square. In most cases, one section of the tumor will probably be sufficient, but in the case of a very large growth, perhaps two to three sections will be required to get the full histological picture. In the few cases which do show a definite variation in grade, and not merely a variation in structural pattern, the most weight must be given to the most malignant part of the growth. Bloom tested these views by cutting two sections from different parts of the periphery of each of 25 consecutive breast cancers. These 50 slides were then labelled with a code number and mixed, the grading being performed, not knowing the code of the accompanying twin to each section. It was found that the pair of sections from each breast had been placed in the same grade of malignancy.

A further objection to this method is that variation exists in the grade between the primary tumor and metastases. However, Bloom found that in 397 unselected cases in which there was involvement of the axillary lymph nodes,

82% of the cases showed the same grade in the primary tumor as in the metastatic lesion. He also found the majority of cases to remain constant in grade following treatment.

A further criticism might arise from the fact that the outcome of breast cancer is not truly revealed in the first five years after treatment. Patients continue to die of the disease in later years, as far as studies have been carried out. A study by Berg[7] involving 1,458 cases of breast cancer has shown that the five year mortality figures represent only 66% of the 20 year breast cancer mortality rate. Berg states that although a small proportion of this persistent risk may be due to the arisal of a primary cancer in the second breast, the more important factor for the patient is late recurrence of the first cancer.[7]

Though this latter objection may place Bloom's work in a different perspective, it should by no means detract from the value of his grading system. Bloom proceeded to gauge prognosis by the five, ten, and fifteen year survival rates. He emphasizes that the term "survival rate" does not necessarily imply freedom from cancer, but merely indicates the percentage of patients actually alive. Though the survival rate continued to fall relentlessly over the entire 15 years, both the ten year results and the 15 year results showed almost three times as many survivors in Grade 1 as

in Grade 3.

The next significant contribution to this field was made by Black, Opler and Speer[8,9], by means of various studies in which they related the survival of breast cancer cases to the nuclear structure present in the cancer tissue of these cases. Though they made their study on 42 different cancer types, the examination did include 869 cases of female breast carcinoma.

The material consisted of hematoxylin and eosin stained sections from surgical pathology files. Nuclear structures were classified from 0 to 4, with nuclei showing a high degree of similarity, delicate chromatin strands, no nucleoli or mitoses being graded as 4+. Those structures showing anisonucleosis, thickened chromatin strands, prominent nucleoli, and numerous mitoses, were given a grade of zero. Intermediate degrees of change were assigned intermediate values in accord with their relation to the extremes of the scale. It should be noted that the numbers used in this grading system have meaning opposite to those of Bloom's system.

Of the total number of breast carcinomas, 49% were assigned 0-1, or the most malignant grade; 30% were assigned grade 2; 20% were assigned grade 3-4, or least malignant. There is a good correlation between nuclear grade and five

year survival. Five-year survival for the most malignant group was approximately 35%; that for the intermediate, or grade 2 group was 62%; that for the least malignant group, grade 3-4, was 90%.

In order to remove the influence of curative therapy on the relationship between nuclear grade and survival, an analogous survival curve was constructed for those patients known to have died of their disease. The slope of the survival curve for this series did not differ markedly from that of the entire group. It was concluded by the authors that individual cancer cases do indeed vary in their degree of nuclear differentiation, and that the degree of this differentiation may be correlated with the lethality of the disease.[9]

Black, Opler, and Speer have also attempted to relate a further microscopical structural finding to the prognosis of breast cancer.[8,10] This factor involves the structure of the regional lymph nodes in breast cancer patients, and specifically the presence of sinus histiocytosis in these lymph nodes. It is their contention that the lethality of breast carcinoma is determined by an interaction between the growth potential of the primary tumor (nuclear grade) and a host resistance factor, which is visualized as sinus histiocytosis in the regional nodes.

Sinus histiocytosis has been described as the disten-

tion of the sinusoids of lymph nodes by elongated histiocytes, having a finely granular, eosinophilic-staining cytoplasm, in a syncytial arrangement. Many of the nuclei in these histiocytes show a definite nucleolus or vesicles. Histiocytes showing cytoplasmic vacuolization, erythrophagocytosis, or fibrillary and fibrotic changes were not considered of significance in grading. Nor were those sinusoids dilated by rounded macrophages, inflammatory cells, or edema fluid designated as sinus histiocytosis.

Material studied consisted of lymph nodes not involved by cancer, or uninvolved portions of partially involved nodes. Grading was performed on a scale of 0 to 4+, with a value of 4+ sinus histiocytosis being assigned to those nodes showing markedly prominent sinusoids filled with eosinophilic histiocytes. In the case of an absence of histiocytic cell proliferation, a 0 grade of sinus histiocytosis was applied. Intermediate intensities of sinus histiocytic reactions were assigned values in relation to the extremes of the scale.

Black, Opler, and Speer[8] reported in 1955 a study of 179 cases of breast carcinoma, in which they applied two factors in order to predict survival. These were sinus histiocytosis and nuclear grade. One hundred fifty-one of the cases were studied for sinus histiocytosis, 26% of which showed a high degree of histiocytic reaction, that is

Grade 3-4. Another 26% showed an intermediate degree of sinus histiocytosis, and 49% showed a slight or no sinus histiocytosis, falling into Grade 0-1. Only 40% of the latter group survived five years, while 90% of the Grade 3-4 group survived five years, and 68% of the intermediate grade survived for this period.

So it is apparent that there is an excellent linear relationship between the sinus histiocytic reactivity of such a group and the incidence of five year survivals, similar to the observed relationship between nuclear grade and survival. Yet it appears that the two types of measurements represent distinctly different phenomena, which occur independently of one another, for the same study showed that either marked, moderate, or minimal histiocytic reactions occurred with all gradations of nuclear differentiation.

Berg was quick to object to the reasoning of Black, et al. in an article entitled "Sinus Histiocytosis: A Fallacious Measure of Host Resistance to Cancer".[11] By using a series of only 42 cases of breast cancer, Berg attempted to show that a low amount of histiocytosis, with its associated poor prognosis was an indirect factor only, and depended upon age-old prognostic factors, namely the quantity of axillary metastases at the time of operation. His data indicated that sinus histiocytosis was most prominent in nodes free of metastatic cancer, and that in positive nodes, wherein there was replacement by

metastatic disease, there was less visible histiocytosis.[11]

This work prompted Black and Speer to re-examine their theory. They did this by evaluating the degree of sinus histiocytosis in the lymph nodes of non-cancer as well as of breast cancer patients. They found that the lymph nodes of 135 non-cancer patients demonstrated only minimal or no sinus histiocytosis, concluding thereby that sinus histiocytosis is an uncommon finding in cancer-free patients. They further determined the frequency of sinus histiocytosis grades for a series of 747 cases of breast cancer in relationship to the absence or presence of axillary metastases. The incidence of sinus histiocytosis of Grade 2 or greater was more than twice as frequent in the class without lymph node metastases as in the class with lymph node metastases. Yet 50% of the group without lymph node spread showed a Grade of less than 2. Thus it was shown that sinus histiocytosis is not necessarily a usual feature of nodes free of metastases. Furthermore, 20% of the group with metastases had a grade of 2 or greater, indicating that node metastasis does not rule out the occurrence of sinus histiocytosis. In addition,,in each of the two groups, distinct differences in the frequency of sinus histiocytosis were found in relation to survival, despite the two groups being divided on the basis of the presence of axillary metastases.

This further data again justified the conclusion that the survival of cancer patients with sinus histiocytosis is greater than the survival of those without such a reaction. The prognostic significance of sinus histiocytosis seems to be independent of the presence or absence of regional node metastases or the lethality of the primary tumor in terms of nuclear grade.[10]

The validity of some of the aforementioned prognostic factors was further investigated by Cutler, et.al.[12] in 1966. They evaluated the reproducibility of classification by nuclear grade and sinus histiocytosis, as well as ascertaining once again that these factors were related to patient survival.

For this study, a sample of 202 tumor tissue specimens and 186 lymph node specimens were selected. Each slide in the series was read independently on two separate occasions by Black, and also by two other pathologists. In the two independent readings of nuclear grade, Black assigned 70% of the slides to the same classification. He achieved an identical percentage of replication for reading of sinus histiocytosis. The averages of his two readings were then compared to those of the other two pathologists. Pathologist A agreed with Black in 65% of the readings for nuclear grade and in 55% of those for sinus histiocytosis.

Pathologist B agreed in only 54% of the readings for nuclear grade, but in 62% of the readings for sinus histiocytosis. It was felt that Black's consistency in his own classification was reasonably good, and that agreement between Black and the other two pathologists was fairly good. It is suggested that sharpening the criteria used may improve the reliability of such indices and enhance their usefulness in study of breast cancer.

Friedell[13] has recently shown yet another factor to be of value in the prognosis of breast carcinoma, when analyzed quantitatively. He has shown that if the presence of blood vessel invasion can be accurately determined in a specimen of breast cancer, this may be associated with a significantly lower five year survival rate.

One hundred fifty-three cases were studied, using sections stained by the Verhoeff technique. All portions of each slide were examined for the presence of blood vessel invasion. Only clearly acceptable invasion with tumor cells surrounded by the elastica of pre-existing blood vessels was recorded. Questionable instances were considered as negative. Blood vessels were distinguished from mammary ducts by the amount of elastic tissue present.

Clinical data for the cases were consulted after such examination to determine survival time as well as the presence

or absence of lymph node metastases. Forty-six per cent of the cases were found to have blood vessel invasion. Of this portion, 36% of those with negative nodes survived five years, and 24% of those with positive nodes survived five years. Of the 54% of the cases showing no blood vessel invasion, 70% of those with negative nodes survived five years, while only 28% with positive nodes survived this period.

This indicated that the best prognosis for five year survival was shown in the women with neither vascular invasion nor lymph node metastases. In the case of positive lymph node metastases, the presence of blood vessel invasion was not demonstrated to represent a significant prognostic factor.[13]

After reviewing the significant theories proposed and tested since 1920, we find that there remains controversy and confusion about the prognostic factors in breast cancer. Not only have widely differing opinions been expressed concerning the above-mentioned characteristics, but in addition, other aspects of prognosis arise from time to time, which tend to further confuse the issue. For instance, do such factors as the age of the patient, the delay in seeking treatment, the size and site of the primary growth, have any bearing on the outcome? Is there

a relationship between prognosis of the breast cancer and such things as sex chromatin or doubling time of the tumor?

Myers, et. al.[14] recently made use of four different parameters for judging the malignancy of breast tumors. These were; (1) axillary node metastases; (2) tumor size; (3) sinus histiocytosis; and (4) nuclear grade. He judged each factor as being either favorable or unfavorable, without describing the methods used. He was able to develop an exponential survival pattern on the basis of these four factors. He found that there was no interaction between these factors, but rather that each had an independent effect.

Breur[15] suggests that most malignant tumors show an exponential growth pattern, and that this can be expressed in terms of the doubling time of the tumor cells. He maintains that a statistically significant increase in the doubling time value can be shown with increasing age, with this value being three times as great for the 60-80 year age as for the 20-40 year group. Breur feels that further studies of the growth rates of tumors can give us more insight into the life history of neoplasms.[15]

Tavares[16] relates a relatively new concept in the prognosis of breast cancer. He states that reports have consistently shown an absence of sex chromatin in a

significant proportion of breast carcinoma (about 1/3). Some feel that a relationship exists between sex chromatin and prognosis in breast cancer, feeling that chromatin-negative cancers present a bad survival risk with greater likelihood of lymph node involvement. More attention has been given to the difference in response to hormone therapy between chromatin-positive and chromatin-negative carcinomas. The chromatin-negative types have been shown to be more responsive to estrogens, while chromatin-positive tumors are better treated with oophorectomy or androgens.[16]

Bloom attempted to answer some of the remaining questions already in 1950.[17] By combining the factors of age and tumor grade, he found that no significant differences in outcome were revealed in the various age groups. He also suggested that it was useless to try to assess the effect of delay in treatment without reference to the histological type of the growth involved. He did not find that the site of the tumor in the breast exerted any striking effect on prognosis. Bloom found that the size of the primary tumor growth was of prognostic importance only in the case of intermediate grades of tumors. Bloom's work cannot necessarily be accepted as the final answer to these questions, but it is important to note his method of investigation.

The effect of various factors, as well as of various types of treatment cannot be accurately assessed without taking into account the inherent malignancy of the tumor. To date it has been shown that the best method for assessing this quality is by histological evaluation of the primary tumor growth with special attention being given to the nuclear structure of the malignant cells. By use of this concept we may, in the future, be able to judge more realistically the effects of the many methods now being proposed for the treatment of breast cancer.

The purpose of this study was to compare Black and Speer's method[8] of nuclear grading with Bloom and Richardson's multi-factorial method[5] for the grading of breast cancer, and to establish their value in the prognosis of breast cancer.

The material used consisted of initial operative specimens or biopsy specimens from 192 patients with breast cancer, treated between 1955 and 1962. One hundred of the cases were selected from the Tumor Registry at the University of Nebraska College of Medicine, on the basis of having a five year follow-up. Slides for these cases were obtained from the Department of Pathology of the University Hospital. The remaining 92 cases were those seen and treated by Charles W. McLaughlin, Jr., MD, at the Nebraska Methodist Hospital during the same time period. Follow-up data for the latter group were obtained from the office files of Dr. McLaughlin, while the tissue sections were obtained from the Department of Pathology at the Nebraska Methodist Hospital. All available H & E stained slides from all of these cases were scrutinized in order to pick one or two slides representative of the malignancy of each particular tumor. In case of a true variation in the malignancy pattern of a tumor, the slides showing the most unfavorable degree of malignancy were used for grading. Available slides of lymph node

metastases were also considered in selecting representative sections to be used for grading. No frozen sections were used for grading. Slides from ten of the University patients were excluded from the study, because the specimen was too small to grade, or no carcinoma could be found in the available sections.

Sections from each case were first graded in regard to nuclear anaplasia, using a scale graded from 1 to 3. Nuclei showing pleomorphism, that is, non-uniformity in size and shape, clumping of chromatin, prominent nucleoli, and numerous mitoses, were given a grade of 1, which refers to the most malignant, or unfavorable end of the scale. Nuclei showing a high degree of similarity, a homogeneous appearance of delicate chromatin strands, absence of nucleoli, or absent mitoses were graded as 3, or least malignant, falling at the favorable end of the scale. Nuclei showing intermediate degrees of change were assigned Grade 2.

The sections were also graded according to the three histological factors suggested by Bloom:

(1) Tubule formation. Sections showing well-marked tubular-acinar arrangement around a central lumen were awarded one point. A moderate attempt at tubule formation warranted two points, and a slight, or absent attempt at

differentiation warranted three points.

(2) Pleomorphism. By this method nuclei showing irregularity in size and shape, clumping of chromatin, and prominence of nucleoli were awarded three points. One point was given if the nuclei were uniform in size and shape, without clumped chromatin or prominent nucleoli. A moderate degree of change warranted two points.

(3) Hyperchromatic and mitotic nuclei. This assessment was made somewhat subjectively, with sections showing more than two to three such figures per high power field being awarded three points. Those with two or three such figures per high power field were given two points, and those sections showing less than two mitotic or hyperchromatic figures per field were awarded only one point.

In use of Bloom's multi-factorial system, the points allocated to each of the three histological factors were added together, giving a total of three to nine possible points. Here the smallest number represents the most favorable degree of malignancy. Cases receiving a total of three, four or five points were placed in Grade 1, indicating the most favorable grade of malignancy. Those receiving six or seven points were placed in Grade 2, indicating an intermediate grade of malignancy, and those with eight or nine points were placed in Grade 3, the most unfavorable grade of malignancy.

Only after such grading was completed, were clinical and follow-up data consulted and analyzed. It was found that 152 of the cases had been followed either to death or a minimum of five years. The tables below show the relationship between the malignancy grades and the five year survivals of these patients. It is obvious from these tables that by either method of grading there exists a linear relationship between the percentage of cases surviving five years and the degree of malignancy indicated by the histological grade. For the nuclear grading method this difference is statistically significant at the 5% level by the Chi square test.

Table 2.--Relationship of Nuclear Grade to 5-Yr. Survival.

Grade of Malignancy:	Favorable	Intermediate	Unfavorable	Total
Number of Cases:	33	79	40	152
5-Yr. Survivors:	27	47	16	90
5-Yr. Survivors %:	82	60	40	59

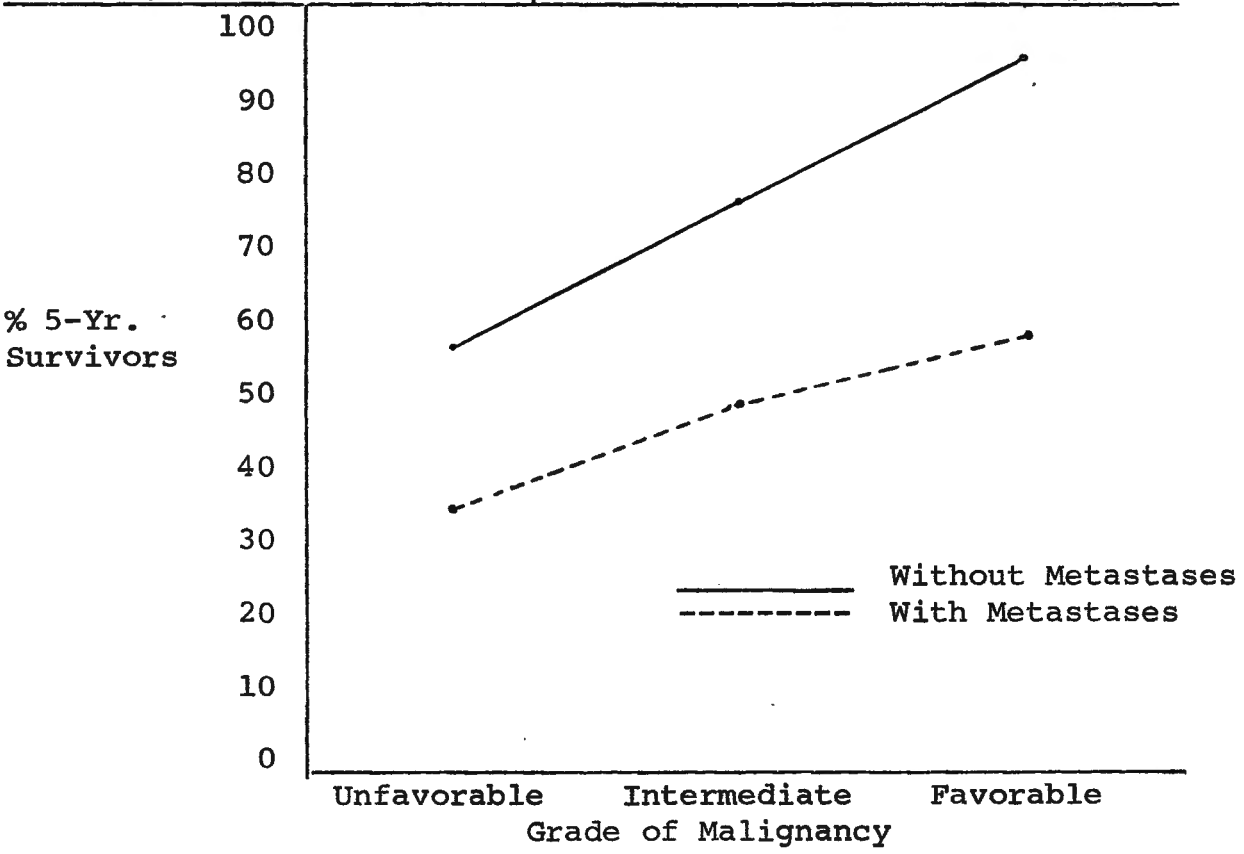
Table 3.--Relationship of Multi-factor Grade to Survival.

Grade of Malignancy:	Favorable	Intermediate	Unfavorable	Total
Number of Cases:	35	71	46	152
5-Yr. Survivors:	27	43	20	90
5-Yr. Survivors %:	77	61	43	59

Information concerning the status of axillary lymph nodes was available for 149 of the cases. Of this portion, 62% (92 cases) were found to have metastatic disease present in the lymph nodes. Table 4 shows the comparison of five

year survival rates when both nuclear grade and axillary metastases are taken into account.

Table 4.--Gland Involvement, Nuclear Grade and Survival.



It is apparent that a more accurate indication of the possible outcome in breast cancer can be derived when the nuclear grade of a tumor is considered together with its extent as determined by the presence or absence of lymph node metastases. ...

In conclusion, it would appear that the degree of malignancy in carcinoma of the breast can be evaluated by studying the nuclear anaplasia of the primary tumor. The practical usefulness of such a study lies in the prognostic

value of the results. In this study, routine pathological sections of tumors showing a high degree of nuclear anaplasia indicated a notably poorer five year survival than for those patients whose tumors showed only a slight degree of nuclear anaplasia. Though clinical staging alone may be of definite value in prognosis, a system of histological grading produces more comparable groups.

Treatment can be accurately assessed only by evaluating its effect on strictly comparable groups. Thus such a system of grouping may eventually help to evaluate the different lines of approach now available for the treatment of breast cancer.

One advantage of this particular system of grading is its simplicity in application. Routine preparations may be used; the criteria are straightforward; the procedure is not time-consuming. It should be emphasized that this system is useful only as a guide to prognosis; one should not expect any degree of mathematical accuracy in predicting outcomes. The most significant differences are seen when the grading system is combined with a consideration of the presence or absence of axillary metastases.

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