Copyright Warning & Restrictions

The copyright law of the United States (Title 17, United States Code) governs the making of photocopies or other reproductions of copyrighted material.

Under certain conditions specified in the law, libraries and archives are authorized to furnish a photocopy or other reproduction. One of these specified conditions is that the photocopy or reproduction is not to be "used for any purpose other than private study, scholarship, or research." If a, user makes a request for, or later uses, a photocopy or reproduction for purposes in excess of "fair use" that user may be liable for copyright infringement,

This institution reserves the right to refuse to accept a copying order if, in its judgment, fulfillment of the order would involve violation of copyright law.

Please Note: The author retains the copyright while the New Jersey Institute of Technology reserves the right to distribute this thesis or dissertation

Printing note: If you do not wish to print this page, then select "Pages from: first page # to: last page #" on the print dialog screen

ABSTRACT

Patient, Disease and Surgical Parameters in the Prediction of Histologic Nodes and Recurrence of Squamous Cell Carcinoma

by
Adolfo A. Ferreira

This research explores the impact of a variety patient, disease and lesion parameters upon the probability of post surgery recurrence of squamous cell carcinoma and the involvement of histologic nodes. It was found that parameters such as number of nodes, Lymph Vascular Space Invasion (LVS), figo stage, growth rate and host response as well as tumor thickness, depth of invasion and lesion size are good predictors. Other parameters such as cell type and condylomas were found to correlate minimally with recurrence and histologic nodes. Surgical parameters such as surgical margin and distance surgical margin were found to have poor correlation with either recurrence or histologic node involvement.

In addition, a statistical model was developed to predict the likelihood of disease recurrence and histological node involvement based on the parameters found significant in this study.

PATIENT, DISEASE AND SURGICAL PARAMETERS IN THE PREDICTION OF HISTOLOGIC NODES AND RECURRENCE OF SQUAMOUS CELL CARCINOMA

by
Adolfo A. Ferreira

A Thesis
Submitted to the Faculty of
New Jersey Institute of Technology
in Partial Fulfillment of the Requirements for the Degree of
Master of Science in Biomedical Engineering

Biomedical Engineering Committee

January 1994

APPROVAL PAGE

Patient, Disease and Surgical Parameters in the Prediction of Histologic Nodes and Recurrence of Squamous Cell Carcinoma

Adolfo A. Ferreira

Dr. Rose Ann Dios, Thesis Advisor — Date
Associate Professor of Mathematics
Director of Undergraduate Studies

Dr. David S. Kristol, Committee Member — Date
Professor of Chemistry
Director of the Center for Biomedical Engineering
Graduate Advisor of Biomedical Engineering

Dr. Peter Engler, Committee Member — Date
Associate Professor of Electrical Engineering

BIOGRAPHICAL SKETCH

Author: Adolfo A. Ferreira

Degree: Master of Science in Biomedical Engineering

Date: January 1994

Undergraduate and Graduate Education:

- Master of Science, Biomedical Engineering,
  New Jersey Institute Of Technology, Newark, NJ, 1994

- Bachelor of Science in Mechanical Engineering,
  New Jersey Institute Of Technology, Newark, NJ, 1986

Professional Background:

The author is a Process Engineer with experience in the development of medical devices and associated manufacturing processes.

U. S. Patents:

Patent Number 5,079,780
Chinstrap Activated Head Adjustment Assembly for a Protective Helmet Assembly

ACKNOWLEDGMENT

The author wishes to express his sincere appreciation to Professor Rose Dios for her kind guidance, friendship, enthusiasm and overall support in the course of this endeavor.

Special gratitude to Professors David Kristol and Peter Engler for serving as members of the committee and to John Comerci, MD, for supplying the necessary data.

The author appreciates the help and suggestions from the many friends who offered suggestions and guidance.

Finally, to my wife and son: For their understanding and continued love and support.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER 1

INTRODUCTION

Squamous cell Carcinoma is a tumor or cancer of the skin. Squamous cells are the flat, scalelike epithelial cells that act as coverage to the body and line the walls of the hollow structures within the body, resting above a homogeneous noncellular basement membrane. The tumor is the result of the keratinization or hardening of the epidermal cells. Keratins are a fibrous protein that forms horny tissues, such as fingernails, and that can also be found in the skin and hair. Keratins are a type of the intermediate filament proteins of 70 to 100 Å in diameter that contribute to the mechanical stability of the sheets of epithelial cells. Thus, keratinization may be defined as the development of a horny growth or nodule in the epidermal tissue. The growth of the horny nodule is usually slow. However, if left untreated it can ulcerate and invade underlying tissues. Metastasis to the regional lymph nodes can also occur.

Exposure to the sun's ultraviolet rays, presence of premalignant lesions such as actinic keratosis, chronic skin irritation, exposure to carcinogens and some hereditary diseases are believed to be involved with development of squamous cell carcinoma. A carcinoma is any cancer that arises in the epithelium and probably metastasize via the lymphatic system. Carcinomas

develop mostly on the sun exposed areas of the body such as face, ears, neck and back of the hands. However, they can be found in other areas of the body. In women, they are often found in the vulva.

Surgery is often the recourse for treatment of squamous cell carcinoma. When recommending surgery, the physician needs to evaluate the likelihood of success: elimination of the carcinoma with no tumor recurrence. By understanding the influence of key parameters that may help predict the outcome of the surgery a better decision for the course of treatment can be made. In a study involving patients who had histologic positive nodes on the neck, 21 % had recurrence after surgery[1]. The same study also indicated that recurrence after a standard dissection was almost invariably fatal. Thus minimizing the likelihood of recurrence is critical for the success of the surgery. The influence of various patient, disease and surgical parameters on the likelihood of recurrence or the metastasis of the nodes involvement is the subject of this study.

---

[1] Gordon B Snow et al, Prognostic Factors in Neck Metastasis; Larson, D.; (eds) *Cancer in the Neck*; Macmillan; NY; 1986

CHAPTER 2

BACKGROUND ON SQUAMOUS CELL CARCINOMA

2.1 What is Squamous Cell Carcinoma?

Squamous cell carcinoma is a cancer of the epithelial tissues. It results in the formation of a hardened, horny "mole" in the epithelial tissues above the basement membrane. If not treated, these moles may ulcerate and metastasize to other parts of the body.

Tumors may be classified as either malignant or benign. Malignant means that the cancer is capable of spreading onto other areas of the body (metastasize). A benign growth will be localized to the tissue from which it generated. Indicators for the transformation from an harmless mole to a cancerous tumor include changes in the shape or size of the mole. The rate of change in itself is also an indicator. If the rate is slow, it is unlikely that the tumor is malignant. Changes involving malignant growths are fast and may occur within a period of months. Thus, one should always pay attention to changing moles.

2.2 Metastases of the Tumors

The danger of any cancer resides principally on it's capability to spread or metastasize. Metastasis is the spread of malignant tumors away from their site of origin. For some reason, the tumor does not trigger an effective rejection response by the host. Otherwise, the early mass of the tumor would be destroyed. The exact reasons for the body not to initiate an effective response are unknown.

The main routes for the spread of the tumor are (1) through the blood stream, (2) through the lymphatic system and (3) across body cavities. Tumors may spread through one or more of these routes. Subcutaneous and intracutaneous metastases may either be transported by the blood or the lymph. If the new deposit is far away from the original tumor and not related to the draining lymph vessels, it is probably blood transported. If the metastasis is in an area anatomically related to the primary tumor it usually is in a line from the primary tumor to the draining lymph nodes. If the route of spreading is the lymphatic system, chances are that a secondary tumor will be found in the lymph nodes. The lymph nodes act as filters or barriers to the spread of the cancer and may and contain a large concentration of malignant cells. Eventually the barrier may be overcome and the cancer may spread to other parts of the body. Squamous cell carcinoma is believed to spread mainly through the lymphatic system.

3.3 Treatments of Squamous Cell Carcinoma

The best treatment for squamous cell carcinoma, or for any other cancer, starts with early detection. Treatment success usually depends on the anatomical localization of the tumor and degree of metastasis. The general population, as well as family physicians, should be aware that a new or a changing mole may possibly be malignant. As with most cancers, early detection and treatment increases the probability of cure and long therm survival. Common treatments for squamous cell carcinoma may be divided onto non-surgical and surgical or both. The choice of treatment depends on various factors including the location of the primary tumor, status of the lymph nodes and level of metastasis.

Some of the conventional non-surgical treatments that may be used include:

Immunotherapy:

Some approaches have involved using antigens isolated from cell membranes. To date these treatments have been largely unsuccessful. Hope resides in the biotechnology field for more effective ways of bolstering the immune system to respond to the spreading of the carcinoma.

Chemotherapy:

Some success has been achieved on shrinking and partially destroying the carcinoma by cancer chemotherapy (1) using a wide range of drugs. A combination of chemotherapy and immunotherapy may offer some hope. However, the successes of chemotherapy can be considered meager on complete eradication of squamous cell carcinoma.

Radiotherapy:

Radiotherapy has been widely used both by itself and in conjunction with surgery. Radiotherapy has been shown to be most efficient in the early stages of squamous cell carcinoma. Radiotherapy has been also used with patients that had tumor recurrence after surgery and in conjunction with surgery to attempt to minimize the risk of recurrence.

All the above therapies have had limited success. Thus, surgical removal of the tumor is the most likely to succeed in eliminating the carcinoma. The surgeons involved with surgical removal of malignant carcinomas are a special breed. They must be familiar with a large number of anatomical areas, make decisions about the metastic potential of the carcinoma and decide the extent of the surgery. Finally, the surgeon must be familiar with reconstruction techniques in order to maximize function restoration while minimizing the cosmetic impact.

After deciding to proceed with the surgery, decisions have to be made as to how widely and deeply to excise the cancer, future follow up procedures and possibility of recurrence. The next chapters deal with estimating the likelihood of success given a series of surgical, anatomical and patient attributes.

CHAPTER 3

PARAMETER SIGNIFICANCE

A total of 117 patients were involved on this study. Due to missing data or other problems, the total number of patients used for the statistical evaluation was reduced to 93. From these, three groups were formed based on the medical treatment history of the patients. Groups 1 included patients which had recurrence, group 2 included patients with node involvement and group 3 included patients with both recurrence and node involvement. Patients in group one or three were used to estimate recurrence while patients in group two or three were use for estimation of the involvement of histologic nodes. For each patient, a series of patient attributes and surgical parameters were determined and the various levels within each parameter tabulated. Appendix two details parameter information. Statistical significance of the levels of the various parameters was assessed level by means of a one-way analysis of variance, least significant difference method.

The analysis of variance is based on the assumption that the basic density function of the data is normal and that errors are normally and independently distributed with mean zero and variance σ^2. However, even in instances were data depart from normality, the analysis of variance can provide a good indication of significance.

The basic mathematics of the analysis of variance are based on a measure of the total variability of the data as a sum of its terms and also that a specific source of variation can be attributed to each term. With reference to this analysis, the two main sources of variation may be due to (1) actual differences in the probability for recurrence or histologic node involvement and (2) experimental error. If x_i bar denotes the mean of the i^{th} sample and x^{ij} denotes the j^{th} observation of the i^{th} sample and SST is the total sum of squares, then the following equation is the basis for the analysis of variance. Where the first

$$SST=n\sum_{i=1}^{k}(xbar_i-Xbar)+\sum_{i=1}^{k}\sum_{j=1}^{k}(x_{ij}-xbar_i)^2$$

term represents the variation among the sample (levels) means while the second term represents variation within the individual samples or levels. They are commonly known as the *treatment sum of squares SS(Tr)* and the *error sum of squares (SSE)* respectively. The second term is also known as *experimental error.*

To assess statistical significance, the analysis of variance uses the F test to determine that the null hypothesis that the samples with means μ_1, μ_2, μ_3,...μ_n are all from the same population. The F ratio can also be called the variance ratio and in the case of the analysis of variance it can be simply expressed as

$$F=\frac{\text{Estimate of } \sigma^2 \text{ based on the variation among the X bars}}{\text{Estimate of } \sigma^2 \text{ based on the variation among the samples.}}$$

When the null hypothesis holds (samples are from the same population), the F ratio should be approximately one and the ratio increases (significance level goes down) as the populations differ.

The analysis of variance is usually reserved for experiments involving more than two samples. However, for simplicity, the analysis of variance was also used for parameters with only two classes. As demonstrated by Snedecor, the F test can be shown equivalent to the t test which is usually used to compare the means of two independent samples. By applying the same test to each parameter, significance was easily ranked.

A cursory inspection of the data clearly shows that it does not follow a normal density function, a basic assumption of the analysis of variance. To confirm the results of the analysis of variance a Kruskal-Wallis rank sums test was also performed on the non-parametric data. Kruskal-Wallis provides a non-parametric alternative for the one-way analysis of variance. These methods are also called distribution free methods since they do not require normality or even knowledge of data distribution. For the test, the data are ranked (rank transformation) and a Chi square is performed on the sum of the ranks assigned to the observations in the samples. That is, the Kruskal-Wallis method tests the null hypothesis that the treatments are the same against the alternative hypothesis that some of the treatments generate larger observations. The test is based on the statistic

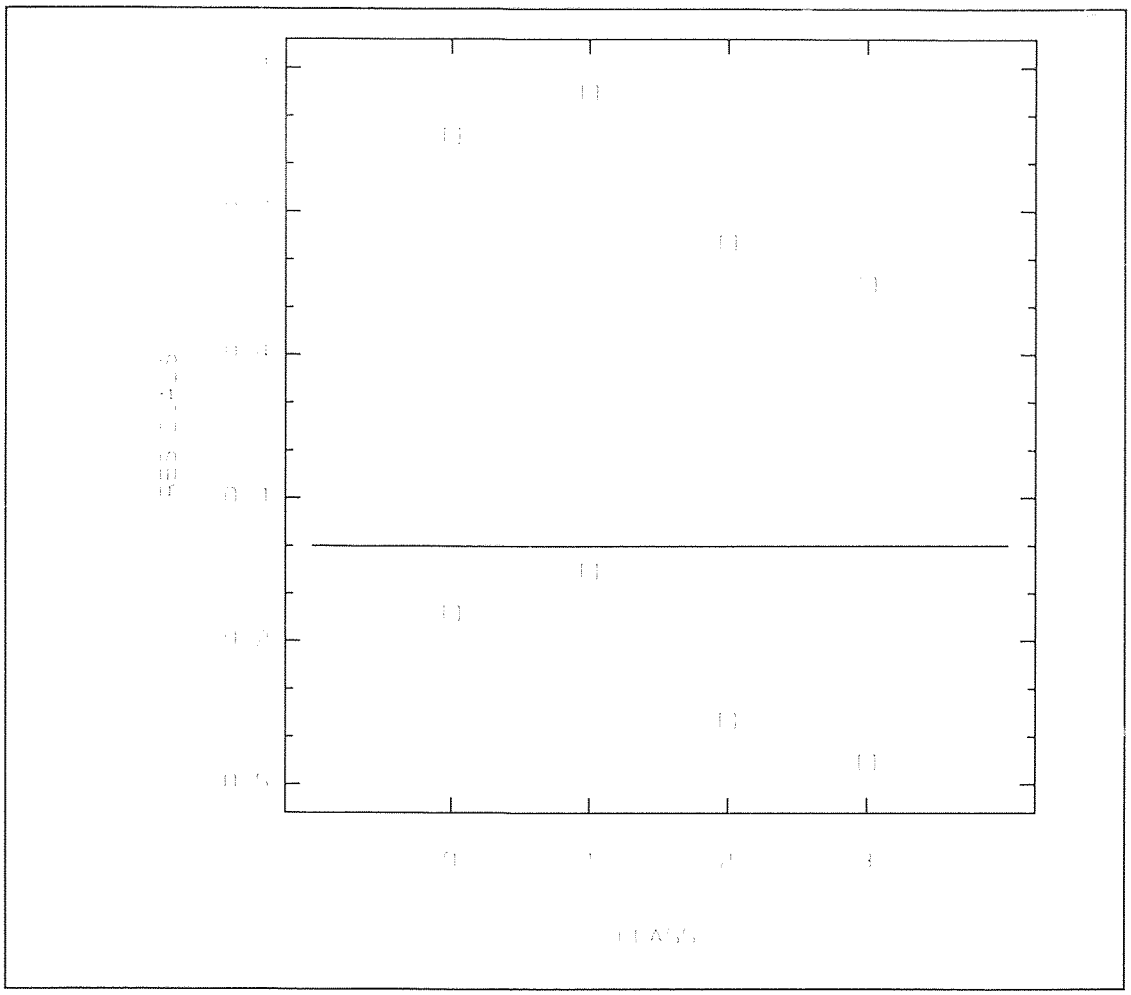

Figure 1 Typical plot of residuals by class

$$H=\frac{12}{n(n+1)}\sum_{i=1}^{k}\frac{R_i^2}{n_i}-3(n+1)$$

If the null hypothesis holds true then the sampling distribution can be approximated with a chi-square distribution with k - 1 degrees of freedom.

Whenever the analysis of variance and the Kruskal-Wallis test yield similar results, the analysis of variance assumptions are reasonably satisfied and the results should hold. In addition to the comparison with non-parametric methods, an analysis of the residuals was also performed on the analysis of

variance. The residuals can provide some indication of patterns on the data. Typical residual plots are shown in Figures 1 and 2.

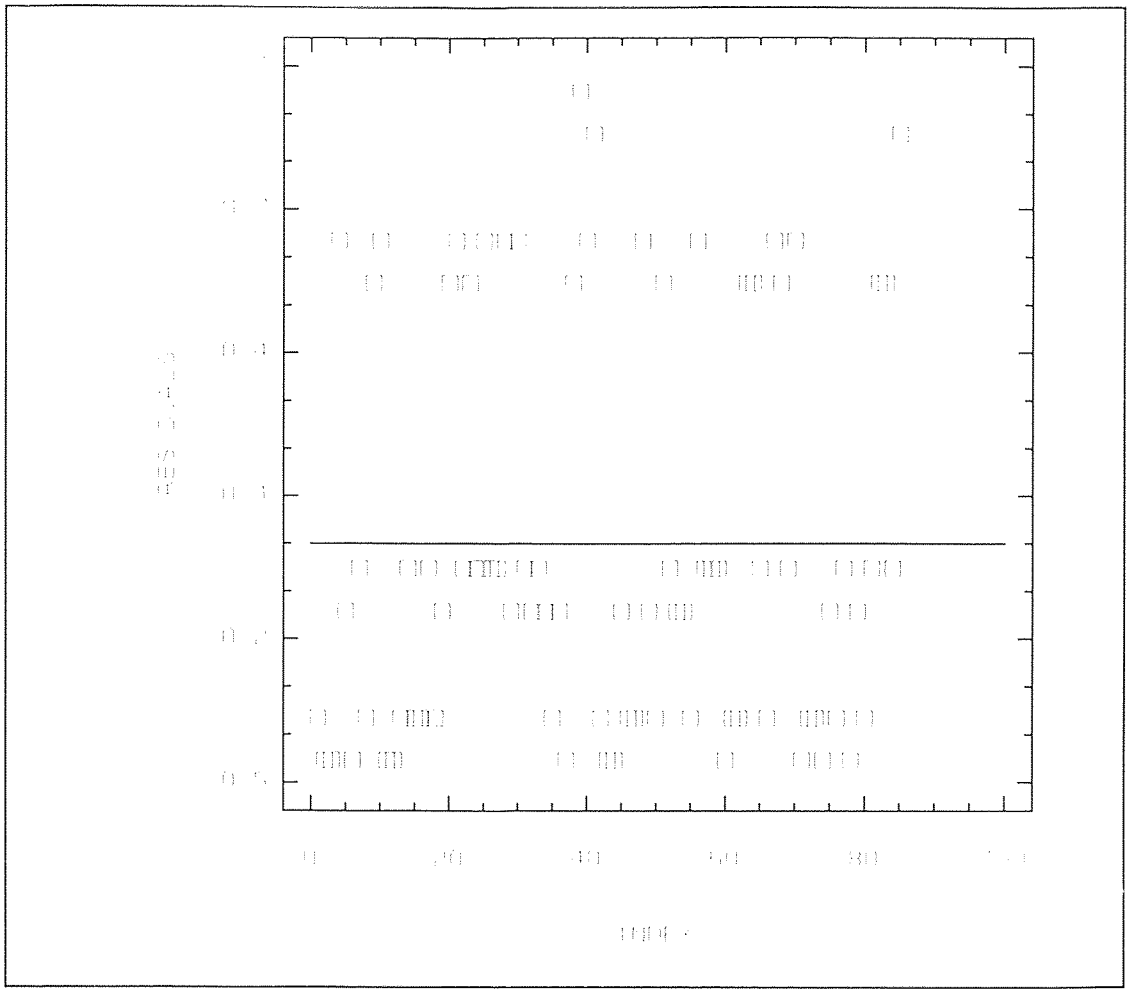

Figure 2 Typical residuals by index

Table 1 shows the decreasing order of significance for predicting the recurrence of squamous cell carcinoma. Both the results of the analysis of variance and the Kruskal-Wallis test are presented. Very good correlation between the two methods is demonstrated. It should be noted that the lower the significance the higher the probability that the factor levels have a relationship with the outcome (such as recurrence).

TABLE 1 Significance of Parameters on Recurrence (Groups 1 or 3, by decreasing significance)

Parameter	ANOVA	Kruskal-Wallis
Figo stage	0.000	0.000
LVS	0.009	0.009
Host Response	0.012	0.014
Lesion Site	0.013	0.015
Histologic nodes	0.030	0.031
Mitosis	0.076	0.077
Number of Nodes	0.128	0.134
Growth	0.139	0.138
Dysplasia	0.175	0.174
CIS	0.206	0.204
Group	0.209	0.207
Grade	0.348	0.344
Surgical Margin	0.502	0.492
Keratin	0.576	0.570
Distance Surgical Margin	0.788	0.783
Cell Type	0.823	0.819
Dystrophy	0.843	0.839
Condylomas	0.976	0.976

Figo stage, lymph vascular space invasion (LVS), host response, lesion site histologic nodes were found to be the best predictors of recurrence while condylomas, dystrophy and cell type were found to have minimal correlation. Gordon (7) found that the most important factor regarding recurrence of

squamous cancer was histologic nodal involvement followed by the number of nodes involved. While this is in general agreement with our findings, Meyers found no significance regarding the number of nodes involved and the probability of recurrence. Table 2 shows the significance of the same parameters for the presence of histologic nodes. Parameters such as LVS, figo stage, growth and group were found to be good predictors.

TABLE 2 Significance of Parameters on Histologic nodes (Groups 2 or 3, by decreasing significance)

Parameter	**ANOVA**	**Kruskal-Wallis**
Figo stage	0.000	0.000
LVS	0.000	0.000
Growth	0.000	0.001
Group	0.003	0.003
Host Response	0.017	0.019
Dystrophy	0.158	0.157
Lesion Site	0.233	0.231
CIS	0.261	0.258
Keratin	0.273	0.269
Distance Surgical Margin	0.500	0.494
Mitosis	0.532	0.526
Surgical Margin	0.661	0.653
Dysplasia	0.688	0.681
Grade	0.875	0.872
Condyloma	0.877	0.873
Cell Type	0.931	0.929

It should be noted that number of nodes, LVS, figo stage, growth and host response are good predictors for both histologic nodes and recurrence.

There are some parameters, that although not statistically significant, warrant further investigation. In some cases, the number of patients within a certain level of a particular parameter was small as compared to the other level(s). A typical example is surgical margin and histologic node involvement, with input values of 0 (some surgical margin) and 1 (no surgical margin) having a frequency of 75 and 4 respectively. Thus, the confidence interval for a response of 1 is very large and the estimated probabilities are difficult to pinpoint. However, a closer look (see Tables 3 and 4) at the expected values for the group shows a 30% difference in probabilities for histologic nodes and a 78% difference for recurrence.

Other parameters exhibited similar patterns. Tables 3 and 4 show the parameters with similar occurrences. It is possible that significant correlations would emerge if a larger data base of patients with diverse responses were available. It is worth noting that surgical margin is present in both tables. Thus, it appears to be an important factor for estimation of the likelihood of recurrence and/or histologic nodes.

To increase the data base for estimating recurrence, all groups were combined and significance reassessed. Table 5 shows the level of significance for the various parameters for all groups along the results for groups 1 or 3.

TABLE 3 Parameters Found Non-Significant With Large Differences in Probabilities For Histologic Nodes

Parameter	Group	Count	P
Surgical Margin	0	75	0.38
	1	4	0.50
Dist. Margin	0	51	0.35
	1	11	0.55
	2	17	0.41

TABLE 4 Parameters Found Non-Significant With Large Differences in Probabilities For Recurrence

Parameter	Group	Count	P
Surgical Margin	0	83	0.28
	1	2	0.50
Grade	0	14	0.14
	1	44	0.34
	2	27	0.25
Growth	0	28	0.14
	1	23	0.35
	2	34	0.34
Dysplasia	0	28	0.32
	1	19	0.16

The increased data base showed significance for surgical margin and Dysplasia. Significance for growth may be considered marginal while significance for grade was not demonstrated.

TABLE 5 Significance of Parameters on Recurrence

Parameter	Groups 1 or 3	All Data
Figo stage	0.000	0.000
LVS	0.009	0.001
Host Response	0.012	0.013
Lesion Site	0.013	0.002
Histologic nodes	0.030	0.015
Mitosis	0.076	0.215
Number of Nodes	0.128	0.176
Growth	0.139	0.221
Dysplasia	0.175	0.058
CIS	0.206	0.141
Group	0.209	0.064
Grade	0.348	0.445
Surgical Margin	0.502	0.054
Keratin	0.576	0.651
Distance Surgical Margin	0.788	0.948
Cell Type	0.823	0.728
Dystrophy	0.843	0.393
Condylomas	0.976	0.560

Parametric parameters, such as lesion size, depth of invasion and tumor thickness were also tabulated. Due to the large range in values, class sizes were deemed too small for an analysis of variance. To assess the influence of these parameters a regression analysis was performed.

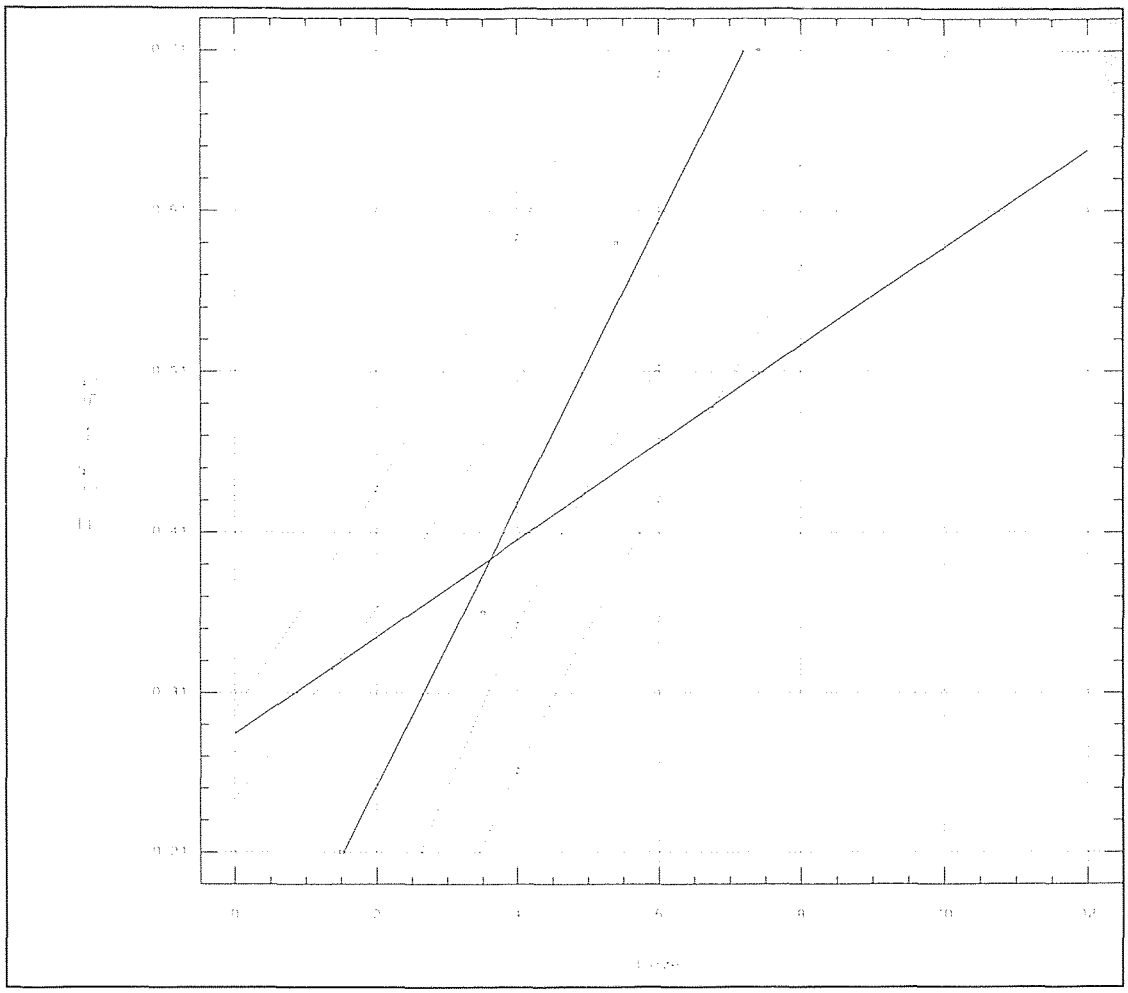

Figure 3 Regression of lesion size on histologic nodes (Steeper slop had one outlier removed)

The correlation coefficients were calculated after placing the data into tabular form with a class size of 2 mm. For tumor thickness and depth of invasion all data above 12 mm were classified into one class. The average thickness for each interval was calculated as well as the corresponding expected probability of recurrence or histologic nodes. The results for each parameter were then regressed with either recurrence or histologic nodes. Again, groups one and three were regressed with the probability of Recurrence while groups two and three were regressed with histologic nodes. A typical result is shown

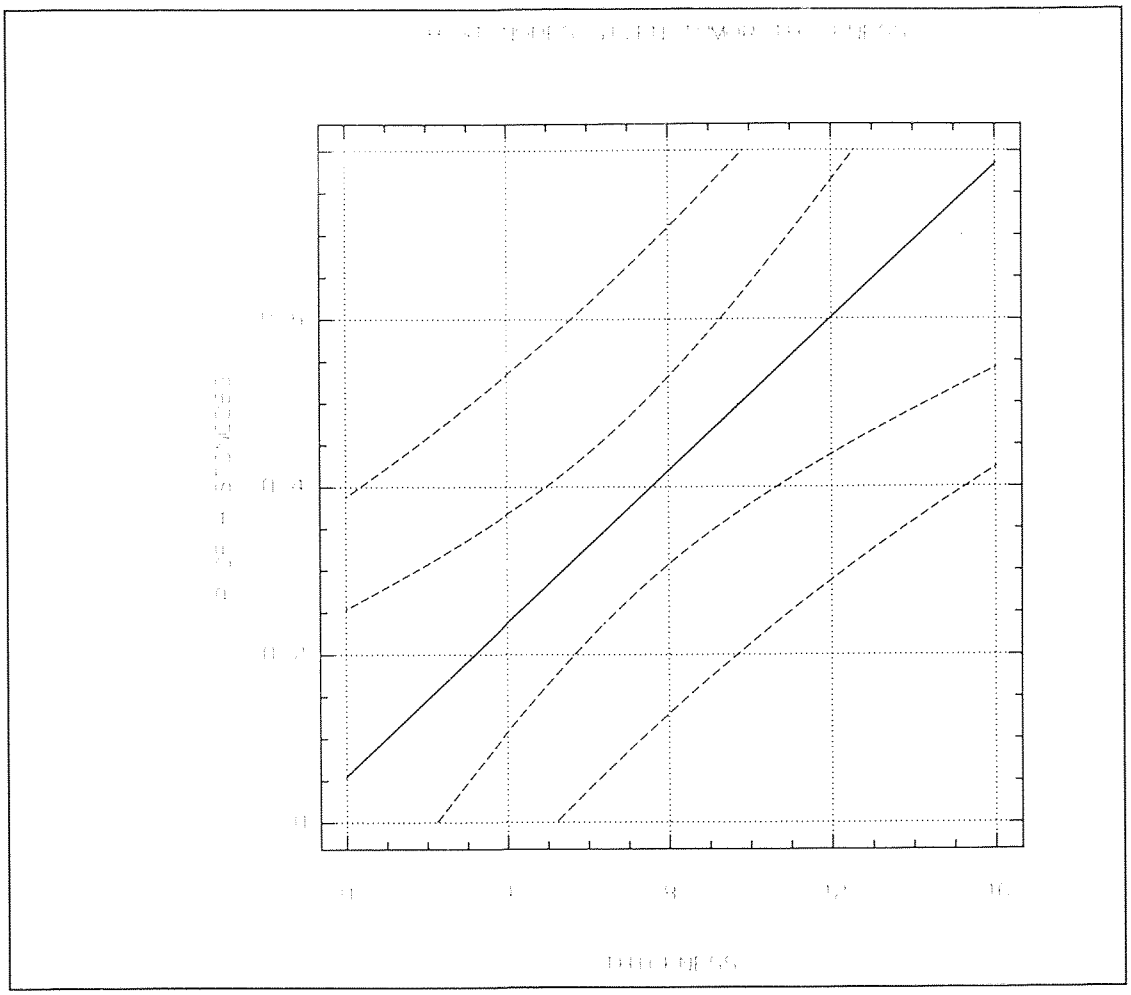

Figure 4 Regression of lesion depth on histologic nodes

in Figure 3. The graph shows the regression line using all groups along with a regression line where an outlier subgroup has been removed from the analysis. The other groups had no evidence of outliers. A typical example is shown in figure 4.

Due to the separation of the data onto classes of equal increments, the outlier had only four data points. Consequently, the confidence interval for probability estimation was very large. Table 6 shows the correlation coefficients and slopes for depth of invasion, tumor thickness and lesion site for

recurrence and histologic nodes. The correlation coefficients are relatively high for this data, and the slopes are significantly different from zero, indicating a strong relationship between these parameters and the probability of recurrence and histologic nodes.

TABLE 6 Correlation Coefficients for Parametric Data

Parameter	Recurrence		Histologic Nodes	
	Corr. Coef.	Slope	Corr. Coef.	Slope
Tumor Thick. (mm)	0.85	0.030	0.94	0.046
Depth of inv. (mm)	0.86	0.050	0.90	0.051
Lesion Size (mm)	0.86	0.052	0.52*	0.030
			0.99	0.088

* With outlier subgroup

In conclusion, some patient attributes and surgical parameters were found to be strong indicators in assessing the likelihood of recurrence of squamous cell carcinoma and on the involvement of histologic nodes. In particular, parameters such as number of nodes, LVS, figo stage, growth, host response, tumor thickness, lesion site and size and depth of invasion were found to correlate well with both recurrence and histologic node involvement.

CHAPTER IV

ESTIMATION OF PROBABILITY RANGES

The probability of recurrence and the involvement of histologic nodes for each class within a given parameter was estimated. The probability p of recurrence or involvement of histologic nodes was estimated by dividing the number of occurrences by the number of patients. The 95% confidence interval for p was also estimated. To calculate the interval, an approximation to the normal distribution was used. The standard deviation of the mean of a binomial distribution is given by

$$\sigma_p = \sqrt{\frac{pq}{n}}$$

Where p is the probability of recurrence and q is the probability of non-recurrence or $1-p$.

Thus, the 95% confidence interval (estimated range for the probability) for p is approximated by $p \pm 2\sigma$.

The range in overall probabilities for recurrence and histologic node involvement are given in Table 7.

TABLE 7 Overall Probabilities

Group (n)	p		95% interval	
	Recurrence	Hist. nodes	Recurrence	Hist. nodes
All (93)	0.31	0.76	0.21 - 0.41	0.67 - 0.85
1 & 3 (85)	0.28	0.75	0.18 - 0.38	0.65 - 0.85
2 & 3 (79)		0.39		0.29 - 0.49

Tables 8 through 10 show the confidence intervals for the various parameters. Whenever the low limit of the interval fell below zero, it was rounded to zero. The upper limit was rounded to one.

It can be seen that, in many cases, the ranges of probability of recurrence or histologic node involvement are quite large and some levels overlap. While this indicates that the parameter levels may not be a significant factor, it can provide a basis for further study. For example, increasing the number of patients will reduce the size of the range and provide for better estimates.

TABLE 8 Confidence Intervals for p of Recurrence (Groups 1 or 3)

Parameter	Class				
	0	1	2	3	4
Figo stage		0.00 - 0.16	0.11 - 0.42	0.35 - 0.81	1.00
LVS	0.10 - 0.30	0.26 - 0.68			
Host response	0.00 - 0.26	0.04 - 0.30	0.28 - 0.60		
Lesion site	0.00 - 0.33	0.00 - 0.15	0.19 - 0.55	0.24 - 0.66	
Hist. nodes	0.09 - 0.33	0.28 - 0.68	0.00 - 0.35		
Mitosis	0.16 - 0.62	0.20 - 0.62	0.07 - 0.29		
# of nodes	0.09 - 0.33	0.01 - 0.59	0.19 - 1.00	0.00 - 1.00	
Growth	0.01 - 0.27	0.15 - 0.55	0.19 - 0.51		
Dysplasia	0.21 - 0.43	0.00 - 0.33			
CIS	0.20 - 0.46	0.07 - 0.35			
Group		0.00 - 0.33	0.20 - 0.42		
Grade	0.00 - 0.33	0.20 - 0.48	0.09 - 0.43		
Surgical margin	0.18 - 0.38	0.00 - 1.00			
Keratin	0.08 - 0.54	0.17 - 0.49	0.08 - 0.36		
Dist. Margin	0.18 - 0.42	0.05 - 0.45	0.06 - 0.46		
Cell type	0.18 - 0.40	0.05 - 0.45	0.21 - 0.87		
Dystrophy	0.15 - 0.43	0.14 - 0.40			
Condylomas					

* For number of nodes, classes above classification 3 were combine onto one class

TABLE 9 Confidence Intervals for p of Histologic Nodes (Groups 2 or 3)

Parameter	Class				
	0	1	2	3	
Figo stage		0.01 - 0.31	0.14 - 0.48	0.51- 0.89	1.00
LVS	0.12 - 0.36	0.57 - 0.93			
Growth	0.01 - 0.29	0.51 - 0.89	0.19 - 0.55		
Group			0.61 1.00	0.23 - 0.45	
Host Resp.	0.00 - 0.45	0.09 - 0.41	0.39 - 0.71		
Dystrophy	0.31 - 0.61	0.17 - 0.47			
Lesion site	0.00 - 0.54	0.03 - 0.47	0.19 - 0.57	0.34 - 0.74	0.0 - 1.0
CIS	0.30 - 0.58	0.14 - 0.48			
Keratin	0.18 - 0.74	0.29 - 0.67	0.15 - 0.45		
Dist. margin	0.22 - 0.48	0.25 - 0.85	0.17 - 0.65		
Mitosis	0.10 - 0.62	0.10 - 0.50	0.29 - 0.59		
Surgical margin	0.28 - 0.50	0.00 - 1.00			
Dysplasia	0.26 - 0.50	0.19 - 0.69			
Grade					
Condylomas	0.28 - 0.52	0.14 - 0.62			
Cell type	0.28 - 0.52	0.00 - 0.71	0.00 - 0.87		

TABLE 10 Confidence Intervals for p of Recurrence (All data)

Parameter	Class				
	0	1	2	3	4
Figo stage		0.00 - 0.16	0.16 - 0.46	0.36 - 0.76	1.00
LVS	0.10 - 0.30	0.37 - 0.73			
Host resp.					
Lesion site	0.00 - 0.33	0.00 - 0.15	0.19 - 0.55	0.33 - 0.71	
Hist. nodes	0.11 - 0.35	0.32 - 0.68	0.00 - 0.35		
Mitosis	0.16 - 0.62	0.22 - 0.62	0.12 - 0.40		
# of nodes	0.12 - 0.36	0.00 - 0.54	0.20 - 0.94	0.09 - 0.91	
Growth	0.05 - 0.33	0.20 - 0.58	0.20 - 0.52		
Dysplasia	0.25 - 0.47	0.00 - 0.29			
CIS	0.24 - 0.50	0.08 - 0.36			
Group		0.00 - 0.33	0.29 - 0.97	0.20 - 0.42	
Grade					
Surgical margin	0.19 - 0.39	0.32 - 1.00			
Keratin	0.16 - 0.62	0.16 - 0.48	0.12 - 0.40		
Dist. Margin	0.18 - 0.42	0.06 - 0.60	0.12 - 0.54		
Cell type	0.22 - 0.44	0.00 - 0.45	0.21 - 0.87		
Dystrophy	0.22 - 0.50	0.14 - 0.40			
Condylomas	0.20 - 0.40	0.14 - 0.62			

* For number of nodes, classes above classification 3 were combine onto one class

CHAPTER V

PREDICTION MODEL

The previous chapters evaluated the relationship of various surgical parameters and patient attributes with squamous cell carcinoma recurrence and histologic node involvement. In this chapter, it is attempted to develop a statistical model that can reasonable predict the probability of recurrence or the involvement of histologic nodes. The model uses only the parameters found significant by the analysis of variance methodology. The model is based on the sigmoidal function of the form:

$$P=P(R)=\frac{A}{1+Be^{-\alpha M}}$$

where A, B, and α are patient and disease parameters while M determines the inflection points.

The output of the sigmoidal function follows an S type curve, as shown in figure 5, approaching a minimum and a maximum value asymptotically. The type of data involved in this study should fit the sigmoidal function. For example, the probability of carcinoma recurrence after surgery should be expected to start at some value above 0 and increase to a maximum of 1. The

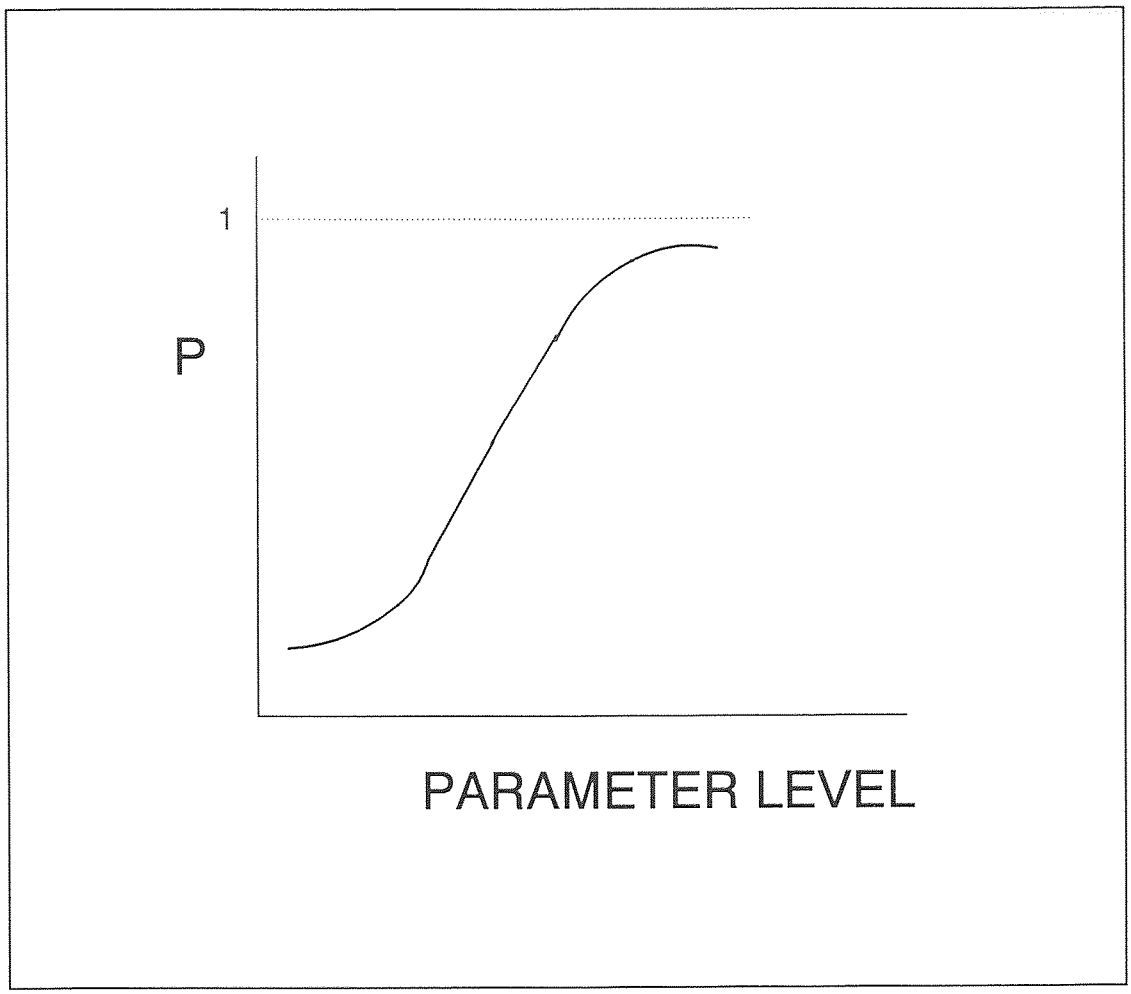

Figure 5 Typical sigmoidal function.

approach to the maximum and minimum should be smooth and is best represented by an asymptotic curve.

In the model presented here, multiple independent variables or parameters are combined onto a single equation of the form outlined by equation 4. For each of the output variables - recurrence or histologic node involvement - one equation was developed for non-parametric and another for parametric data.

The overall model development consists of a series of steps. Development of the equation for predicting recurrence based on non-parametric inputs is detailed here. Similar steps were used to develop the equations for the parametric data and for estimation of histologic node involvement and are shown in the Appendix.

For each input variable found significant by a one way analysis of variance, the probability of recurrence was simply calculated by dividing the patients with recurrence by the number of patients involved. The data for each input variable was fitted onto the model $y = Ae^{Bx}$, where y is the probability of recurrence. Transformation of this equation yields

$$LnY = LnA + b_0 + bx$$

and further

$$Z = C_0 + C_1 X$$

the familiar linear model. Thus, the Ln of the probability p of recurrence at a given level was regressed, by means of a least squares linear regression, with that variable level. Table 11 lists the results of the regressions for the significant parameters.

TABLE 11 Logistic Regression for Parameters Influencing Recurrence

Parameter	**Intercept (C_0)**	**Slope (C_1)**	**Correlation (R)**	**C_1*R**
Figo stage	-3.2	0.83	0.98	0.81
LVS	-1.6	0.85	1	0.85
Host Resp.	-2.2	0.61	0.95	0.58
Rec. Site	-2.3	0.47	0.72	0.34
# of Nodes	-1.5	0.33	0.89	0.29
Growth	-1.8	0.45	0.87	0.39
Surgical Margin	-1.3	0.58	1	0.58
Mitosis	-0.8	-0.39	0.44	-
Hist. Nodes	-1.3	-0.08	0.14	-

The above parameters were then combined onto a single equation of the form

$$P(R) = \frac{A}{1 + B^{-\alpha M}}$$

where A is the maximum probability of recurrence and therefore must be equal to one. B can be calculated if the intercept of the Y axis as the independent variable equals zero is known. The Y intercept can be estimated by calculating the average intercept C_0. For **N** variables the intercept may be approximated by

$$P(R_{X=0}) = e^{\left(\frac{\sum_{C_0=1}^{N} C_0}{N}\right)}$$

In our case $P(R_{X=0}) = 0.14$. Thus, under normal circumstances a patient with minimal involvement with the above parameters may have a 14% chance that

recurrence will occur. **B** is then easily calculated by plugging in the values with α**M = 0, A = 1 and** $P(R_{x=0})$ **= 0.14.**

The values for α**M** are calculated from the values for the slope and correlation coefficient. Parameters with low correlation, such as mitosis and histologic node involvement were not used for the development of the general equation. The slopes for each parameter were weighted by multiplying with the correlation coefficient. Thus, parameters with lower correlations will have less of an influence on the general equation. Further, the correlation coefficient is somewhat related to the inflexion points of the general curve. In addition, since multiple parameters are used on the general equation, the transformation must account for the number of parameters. To that end, α**M** can be calculated as follows

$$\alpha M = \frac{\sum_{C_1=a}^{N} C_{1a} R_a}{N} + \ldots + \frac{\sum_{C_1=a}^{N} C_{1N} R_N}{N}$$

Substitution yields, for recurrence, α**M = 0.21 Figo + 0.22 LVS + 0.15 Host Resp. + 0.09 Rec. Site + 0.08 # Nodes + 0.1 Growth + 0.15 Sur. Margin**. Overall, the results agree with the empirical data.

A similar approach was used for developing the general equations for the probability of recurrence using the parametric parameters as well as for the general equations for histologic involvement. These equations can be found in the Appendix.

CHAPTER V

CONCLUSION

In conclusion, patient parameters such as number of nodes, LVS, figo stage,host response, tumor thickness, depth and size were found to be good predictors of recurrence and/or histologic node involvement. Surgical parameters such as Surgical margin and distance surgical margin were found to have minimum impact.

Further, a statistical model was developed that may be used to estimate the probability of recurrence based the attributes found significant in the course of this research. The model should be particularly useful for aiding the surgeon determining potential parallel treatments to surgery.

APPENDIX ONE

Calculations for the general equations

Recurrence using parametric data - Groups 1 & 3

Parameter	Intercept	Slope	Correlation
Size	-2.2	0.19	0.82
Depth	-2.1	0.15	0.87
Thick	-2.0	0.10	0.79
Σ	-6.3	0.44	
Σ/n	-2.1		

Estimate of intercept = $e^{-2.1}$ = 0.12

From P(C=0) = 0.12 then B = 7.3

and αM = 0.35 Size + 0.30 Depth + 0.18 Thickness

Histologic node involvement using non-parametric data: Groups 2 & 3

Parameter	Intercept	Slope	Correlation
Figo stage	-2.4	0.63	0.99
LVS	-1.4	1.14	1
Growth	-1.5	0.45	0.58
Host Response	-2.1	2.68	1
Σ	-7.4	4.9	
Σ/n	-1.9		

Estimate of intercept = $e^{-1.85}$ = 0.16

From P(C=0) = 0.16 then B = 5.3

and αM = 0.13 Figo + 0.23 LVS + 0.07 Growth + 0.67 Host

Histologic node involvement using parametric data: Groups 2 & 3

Parameter	Intercept	Slope	Correlation
Size	-1.3	0.08	0.72
Depth	-1.9	0.13	0.84
Thick	-3.1	0.23	0.60
$\sum$	-6.3	0.44	
$\sum/n$	-2.1		

Estimate of intercept = $e^{-2.1}$ = 0.12

From P(C=0) = 0.12 then B=7.3

and αM = 0.13 Size + 0.25 Depth + 0.31 Thick

PROBABILITIES OF RECURRENCE
Based on the Proposed Model

Non - Parametric			Parametric		
Parameter	**Parameter Level**	**P**	**Parameter**	**Parameter level**	**P**
Figo	0	0.14	Size	0	0.14
LVS	0		Depth	0	
Host	0		Thickness	0	
Site	0		Size	1	0.23
#Nodes	0		Depth	1	
Growth	0		Thickness	1	
Margin	1		Size	2	0.34
Figo	1	0.31	Depth	2	
LVS	1		Thickness	2	
Host	1		Size	3	0.48
Site	1		Depth	3	
#Nodes	1		Thickness	3	
Growth	1		Size	4	0.62
Margin	1		Depth	4	
Figo	2	0.45	Thickness	4	
LVS	1		Size	5	0.75
Host	2		Depth	5	
Site	2		Thickness	5	
#Nodes	2		Size	6	0.84
Growth	2		Depth	6	
Margin	1		Thickness	6	

PROBABILITIES OF HISTOLOGIC NODE INVOLVEMENT
Based on the Proposed Model

Non - Parametric			Parametric		
Parameter	Parameter Level	P	Parameter	Parameter level	P
Figo	0	0.16	Size	0	0.12
LVS	0		Depth	0	
Host	0		Thickness	0	
Growth	0		Size	1	0.20
Figo	1	0.36	Depth	1	
LVS	1		Thickness	1	
Host	1		Size	2	0.30
Growth	1		Depth	2	
Figo	2	0.56	Thickness	2	
LVS	1		Size	3	0.44
Host	2		Depth	3	
Growth	2		Thickness	3	
Figo	3	0.61	Size	4	0.58
LVS	1		Depth	4	
Host	2		Thickness	4	
Growth	2		Size	5	0.71
Figo	4	0.64	Depth	5	
LVS	1		Thickness	5	
Host	2		Size	6	0.82
Growth	2		Depth	6	
			Thickness	6	
			Size	7	0.89
			Depth	7	
			Thickness	7	
			Size	8	0.93
			Depth	8	
			Thickness	8	

APPENDIX TWO

PARAMETER LEVEL DEFINITION

Group . . . . . 1-Recurrence; 2-Node; 3- Both

Figo (FIGO 1988) 1-I; 2-II; 3-III; 4-IVa

LVS (Lymph Vascular Space Invasion) 0-Yes; 1-No

Host Response 0-Marked; 1-Moderate; 2-Mild

Lesion Site . . . . . 0-Clitoris; 1-Labia minora; 2-Labia majora; 3-All

Lesion Size . . . . . mm

Histologic Nodes . . . . . 0-Yes; 1-No; 2-lost to follow up

Mitosis . . . . . 0-(0-5); 1-(5-10); 2 (>10)

 # Nodes . . . . . Number of Nodes

Growth 0-Pushing; 1-Mixed; 3-Infiltrating

Dysplasia 0-Yes; 1-No

CIS (Carcinoma in Situ) 0-Yes; 1-No

Grade (Histologic Grade) . . 1-Well differentiated; 2- Moderately; 3-Poorly

Surgical Margin 0-Yes; 1-No

Keratin . . . . . 0-(.50%); 1-(25-50%); 2-(1-25%)

Distance Surgical Margin . . . . . 0-(>5mm); 1-(=/<5mm)

Cell Type. 0-Large Cell Keratinizing; 1-Large Cell Nonkeratinizing; 3-Small Cell

Dystrophy 0-Yes; 1-No

APPENDIX THREE

ORIGINAL DATA

Pat	Grp	Sur Mar	DMar	Depth inv	Thick	Growth	LVS	Mito	Kera	Grad	Cell	Hst Rsp	CIS	Dysp	Dist	Cond	Histo Nodes	#No	Rec	Rec Site	Les Size	Les Site	Figo
1	3	0	0	3.3	1.5	0	0	0	1	0	0	0	0	0	1	1	0	0	0		1	2	1
2	3	0	2	2.6	2.8	0	0	2	2	2	0	1	1	0	0	0	0	0	0		3	3	2
3	2	0	1	5.04	8	1	1	1	0	1	0	1	0	0	0	1	0	0	1		8	3	3
4	1	0	0	9	9	1	1	1	0	1	0	0	0	1	0	0	3		0		4	3	2
5	1	0	0	6	6	2	1	1	0	1	0	2	0	0	0	0	3		1	2	6	2	2
6	2	0	1	9.5	9.5	2	1	2	2	2	0	2	0	0	0	0	1	6	1	2	5	3	3
7	3	0	0	10	10	1	0	0	2	2	2	1	0	0	0	0	0	0	0		10	0	2
8	3	0	0	2.7	3	2	0	2	2	1	1	0	0	1	1	1	0	0	0		1	3	1
9	3	0	0	1.8	2.7	2	1	2	2	2	0	2	0	0	0	0	0	0	0		2	1	3
10	3	0	2	6	6	1	1	2	2	2	0	1	1	1	0	0	1	1	0		6.5	2	3
11	3	0	0	19	13	1	1	0	1	1	0	2	0	0	1	1	1	6	1	2	6	3	2
12	3	1	2	5.04	12	2	0	1	2	2	0	2	0	0	1	0	0	0	1	3	5	2	2

ORIGINAL DATA
(Continued)

Pat	Grp	Sur Mar	DMar	Depth inv	Thick	Growth	LVS	Mito	Kera	Grad	Cell	Hst Rsp	CIS	Dysp	Dist	Cond	Histo Nodes	#No	Rec	Rec Site	Les Size	Les Site	Figo
13	1	0	0	4	4	2	0	1	1	1	0	2	0	1	1	0	3		0		3	3	2
14	3	0	0	2.5	4.5	0	0	0	2	0	0	1	0	0	1	1	0	0	0		1.5	3	1
15	3	0	1	3	7	2	0	2	0	1	0	2	0	1	0	0	0	0	0		3	2	2
16	3	0	0	2	7	0	0	2	2	1	0	1	1	1	1	1	0	0	0		2	1	1
17	3	0	0	3.6	6	2	1	2	2	1	0	2	0	0	1	0	0	0	0		5	2	2
18	1	0	0	6	10	1	1	0	1	1	0	1	0	0	1	0	1	5	0		6	2	3
19	3	0	0	2.4	3	0	0	1	2	2	0	0	1	0	0	0	0	0	0		1.5	1	1
20	3	0	1	5.04	5	1	0	0	0	0	0	1	0	0	1	0	1	1	0		3.5	2	2
21	1	0	0	3	5	1	0	2	1	0	0	2	0	1	1	0	3		0		1.5	0	1
22	3	0	2	6.5	9.5	2	1	0	2	1	0	2	0	0	0	0	1	2	1	1	6	3	3
23	3	0	0	10	10	1	0	0	1	1	0	2	0	0	0	0	1	1	1	1	6	2	3
24	3	0	2	3.5	3.6	2	0	1	2	2	0	2	0	1	1	1	0	0	0	2	1	1	
25	3	0	0	10	10	0	0	1	2	2	0	2	1	0	0	0	0	0	1	1	3.5	3	3
26	3	0	0	1.8	3	2	0	0	1	1	0	2	0	0	1	0	0	0	0		1.5	1	1

ORIGINAL DATA
(Continued)

Pat	Grp	Sur Mar	DMar	Depth inv	Thick	Growth	LVS	Mito	Kera	Grad	Cell	Hst Rsp	CIS	Dysp	Dist	Cond	Histo Nodes	#No	Rec	Rec Site	Les Size	Les Site	Figo
27	3	0	1	4	4.5	2	0	2	1	1	0	1	1	0	1	0	0	0	1	1	3.5	2	3
28	1	0	1	3.8	4	2	0	2	0	0	0	1	1	1	1	0	3		0		2.7	1	2
29	3	0	0	2.1	2.9	2	0	2	2	2	0	2	0	0	0	0	0	0	0		1.3	1	1
30	2	0	0	8	8	0	0	2	2	2	0	2	0	1	1	0	1	1	0		1.4	1	3
31	3	0	0	5	5	2	1	1	1	1	0	2	0	0	1	0	1	3	1	5	2	2	3
32	3	0	1	3.6	4	2	0	1	1	1	0	2	0	0	1	0	1	1	0		1	0	1
33	3	0	0	2.5	5	0	0	0	0	0	0	1	0	0	0	0	0	0	1	1	9	2	2
34	3	0	1	8.9	9	1	1	2	1	1	0	2	0	0	0	0	1	3	0		5	1	2
35	3	0	1	5	5	2	1	2	1	1	0	2	0	1	0	1	1	1	0		1.5	0	1
36	3	0	0	5.04	7	2	0	2	1	1	0	1	0	0	0	1	0	0	0		1	1	1
37	3	0	0	2.55	2.6	2	1	2	2	2	0	2	1	0	0	1	0	0	0		3	0	2
38	3	0	1	10	10	2	1	2	1	1	0	2	1	0	0	0	0	0	0		5	2	3
39	3	0	0	5.5	5.5	1	0	1	1	1	0	2	0	0	1	0	0	0	0		3	0	2
40	3	0	0	2.97	3	0	0	2	0	0	0	1	0	0	1	0	0	0	0		1	3	1

ORIGINAL DATA
(Continued)

Pat	Grp	Sur Mar	DMar	Depth inv	Thick	Growth	LVS	Mito	Kera	Grad	Cell	Hst Rsp	CIS	Dysp	Dist	Cond	Histo Nodes	#No	Rec	Rec Site	Les Size	Les Site	Figo
41	3	0	0	6.5	6.5	1	1	2	2	2	0	2	0	0	0	1	1	1	1	1	4	3	3
42	3	0	2	4.2	4.5	2	0	1	2	1	0	1	0	0	1	0	0	0	1	1	2	1	1
43	3	0	0	7	7	2	1	2	1	1	0	2	0	0	0	0	1	2	1	7	6.6	2	2
44	3	0	0	12	25	1	1	2	2	2	1	2	1	0	1	0	1	2	1	4	3.5	0	3
45	3	0	2	9	9	2	1	2	2	2	0	2	0	0	0	0	1	2	0		2.5	2	3
46	3	0	0	1	2.7	0	0	1	2	2	1	0	1	0	0	0	0	0	0		2	3	1
47	2	1	2	10	13	1	1	2	2	2	0	2	0	0	1	0	1	0	1	1	4	3	2
48	3	0	0	1.35	2	0	0	2	2	1	0	2	0	0	1	0	0	0	0		8	3	2
49	1	0	0	4	4	2	0	0	0	0	0	2	1	0	1	0	3		0		1	0	1
50	3	0	0	1.8	2.5	0	0	2	2	2	0	1	1	1	0	0	0	0	0		4	2	2
51	2	0	0	6	16	2	0	1	1	1	0	1	0	0	1	0	1	2	0		6	3	3
52	3	0	0	1.95	15	1	0	2	0	0	0	1	0	0	0	0	1	1	0		7	2	3
53	3	0	1	4.8	5	1	0	0	0	1	0	2	1	0	1	0	1	1	1	1	3	2	2
54	3	0	0	2.93	3	2	0	2	1	1	0	0	0	0	1	0	0	0	0		1.5	0	1

ORIGINAL DATA
(Continued)

Pat	Grp	Sur Mar	DMar	Depth inv	Thick	Growth	LVS	Mito	Kera	Grad	Cell	Hst Rsp	CIS	Dysp	Dist	Cond	Histo Nodes	#No	Rec	Rec Site	Les Size	Les Site	Figo
55	3	0	0	2	10	0	0	0	0	0	0	1	0	0	1	0	0	0	0		6	2	2
56	3	0	0	0.75	2.7	0	1	2	1	1	0	1	1	0	1	0	0	0	1	1	4	3	2
57	1	0	0	1.5	2.2	0	0	1	0	0	0	2	1	1	1	0	3		0		3	1	2
58	1	0	2	1.05	1.2	0	0	2	2	2	1	2	1	0	0	0	3		0		1	0	1
59	3	0	0	3	4	2	0	1	1	1	0	1	1	0	1	0	0	0	0		1.5	0	1
60	3	0	2	2.2	2.5	0	0	2	2	1	0	1	1	0	1	0	0	0	0		1	2	1
61	3	0	0	3.5	4	2	0	2	0	0	0	2	1	0	0	1	0	0	1	1	5	2	2
62	3	1	2	5.04	14	0	0	2	2	2	1	1	1	0	1	0	0	0	0		4	1	2
63	3	0	0	1.65	4	0	0	2	2	2	0	2	1	0	1	0	0	0	0		4	1	2
64	1	0	0	2.4	3	0	0	2	2	2	1	1	1	0	0	0	3		0		0.6	1	1
65	3	0	0	4.8	5	1	0	0	0	1	0	1	0	0	1	0	0	0	0		2	3	1
66	3	0	1	13	20	0	0	1	2	1	1	1	0	0	1	0	0	0	0		1	2	1
67	3	0	2	7	7	2	0	2	1	1	0	0	1	0	0	0	0	0	0		6	2	2
68	3	0	0	15	15	1	1	2	1	1	0	1	0	0	0	0	1	5	1	1	4	3	4

ORIGINAL DATA
(Continued)

Pat	Grp	Sur Mar	DMar	Depth inv	Thick	Growth	LVS	Mito	Kera	Grad	Cell	Hst Rsp	CIS	Dysp	Dist	Cond	Histo Nodes	#No	Rec	Rec Site	Les Size	Les Site	Figo
69	3	0	0	10	10	1	1	1	1	2	0	2	0	0	1	0	1	4	1	1	10	3	3
70	3	0	0	2.25	3	0	0	0	1	1	0	1	1	0	0	0	0	0	0		2.5	1	2
71	1	0	2	1.5	1.5	0	0	2	1	0	0	1	1	0	1	0	3		0		10	2	2
72	3	0	2	4.5	5	2	0	0	2	1	0	2	0	0	1	0	0	0	1	2	4	2	3
73	3	0	0	5.04	15	0	0	1	2	2	2	2	0	0	0	0	0	0	1	4	10	3	2
74	3	0	2	5	5	0	1	2	2	2	1	2	1	0	0	0	1	3	0		1	1	1
75	1	0	2	15	15	2	1	0	1	2	1	1	0	0	0	0	3		1	3	7	2	3
76	3	0	0	3	3.5	1	0	2	1	1	0	1	0	0	1	0	1	4	0		2	3	1
77	3	0	0	7	10	1	0	2	2	2	0	1	1	1	1	1	0	0	0		6	2	2
78	2	0	0	5.04	7	0	0	2	0	0	0	2	0	0	0	0	1	2	1	6	5	3	2
79	3	0	0	5.04	3	1	0	1	0	0	0	1	1	1	0	1	1	2	0		8	2	3
80	3	0	0	9.5	10	1	0	1	1	1	0	2	0	0	1	0	0	0	0		3	3	2
81	3	0	2	7	7	0	0	2	2	1	0	1	0	0	0	0	0	0	0		1.5	0	1
82	2	0	0	5.04	9	1	0	2	2	2	0	2	1	1	1	0	1	6	0		8	3	3

ORIGINAL DATA
(Continued)

Pat	Grp	Sur Mar	DMar	Depth inv	Thick	Growth	LVS	Mito	Kera	Grad	Cell	Hst Rsp	CIS	Dysp	Dist	Cond	Histo Nodes	#No	Rec	Rec Site	Les Size	Les Site	Figo
83	3	0	0	9	10	2	0	2	1	1	0	0	1	1	1	0	0	0	0		4	2	3
84	1	0	0	0.35	0.5	0	0	0	2	1	1	1	1	0	0	0	3		0		0.5	1	1
85	1	0	2	0.9	2	2	1	2	2	1	0	1	0	0	0	0	3		0		3.3	3	2
86	3	0	2	3	3.2	0	0	2	1	1	0	1	0	0	1	0	0	0	0		1	0	1
87	3	0	2	1.2	3.3	2	0	2	1	2	2	0	0	0	0	0	1	1	0		6	2	2
88	3	0	0	0.6	0.7	0	0	1	2	2	0	1	1	1	0	0	0	0	0		2	1	1
89	3	0	0	12	12	2	0	1	0	1	0	2	0	1	0	1	1	6	1	1	5	3	4
90	3	0	0	6	45	2	1	2	1	1	0	2	1	1	1	0	1	3	1	3	4.6	3	3
91	2	1	2	6	12	0	1	2	2	1	0	1	1	0	0	1	1	5	1	1	12	3	3
92	3	0	0	2.8	3.5	1	1	2	1	2	0	0	1	0	0	0	1	1	0		4	1	2
93	3	0	0	1.35	2.4	1	0	1	1	1	0	0	0	1	1	0	0	0	1	1	2	0	1

REFERENCES

1. Hong, W. K., I. W. Dinery, "Adjuvant Chemotherapy in the Head and Neck Cancer", Larson David et al, (eds), *Cancer in the Neck*, Macmillan, NY, 1986.

2. MacKie, Rona M., *Pigment Cell*, Karger, NY, 1983.

3. Bennet, S.H. et al, *Prognostic Significance of Histologic Response in Cancer of the Larynx and Hipolarynx*, Cancer, 28:1255-65

4. Harwood, A. R., "Role of Radiation in the Treatment of Melanoma", Larson David et al (eds), *Cancer in the Neck*, Macmillan, NY, 1986.

5. Stryer, L., *Biochemistry*, W. H. Freeman and Co., NY, 1988.

6. Hoel, Paul G., *Introduction to Mathematical Statistics*, John Wiley & Sons, NY, 1984.

7. Freund, John E., *Modern Elementary Statistics*, Fourth edition, Prentice-Hall, Englewood Cliffs, 1973.

8. Snedecor W. G., and W. G. Cochran, *Statistical Methods*, Seventh edition, Iowa State University Press, Ames, 1980.

9. Montgomery, Douglas C., *Design and Analysis of Experiments*, Third edition, John Willey & Sons, NY, 1991.

10. Box, G. E. P. and N. R. Draper, *Empirical Model Building and Response Surfaces*, John Willey & Sons, NY, 1987.

11. Draper, N. and H. Smith, *Applied Regression Analysis*, Second edition, Wiley, NY, 1981.

12. Snow, Gordon B., et al, "Prognostic Factors in Neck Metastasis", Larson, D., Cancer in the Neck, Macmillan, NY, 1986.

13. Meyers, E. N., et al, "The Significance of Extracapsular Extension of Squamous Cancer in Lymph Nodes", Larson, D., *Cancer in the Neck*, Macmillan, NY, 1986.

REFERENCES
(Continued)

14. Dios, Dr. Rose A., et al, "Lesion Impulses: A Model for Neurological Diseases",

15. Parlar, Y., et al, "The Logistic Model in Lesion Localization for Neurological Diseases", Annual conference of the IEEE Engineering in Medicine and Biology Society, Vol. 13, N° 3, 1991.

16. Parlar, Y., et al, "Estimation of Lesion Probabilities Using a Neurological Test Database", Annual conference of the IEEE Engineering in Medicine and Biology Society, Vol. 12, N° 3, 1990.

GLOSSARY OF TERMS

Dysplasia: Abnormal development of tissue.

Dystrophy: Disorder of tissue due to impaired nourishment of the affected part.

Figo Stage: Classification used to define the extent of spread of certain types of cancer.

Histologic Grade: Classification to differentiate tumors.

Keratin: Fibrous protein that forms horny tissues.

LVS: Lymph Vascular Space Invasion.

Mitosis: Mitotic index