Effectiveness of Radical Mastectomy for Mammary Cancer: *

An Analysis of Mortalities by the Method of Probits

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THIS STUDY is mainly an attempt to define the phylogenetic characteristics of mammary cancer which must be known before the relative merits of different therapies may be evaluated. The characteristics of mammary cancer with which we were concerned particularly are: 1) the different cellular growth patterns; 2) the frequency of axillary nodal metastases; 3) sizes of the primary tumors; and 4) the relationship of postoperative survival to these characteristics.

After working upon the problem for a few months we realized that definitive interpretations of the data could not be effected well by using ordinary and simple statistical methods. By virtue of the fact that plots of accumulative mortalities were found to be ogives (sigmoid curves) (Fig. 1), probit analysis [5] was hit upon as a possible solution of the statistical problem (Fig. 2). After determining that the probit method was appropriate and applying it to all of our data and to those of McWhirter [11] and Greenwood,[6] the earlier statistical work by Boag was found to have examined the utility of the probit method for the evaluation of cancer therapy.[2-4] Because Boag's papers deal extensively with the theory of the probit method and its appropriateness for the examination of the cancer problem in general, we will not discuss the use of probits at all in this paper; except to say that their use permits rather precise and dependable statements regarding the time-mortality relationships of various mammary cancers.

Cellular Growth Patterns: a Basis for a Biological Classification of Mammary Cancer

This method of classification was developed by Tornberg after studying the biologic behavior of human mammary cancers in the Karolinska Institute, Stockholm, Sweden.[9] This classification, with but a few modifications is as follows:

I. Nonmetastasizing (not invasive)

This type consists of intraductal or comedo carcinoma without stromal invasion. The manual expression of necrotic tumor from enlarged or thickened mammary ducts after incising the biopsy is peculiar to Type I mammary cancers. When this type of neoplasm affects the epithelium of the nipple the signs of Paget's disease of the breast may exist.

II. Rarely Metastasizing (always invasive)

1. Pure extracellular mucinous or colloid cancer.
2. Medullary cancer with lymphocytic infiltration.
3. Well-differentiated adenocarcinoma (Grade I of Tornberg).

The pure mucinous carcinomas of Type II are recognized easily. When the biopsy is cut the tumor is seen to be circumscribed and is homogenously gelatinous. They are soft and have a gray to reddish brown

* Presented before the American Surgical Association, Boca Raton, Florida, March 21–23, 1961.

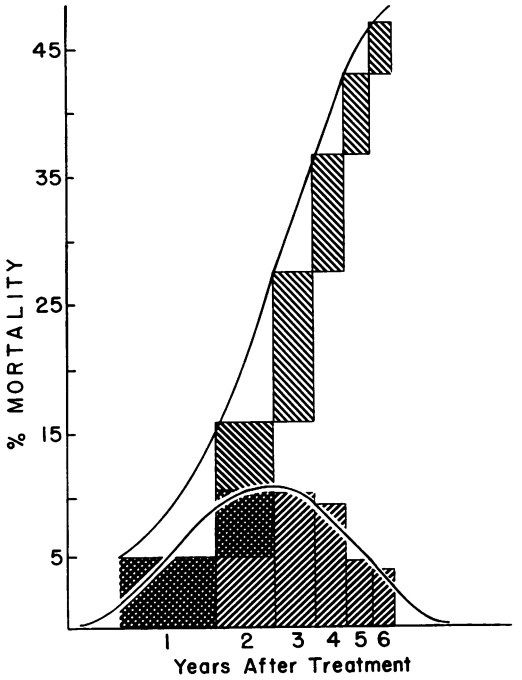

FIG. 1. The log normal distribution of the mortality from mammary cancer treated by radical mastectomy at the Barnes and Ellis Fischel Cancer Hospitals is illustrated below. If the accumulative mortality is plotted against log-time the ogive drawn above results.

color. The mucin is always extracellular. Medullary cancers of Type II have sharply delimited margins, are uniformly soft, have a light-gray color and may contain small focal necroses. Lymphocytic infiltration is prominent. Medullary cancers may be mistaken grossly for fibroadenoma. Well-differentiated Grade I adenocarcinomas microscopically have discretely circumscribed borders and are highly and uniformly cellularly differentiated.

Papillary carcinoma with stromal invasion also are classed as Type II. They are considered Type I when no stromal invasion is demonstrated.

III. Moderately Metastasizing (always invasive)

1. Adenocarcinoma (Grade II of Tornberg).

2. Intraductal carcinoma with stromal invasion.

Type III tumors comprise those intraductal carcinomas invading the stroma as well as the ordinary infiltrative adenocarcinomas. Actually, all cancers not definitely classified as Types I, II or IV constitute Type III.

IV. Highly Metastasizing (always invasive)

Undifferentiated carcinoma (Grade III of Tornberg).

Type IV cancers include the undifferentiated carcinomas having cells without ductal or tubular arrangement and without cellular inflammatory response about them *and all types of tumors indisputably invading blood vessels.*

The differentiation of mammary cancer into these types can be made solely from properly prepared and selected "permanent" tissue sections of the primary tumor. In fact, the differentiation of the first two (Types I, II) from the last two (Types III, IV) can be effected with a high degree of certainty by visual examination and from frozen sections.

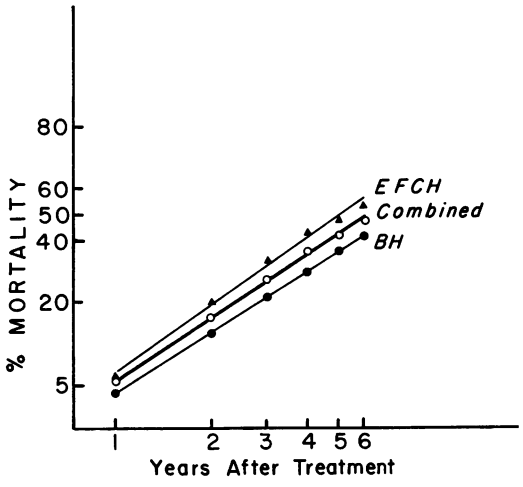

FIG. 2. This graph shows the probit transformation of the mortality data from the Ellis Fischel Cancer Hospital (EFCH) and from the Barnes Hospital (BH). The sigmoid curve in Figure 1 becomes linear when the data of the combined series are converted to probits.

Material

The gross sample consisted of two parts: from the Barnes Hospital, 425 cases (1/1/50–1/1/55, Table 1) and from the Ellis Fischel Cancer Hospital, 364 cases (1/1/40–1/1/50, Table 2). Forty-nine of the 425 individuals treated by mastectomy in the Barnes Hospital were excluded from the working sample because they had cancers in both breasts ("double risk cases"—21), were men (4), had simple mastectomies (6), did not have mammary cancer when Dr. Ackerman reviewed the sections (2), and the available tissue sections did not permit histologic classification with any surety (16). One case treated by radical mastectomy was excluded from the women with unilateral mammary cancer in the Ellis Fischel sample because the available sections did not permit classification. The total working sample contains 739 cases (Table 9).

The patients in these series for the most part were selected for radical mastectomy by the rules of operability used by Haagensen and Stout.[7] The technic of the radical mastectomies performed and the thoroughness of examination of the operative specimen also were similar in the two series. Each specimen had all quadrants of the

TABLE 1. *Series I. Radical Mastectomy for Mammary Carcinoma, Barnes Hospital, 1950 to 1955*

Clinical Stage of Cancer*	No. Patients	No. Patients Surviving 5 Years After Treatment
A	216	164 (76%)
B	135	65 (48%)
C	48	23 (48%)
D	26	3 (11%)
	425**	255 (60%)

* Table 3.

** One hundred ten other women had persistent cancer after mammary operations at another hospital or before 1950 in the Barnes Hospital. Sixty-six had untreated mammary cancers with distant metastases. Only 5 of these were known to be alive more than 60 months after first being examined at Washington University.

TABLE 2. *Series II. Radical Mastectomy for Mammary Carcinoma, Ellis Fischel Cancer Hospital, 1940 to 1950*

Clinical Stage of Cancer*	No. Patients	No. Patients Surviving 5 Years After Treatment
A	189	119 (63%)
B	85	36 (42%)
C	69	30 (43%)
D	20	4
	363	189 (52%)

* Table 3.

TABLE 3. *Criteria for the Clinical Stages of Mammary Cancer**

Stage A. Patients with no axillary nodes thought to contain metastases and no "grave" local signs or distant metastases.

Stage B. Patients with a palpable axillary node (or nodes) thought to contain cancer, which is not fixed, less than 2.5 cm. in transverse diameter. All "grave" signs must be absent.

Stage C. Patients exhibiting any one of the following "grave" signs: edema of limited extent, axillary nodal mass greater than 2.5 cm. in transverse diameter, fixation of axillary nodes to skin or deep structures, ulceration (excepting Paget's disease), solid fixation of the tumor to the chest wall.

Stage D. Patients having any two of the "grave" local signs, distant metastases, satellite nodules, extensive edema, or inflammatory carcinoma of the breast.

* Haagensen.[8]

TABLE 4. *Age Distribution of 739 Women Ill of Mammary Cancer*

Age Interval	Series I Barnes Hospital No. Patients	Series II Ellis Fischel Cancer Hospital No. Patients	Total
<40	30	21	51
40–49	112	61	173
50–59	101	78	179
60–69	92	118	210
70+	41	85	126
	376	363	739
No. expected to die in 5 years of all causes*	30 (8%)	44 (12%)	74 (10%)

Comparing Series I with Series II
Chi Square = 30.9
P (I = II) = <.001

* Calculation from U. S. Vital Statistical Tables (1950).

breast parenchyma and a mean of 27 axillary nodes examined microscopically. The physical signs used to classify the clinical stages of the mammary cancers in these series are those shown in Table 3.[8] The permanent sections of the primary mammary neoplasms were reexamined and the tumor classified by Dr. B. Tornberg without knowledge of what had happened to any case.

Results

1. The differences in the age distributions of the Barnes Hospital (Series I) and the Ellis Fischel Cancer Hospital (Series II) are shown in Table 4. The normal mor-

TABLE 5. *Incidence of Axillary Nodal Metastases by Clinical Stage of the Breast Cancer Treated by Radical Mastectomy*

Clinical Stage of Cancer	Series	No. Patients	No. Axillary Lymph Nodes Containing Cancer			% of Patients with less than Three Axillary Nodes Containing Cancer
			None	1 or 2	3 or more	
A	I	214	144 (67%)	37	33	85
	II	189	106 (56%)	38	45	76
B	I	135	33 (24%)	36	66	51
	II	85	18 (21%)	21	46	46
C	I	48	5 (10%)	4	39	19
	II	69	16 (23%)	10	43	38
Totals	I*	397	182 (46%)	77	138	65
	II	343	140 (41%)	69	134	61

* Two patients (Stage A) did not have axillary nodes examined microscopically.

TABLE 6. *Relationship of Diameters of 717 Mammary Cancers to the Frequencies of Axillary Nodal Metastases and of Death of Patients Within Five Years After Radical Mastectomy (Series I and II Combined)*

Diameter of Breast Cancer (cm.)	No. Patients Whose Cancers were Measured*	No. Associated with Axillary Nodal Metastases**	No. Patients Dying in the 60 Months after Radical Mastectomy
1	63	7 (11%)	6 (9%)
1– 2	151	60 (40%)	43 (28%)
2– 3	190	99 (52%)	72 (38%)
3– 4	136	102 (75%)	70 (51%)
4– 5	75	56 (74%)	47 (63%)
5– 6	37	29 (78%)	30 (81%)
6– 7	24	21 (87%)	19 (79%)
7–10	30	25 (83%)	24 (80%)
10+	11	8 (73%)	7 (64%)
Totals	717	407 (57%)	318 (44%)

* The measurements are those made when the operative specimen was examined. (Patients having bilateral breast cancer and those without diameters recorded are excluded.)

** The frequency of three or more axillary nodal metastases among the patients having them also was higher the larger the tumor.

TABLE 7. *Relationship of Size of the Primary Cancer of the Breast to the Survival of Patients After Radical Mastectomy when no Axillary Nodal Metastases Were Found and all "Grave Clinical Signs" were Absent*

Series	Size* (cm.)	No. Patients	No. Patients Dead	No. Patients Living Five Years	Chi Square	Probability (a = b)
I	a) <2	90	12	78		
	b) 2–5	64	19	45	6.22	.013
	5–10	2	1	1		
	>10	1	0	1		
II	a) <2	36	8	28		
	b) 2–5	72	17	55	.026	.88
	5–10	13	9	4		
	>10	2	1	1		

* Measured in the operative specimen.

TABLE 8. *Relationship of Size and Biologic Type of the Cancer to Survival Among Patients Treated by Radical Mastectomy Who had no Nodal Metastases or "Grave Local Signs"*

Series	Diameter (cm)	No. Patients	No. Patients Dead 0–5 Years After Treatment	Type of Mammary Cancer		
				I & II	III	IV
I' a)	<2	90	12	30 (33%)	45	15
b)	2–5	64	19*	9 (14%)	39	16
II a)	<2	36	8	13 (36%)	18	5
b)	2–5	72	17	24 (33%)	41	7

* The frequency of Type I and II cancers among women with cancers 2–5 cm. in diameter in Series I was significantly less than in women with cancers <2 cm. in diameter in Series I (Chi Square = 5.63, P = .01). Similarly the survival rate of the former group was less than that of the latter (Chi Square = 6.22, P = .013). The age corrected survival rates of Series I (a), II (a) and II (b) and the incidences of Types I and II cancers do not differ significantly. The low survival rate in Series I (b) is best explained by the low incidence of Types I and II cancers.

TABLE 9. *Primary Data used in Calculating Probit Curves*

Series	Interval After Radical Mastectomy											
	1 year		2 years		3 years		4 years		5 years		6 years	
	No. Followed	No. Dead	No. Followed	No. Dead	No. Followed	No. Dead	No. Followed	No. Dead	No. Followed	No. Dead	No. Followed	No. Dead
Barnes Hospital	376	20	376	70	376	85	376	116	376	144	376	160
Ellis Fischel State Cander Hospital	363	20	363	73	363	119	363	155	363	174	363	188
Totals	739	40	739	123	739	204	739	271	739	318	739	348
Biological Types of Mammary Cancer												
I & II	101	4	101	8	101	9	101	11	101	12	101	13
III	412	18	412	52	412	90	412	130	412	155	412	177
IV	226	18	226	63	226	105	226	130	226	151	226	158
Totals	739	40	739	123	739	204	739	271	739	318	739	348

tality expectancy was four per cent greater in Series II than it was in Series I.

2. The data presented in Tables 1 and 2 show that the extent of the tumors estimated by their physical signs roughly correlated with the likelihood of dying. The frequency and extent of axillary nodal metastases in women afflicted by mammary cancers also are related to the physical manifestations of their cancer (Table 5).

TABLE 10. *Probit Analysis of Mortality from Mammary Cancer*

Log-Time (x)	No. Cases (n)	No. Dead (r)	%	Empirical* Probit
0	739	40	5.4	3.40
.3	739	123	16.7	4.04
.48	739	204	27.6	4.41
.6	739	271	36.7	4.66
.7	739	318	43.0	4.82
.78	739	348	47.1	4.92

* The expected probit (Y) is read from the line drawn by estimation through the empirical probit points. The values of (n) are weighted for each expected probit (W = weighting coefficient). After working probits are established the following values are calculated for each value of x, and summed (S): nw, nwx, nwy, nwx^2, $nwxy$, nwy^2. Then, means

$$\bar{x} \text{ and } \bar{y} = \frac{Snwx}{Snw} \quad \text{and} \quad \frac{Snwy}{Snw},$$

(Finney[5]).

$$\text{Probit slope } (b) = \frac{Sxy}{Sxx} = \frac{Snw\ (x - \bar{x})(y - \bar{y})}{Snw\ (x - x)^2}$$

$$\text{and} \quad Y = \bar{y} + b(x - \bar{x}).$$

The variance about the time of 50% mortality

$$= V_{m1} = \frac{(S_1)^2}{N}\, x\, E.$$

S_1 = value of x where $y = 1 -$ Variance of $S_1(V(s))$

$$= \frac{(S_1)^2}{N}\, x\, G.$$

E and G = constants for a given value of x' (Bliss[1]),

$$x' = \frac{T - m_1}{S_1}.$$

T = point of truncation (log-time).

m_1 = log-time of 50% mortality (when $y = 5.00$). Confidence limits of log-time (x) at any mortality value may be calucalted from

$$V(X) = V\bar{x} + (y - 5)^2 V(s).$$

(X) = log-time at mortality probit y.

3. The relationship of size of the primary mammary cancer to survival and to the incidence of axillary nodal metastases after radical mastectomy is shown in Table 6. The sizes of the cancers in Series II were larger than in Series I even among those without nodal metastases and the signs of advanced cancer (i.e., the signs of clinical Stage C—Table 7). The mortality in Series I associated with the primary tumors 2.0 to 5.0 cm. in maximal chordal dimension was greater than the mortalities associated with tumors of similar size in Series II and with smaller tumors in Series I and II. This difference is attributable to the variation in the frequencies of the biologic types of cancers in these groups (Table 8).

4. The correlations of the frequencies of axillary metastases and of dying after radical mastectomy with the various biological types of mammary cancer are shown in Tables 9 and 11.

5. The probit-mortality lines and time-mortality curves for the different types of mammary cancer treated by radical mastectomy were calculated from the data shown in Table 9 using the formulas shown in Table 10. Figures 3 and 4 compare these data graphically with the mortality from untreated mammary cancer dealt with similiary.[6] The mortality following simple mastectomy and irradiational therapy for mammary cancers initially without distant metastases is shown in Figures 5 and 6. (The mortality data reported by Dr. McWhirter[11] was corrected to conform with our sample as nearly as possible by adding 63 cases. Actually, the comparability of the McWhirter and the Washington University Series cannot be established from the data available.)

Discussion

We agree with Boag that the use of probits for the analysis of cancer mortality allows an accurate statistical evaluation of the mortalities attending mammary cancers of different types (Fig. 3). Women treated

by radical mastectomy for Types I and II mammary cancers died at rates which hardly exceeded those expected among women of similar ages without mammary cancer (only 2 of 101 actually died of cancer during five postoperative years).

The rates of dying from Types III and IV were much higher. The probit slope for the Type IV cancers is slightly greater than the slope for Type III cancers. That the lethalness of Type IV tumors is greater than that of Type III tumors also is supported by other observations. The times requisite for a 50 per cent mortality to occur after radical mastectomy for Types III and IV cancers were 7.1 and 3.5 years respectively. For the most part, the difference in mortality from Types III and IV cancers is ascribable to the different rates with which women with Type III cancer without nodal metastases and those with Type III cancer with nodal metastases died (Fig. 7–10). Those women with nodal metastases from Type III cancer and those with Type IV cancer with and without axillary metastases died at nearly the same rates and actually their rates of dying approached those of the untreated Greenwood series (probit line slopes Types III = 2.60, Type IV = 2.64, untreated series = 2.83.

Because the Greenwood Series is constituted of all types of mammary cancer the no treatment curve for Type IV tumors must be somewhat steeper than the curve

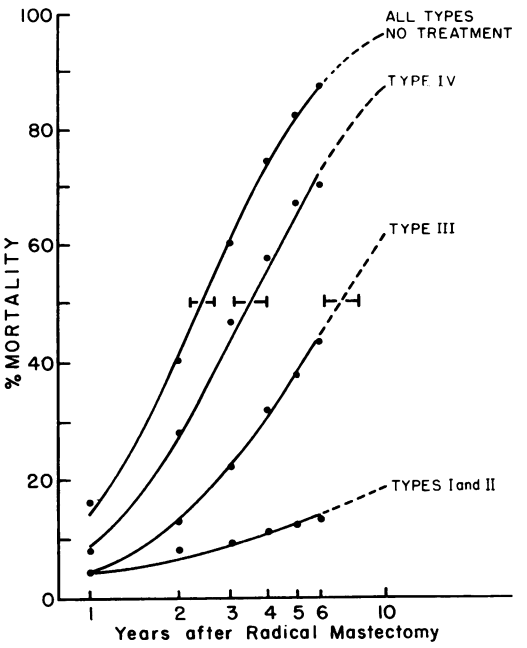

FIG. 3. This graph compares the mortality expectancy of the different types of mammary cancer treated by radical mastectomy with the untreated series of Greenwood. The lines are calculated from the corresponding fitted probit transformation (Fig. 4). The dots about the lines are data points. The confidence limits (95%) for the time of median lethality are represented by the bars to the left and right of the point of 50% mortality.

derived from his total sample. Nevertheless, this does not prevent the use of the Greenwood data as a comparison base for ascertaining whether or not radical mastectomy has appreciable value for the treatment of undifferentiated carcinomas of the breast. Really, the use of the Greenwood

TABLE 11. *Data Used in Calculating Probit Curves*

Biological Type of Mammary Cancer	Axillary Nodal Metastases	Interval after Radical Mastectomy											
		1 year		2 years		3 years		4 years		5 years		6 years	
		No. Followed	No. Dead	No. Followed	No. Dead	No. Followed	No. Dead	No. Followed	No. Dead	No. Followed	No. Dead	No. Followed	No. Dead
Type III (412)	Absent	172	8	172	16	172	26	172	33	172	38	172	42
	Present	240	10	240	36	240	64	240	97	240	117	240	135
Type IV (226)	Absent	47	4	47	12	47	18	47	23	47	26	47	28
	Present	179	14	179	51	179	87	179	107	179	125	179	130
Type I & II (101)		101	4	101	8	101	9	101	11	101	12	101	13
Total (739)		739	40	739	123	739	204	739	271	739	318	739	348

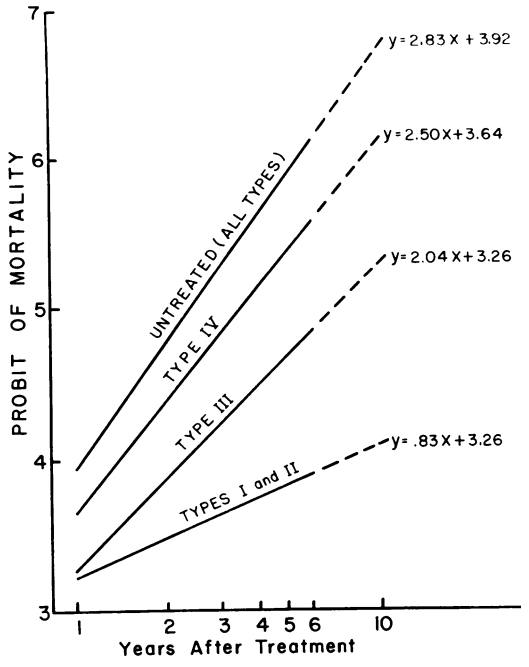

FIG. 4. The probit transformation of the mortality data listed in Table 11 resulted in the linear relationships shown in this graph. The linear equations on the right define the respective probit lines.

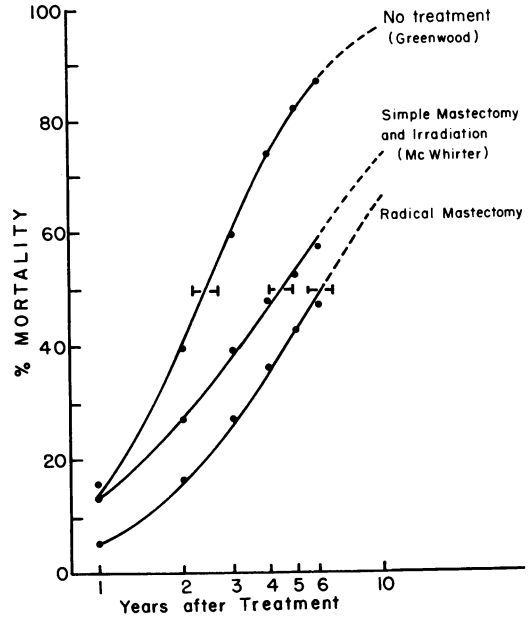

FIG. 5. The mortality expectancy calculated from the fitted probit transformations (Fig. 6) are represented by the solid lines. The dots represent the actual data points of the working samples.

data as the comparison base serves only to minimize the effectiveness of radical mastectomy. Actually there are differences between the untreated series, and Types III and IV mammary cancers with nodal metastases. The time lapse necessary for 50 per cent of the Type IV cancers (the undifferentiated group) treated with radical mastectomy to die was significantly longer than the time lapse necessary for 50 per cent of Greenwood's untreated series to die. Consequently, this constitutes fair proof that radical mastectomy, even when used only in cases of undifferentiated tumors with nodal metastases, is a measurably effective way to treat cancer of the breast.

The rate of dying from Type III mammary cancers without axillary nodal metastases was significantly slower than that for Type III with axillary metastases, and for Type IV cancers with and without axillary metastases (Fig. 9, 10). In fact the probit derived rate of dying from Type III

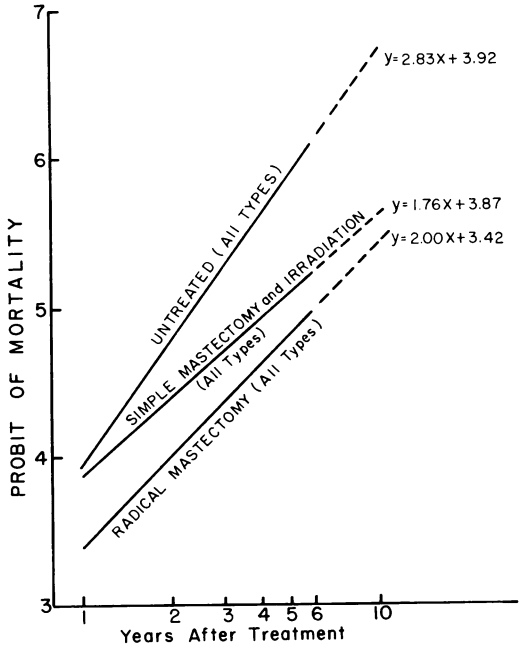

FIG. 6. The probit transformations of the mortality data (Fig. 5) of Greenwood (untreated), of McWhirter (simple mastectomy and irradiation), and of Washington University (radical mastectomy) are shown graphically and algebraically.

cancers having no axillary metastases is so slow that about 20 postoperative years need elapse for 50 per cent of the women who have this type of tumor removed by radical mastectomy to die. However, this same period is only 4.9 years for the Type III tumors with nodal metastases, 4.3 years for Type IV cancers without axillary metastases and 3.3 years for the Type IV with axillary metastases. Obviously, although the existance of nodal metastases remarkably reduces the therapeutic effectiveness of radical mastectomy for Type III tumors it does not alter its effectiveness for Type IV cancers. In other words, the postoperative prognosis of Type III cancers without axillary metastases is much better than it is for Type III cancers with axillary metastases but the prognosis of Type IV cancers is nearly the same whether there are axillary metastases or not.

Probit analysis also permits the examination of what constitutes an adequate follow up period. Actually the effectiveness of any

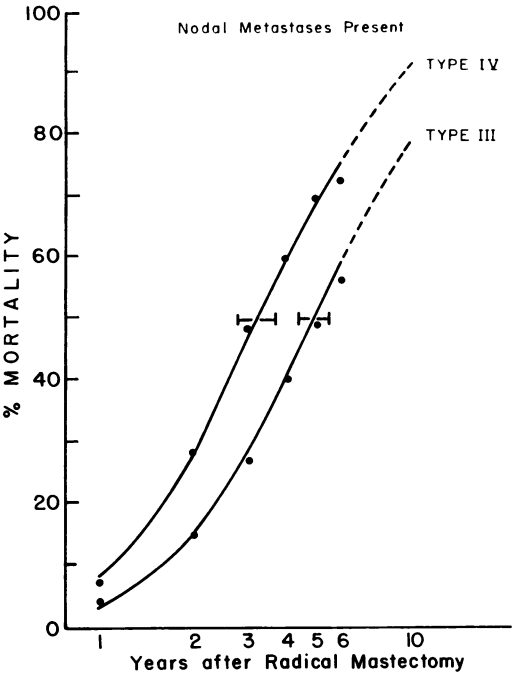

FIG. 8. The mortality expectancy calculated from the respective probit transformations are shown for Types III and IV mammary cancer associated with axillary nodal metastases.

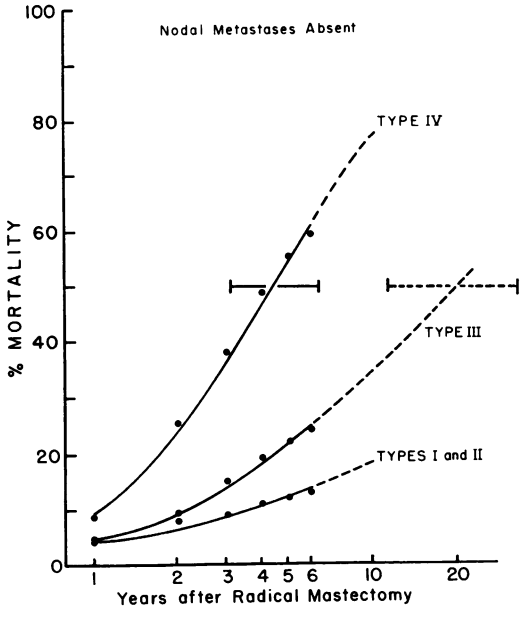

FIG. 7. The mortality expectancy calculated from the respective probit transformations are shown for the different types of mammary cancer unassociated with axillary nodal metastases.

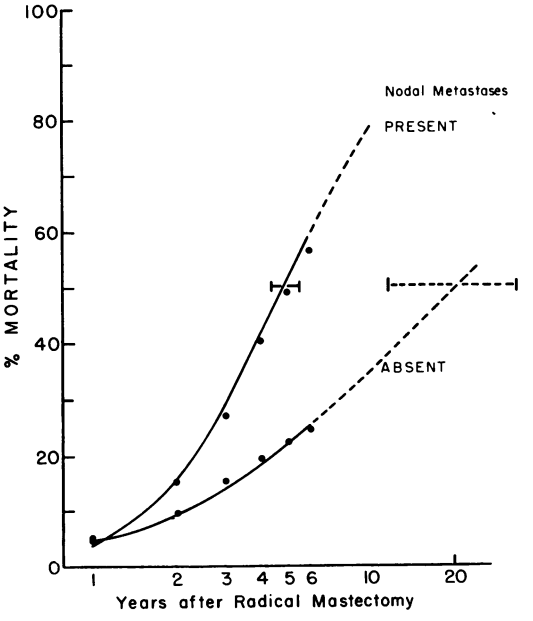

FIG. 9. The mortality expectancy calculated from the respective probit transformations are shown for Type III mammary cancer with and without axillary nodal metastases.

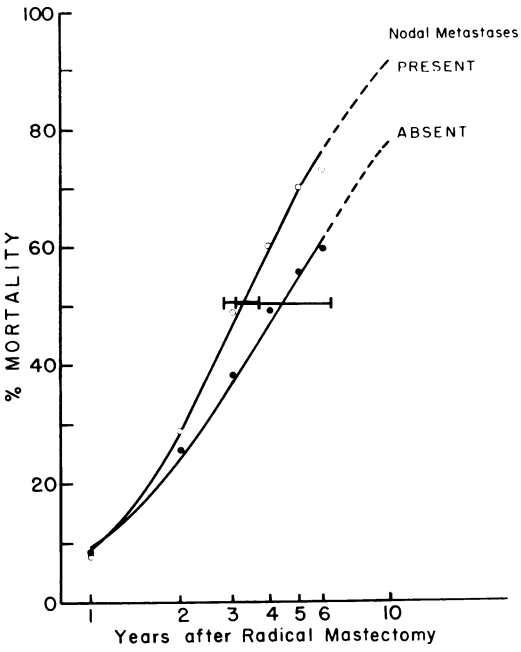

FIG. 10. The mortality expectancy calculated from the respective probit transformations are shown for Type IV mammary cancer with and without axillary nodal metastases.

treatment for mammary cancer can be assessed only after the women stop dying from the mammary cancer for which the treatment was used. How long must we wait before being able to say that a person is almost assuredly cured? Examination of the fitted probits will answer this question at least in part. In the case of unclassified cancer of the breast treated by radical mastectomy the women alive at the end of the sixth postoperative year from then on die no more rapidly than "normal" women of similar ages do. Between the seventy-second and one hundred and twentieth month after the radical mastectomy was performed, the accumulative mortality among the 739 cases of mammary cancer increased nine per cent, mean annual increase in mortality of 2.2 per cent. The mortality among women of similar age without mammary cancer is 8 per cent over these same four years, or a mean annual increase of 2.0 per cent. Our data, though incomplete beyond the sixth year after radical mastectomy, show that after the sixth postoperative year the increment in mortality among women who had cancers of the breast removed by radical mastectomy is the same as that of "normal" women. In other words, after the sixth year so few die of cancer that as a group the women still alive six years after radical mastectomy die no more rapidly than women of like ages without mammary cancers do (Fig. 11). This indicates that the appropriate duration of follow up for radical mastectomy for unclassified mammary cancer is six years rather than five, or seven, or more.

However, the appropriate time lapse necessary for the evaluation of the effectiveness of any treatment for carcinoma of the breast varies with the type of mammary cancer. Persons treated by radical mastectomy for Types I and II neoplasms die so rarely of cancer that they die essentially at "normal" rates from the very time of their treatment and a follow up period of any length would be appropriate for them. While in the case of Type III cancers, four postoperative years must elapse before the women having had them die at a near normal rate. Consequently, a four year follow up period is most appropriate to Type III cancers without axillary metastases. However, the women having Type IV and Type III cancers with nodal metastases die from them with an appreciable frequency up to the seventh postoperative year. Consequently, a seven or eight year follow up period is most appropriate to these types of cancers.

The point at which the rate of dying among a group of persons treated for cancer becomes equal to the rate of dying of the general population of similar age is the point in time which Bliss defines as the point of biological truncation. With probit analysis this point is readily determined because it is at this point that the data no longer fits the probit line that was derived from the rates of dying of the afflicted

group before this. The use of longer and longer periods of follow up in attempts to define the "true cure rate" is not necessary and is superfluous should the follow up period be extended beyond the point of truncation.

Really, any person with a particular cancer who lives longer than the point of truncation without any detectable persistence of tumor may be considered "cured." The fact that a few women harboring cancer may live for decades after radical mastectomy without signs of the cancer does not invalidate this concept because such things happen only rarely. In other words, the point of truncation of the probit line defines the appropriate follow up period with sufficient exactitude to render the use of longer follow ups practically meaningless.

Today there is greater need for better methods of evaluating what we accomplish with treatment of cancer of the breast than ever before. The wounds are being bathed in cancerocidal drugs even for days postoperatively; the cancer therapeutic drugs are being given parenterally before, during, and after mastectomy; irradiational therapy combined with simple mastectomy is being used increasingly to treat mammary cancers; ovariectomy or irradiation of the ovaries is more often being combined with radical mastectomy to treat mammary cancer especially among young women and all this is happening without there having been developed any but rather primitive methods of statistical analysis of the results.

The statistical analysis of the treatment of breast cancer as it has been generally practiced is somewhat analogous to attempting the collective assessment of the poisonous propensity of a pen full of varied kinds and sizes of snakes—including small, medium sized and larger garter snakes, water moccasins, rattle snakes, and king cobras—without any knowledge of the numbers of the various kinds of snakes within the den. Obviously, without knowledge of the proportions of the various kinds of snakes that exist in the pen no real quantitative determination of the effects of pulling the fangs can be made.

Actually, the inclusion of individuals having Types I and II mammary cancers in any sample of breast cancer to be used for the assessment of the relative merits of radical mastectomy or any other manner of treatment would be almost as illogical as including fibromas of the breast in the sample. Only 12 of 101 women who had these types of cancers died within five years after radical mastectomy and only two of these died of cancer of the breast. Actually, even when the Type III cancers without nodal metatstases are included in the sample with the Type I and II the results of radical mastectomy are so good (92% five-year age-corrected survival among 273 cases) that to include this group, which constitutes 37 per cent of the total, in the series treated by such methods as radical mastectomy plus ovariectomy, or radical mastectomy plus cancer chemotherapeutic drugs would

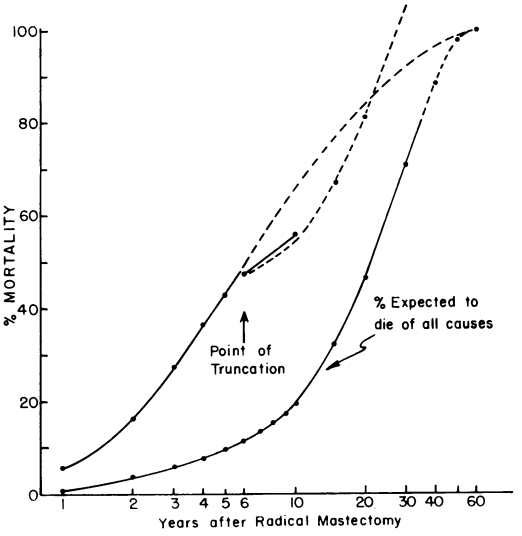

FIG. 11. The line above is the mortality curve for mammary cancer calculated from the probit line $Y = 2.00x + 3.42$. The point of truncation occurring six years after radical mastectomy is where the accumulative mortality rates deviate from this line and follow more closely the increments in the mortality rates of a population sample of similar age without mammary cancer.

TABLE 12. *Mammary Cancer Mortality after Radical Mastectomy. The Mortality Expectancy* Derived from Probits*

Time after Radical Mastectomy (Months)	Combined Series, Barnes Hospital 1950–1955, Ellis Fischel Cancer Hospital, 1940–1950 ($Y = 2.00\,x + 3.42$)
6	.015
12	.057
18	.110
24	.162
30	.218
36	.267
42	.310
48	.353
54	.391
60	.430
66	.460
72	.493

* 1.00 = 100% mortality.

be rather illogical and difficult to defend. To include these cases would merely render the statistics uncertain because one cannot assume that any unclassified sample of mammary cancers would have the same proportions of the 92 per cent five-year surviving group (Types I, II, and III without lymph node metastases) and the 47 per cent five year living group composed of Types III (with lymph nodes metastases) and all of Type IV. In other words, the inclusion of only Type III with lymph node metastases and Type IV with and without metastases would best serve to test the effectiveness of radical mastectomy alone relative to any other method used.

Obviously, we cannot really assess the effectiveness of radical mastectomy alone versus simple mastectomy when combined with irradiation. However, let us examine theoretically the relative merits of radical mastectomy and of simple mastectomy and irradiation. Type III and IV mammary cancers were present in 638 of 739 women. In this group, there were 219 who had no axillary metastases. These are certainly as effectively treated by simple mastectomy and irradiation as by radical mastectomy, and in these the irradiation as well as the axillary dissections were unnecessary. Of the remaining 419 with axillary metastases 242 died within five years. The question is, would more or less have died if these persons had been treated with simple mastectomy followed by irradiation? It is clear that until we will randomly apply radical mastectomy for one individual and simple mastectomy and irradiation for another, all of whom have been demonstrated to have axillary metastases by biopsy before these therapies are applied, the relative merits of these two forms of treatment cannot be assessed certainly. However, from the data we can assess the relative merits of simple and radical mastectomy for the total group of 739 patients. First, simple mastectomy can be reckoned the therapeutic equal of radical mastectomy for the following categories of cases: those persons in whom axillary metastases were absent whether they subsequently died of cancer or not, and those with axillary metastases who died before the point of truncation of the probit line for their particular tumor. Radical mastectomy must be reckoned superior to simple mastectomy for those cases having axillary metastases who lived beyond their truncation limits. Treating these data in this way it was found that the proportion of women with mammary cancer in a consecutive series who might survive as well after simple mastectomy as after radical mastectomy is rather high (750/1,000).

However, simple mastectomy alone is unquestionably biologically inferior to radical mastectomy for the treatment of Types III and IV tumors with axillary metastases, it must leave tumor behind. Consequently, it can be fairly assumed that any individual with axillary metastases treated by simple mastectomy would be likely to die of this residual cancer within the pre-truncation period appropriate to the primary tumor. After radical mastectomy 105 women of 240 who had Type III tumors with axillary metastases were alive at the truncation point of six years, and 49 women of 179

who had Type IV tumors with axillary metastases were alive at the truncation point of six years, a six-year cure rate for these two types with axillary metastases of 154 of 419 or 36 per cent. Undoubtedly, this could not have been achieved by simple mastectomy.

Whether or not irradiation of the axilliary supraclavicular and parasternal zones after simple mastectomy would effect as good control of Types III and IV cancers with axillary metastases as radical dissection of the axilla with removal of the breast cannot be answered by the analysis of this or any other extant data. There is no way of knowing how many of the cases treated by simple mastectomy and irradiation, reported by McWhirter and others,[10-12] had axillary metastases. However, the means of solving this question are now clear and have been discussed previously.

Summary

The survivals of 739 women who had radical mastectomies for mammary cancer were correlated with the cellular patterns of their primary tumors, the frequency of axillary nodal metastases, and the sizes of the primary neoplasms in an attempt to define the phylogenetic characteristics of mammary cancer which need be known before the relative merits of different therapies may be evaluated objectively.

The mortality expectancy (calculated by the probit method) was found to differ according to the biological type (I to IV) of mammary cancer present. Actually, knowledge of the type of mammary cancer proved to be a most important and necessary requisite for the objective evaluation of therapeutic results. Though the clinical stages and sizes of the primary tumors were related to survival, these parameters alone do not insure comparability of different therapeutic samples.

Analysis of the data by the methods of probits permits the estimation of adequate follow up periods for the different types of mammary cancer. The point of truncation of the probit line defines the appropriate follow up period with sufficient exactitude to render longer periods unnecessary.

The data suggest that the proportion of women with mammary cancer in a consecutive series who might survive as well after simple mastectomy as after radical mastectomy is rather high (75%). The likely reason for this is the inclusion in the statistic of Types I and II cancers, and of Types III and IV cancers without nodal

TABLE 13. *Probit Analysis of Mortality from Mammary Cancer*

Treatment	Population Sample Source	Population Sample No.	Biological Type	Probit Y	Slope (b)	Time of 50% Mortality (years)	95 Percent Confidence Limits (years) From	95 Percent Confidence Limits (years) To
None	Greenwood	651	All	$2.83x + 3.92$	2.83 **	2.4	2.2	2.6
Simple Mastectomy	McWhirter	1209*	All	$1.76x + 3.87$	1.76	4.4	4.0	4.8
		739	All	$2.00x + 3.42$	2.00	6.2	5.6	6.8
		101	I & II	$0.83x + 3.26$	0.83	112	23	170
	Barnes and	412	III	$2.04x + 3.26$	2.04	7.1	6.2	8.2
	Ellis Fischel	(240)	III (N+)**	$2.60x + 3.21$	2.60	4.9	4.3	5.5
	State Cancer	(172)	III (N−)	$1.29x + 3.32$	1.29	20.0	12	33
	Hospitals	226	IV	$2.50x + 3.64$	2.50	3.5	3.1	4.0
		(179)	IV (N+)	$2.64x + 3.64$	2.64	3.3	2.8	3.7
		(47)	IV (N−)	$2.07x + 3.68$	2.07	4.3	3.0	6.2

* Corrected to include deaths from intercurrent disease.
** N+ =nodal metastases present; N− =nodal metastases absent.

metastases. Such cases do not constitute an actual test of the effectiveness of radical mastectomy.

The question of the relative effectivesss of radical mastectomy alone and of simple mastectomy when it is combined with irradiational therapy will best be answered by testing these therapeutic methods among persons with Types III and IV mammary cancers in whom axillary nodal metastases have been proven to exist.

References

1. Bliss, C. I. and W. L. Stevens: The Calculation of the Time-Mortality Curve. Ann. Applied Biology, **24**:815, 1937.
2. Boag, J. W.: Maximum Likelihood Estimates of the Proportion of Patients Cured by Cancer Therapy. J. Royal Statistical Soc., **11**:15, 1949.
3. Boag, J. W.: The Presentation and Analysis of the Results of Radiotherapy. Part I. British J. Radiol., **21**:128, 1948.
4. Boag, J. W.: The Presentation and Analysis of the Results of Radiotherapy. Part II Mathematical Theory. British J. Radiol., **21**: 189, 1948.
5. Finney, D. J.: Probit Analysis. London, Cambridge University Press, 1952.
6. Greenwood, M.: The Natural Duration of Cancer Reports on Public Healths and Medical Subjects. No. 33. His Majesty's Stationary Office, 1926.
7. Haagensen, C. D.: Diseases of the Breast. Philadelphia, W. B. Saunders, Co., 1956.
8. Haagensen, C. D.: The Choice of Treatment for Breast Carcinoma: Current Surgical Management. Philadelphia, W. B. Saunders Co., 1960.
9. Hultborn, K. A. and Bo Tornberg: Mammary Carcinoma: The Biologic Character of Mammary Carcinoma Studies in 517 Cases by a New Form of Malignancy Grading. Acta Radiologica Supplementum 196, Stockholm, 1960.
10. Larioschenko, T. G., V. I. Yanishevsky and A. N. Nemyrya: Experiences in the Treatment of the Mammary Gland According to Data of the State P. A. Guertzen Oncological Institute. Kirwigia, **8**:11, 1960.
11. McWhirter, R.: The Value of Simple Mastectomy and Radiotherapy in the Treatment of Cancer of the Breast. Brit. J. Radiol., **21**: 599, 1948.
12. Williams, I. G., R. S. Murley and M. P. Curwen: Cancer of the Female Breast: Conservative and Radical Surgery. British Med. J., **11**:787, 1953.