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Relationship Between Estrogen Receptor Values and Clinical Data in Predicting the Response to Endocrine Therapy for Patients with Advanced Breast Cancer

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Abstract—*Data on* 451 *trials of endocrine therapy in* 366 *patients from* 8 *cities are reported. The relative odds relating the results of the ER assay to the probability of tumor regression following endocrine therapy, when adjusted for hospital, was estimated at* 15.47, *a highly significant result. For these data the dominant site of metastasis was not important in predicting response to endocrine therapy, but hospital, disease free interval, and the site of visceral metastasis were found to increase our ability to predict even when the results of the ER assays were known. The clinical variables analyzed in the report do not allow us to explain entirely why some* 41% *of patients with ER+ tumors failed to regress following endocrine therapy, but in one subgroup of* 71 *patients the regression rate for ER+ tumors was* 78.9%. *The response to a first course of endocrine therapy improved predictions based on the ER assay alone concerning response to a second course of endocrine therapy.*

INTRODUCTION

NUMEROUS reports have shown that assays of breast cancer tissue for estrogen receptors (ER) are useful in predicting response to endocrine therapy [1]. Breast cancers have often been designated as "ER+", "ER−" or "ER±", depending on the concentration of estrogen receptor protein detected in the tumor tissue. In our data only 59% of those patients with ER+ tumors responded favorably to endocrine therapy. It was thus of interest to determine whether clinical information such as the patient's menopausal status, the length of the disease free interval, the dominant site of metastasis, the site of visceral metastasis, and the response to previous endocrine therapy, could be used along with the results of the ER assay to make more precise predictions of response to endocrine therapy and to help explain why not all patients with ER+ tumors respond favorably.

MATERIALS AND METHODS

The data in this report are based on 451 treatment courses in 366 patients. All these patients had an ER assay at some time during their course, although not all were performed by the same method. For this reason, we accepted the investigators' designations of ER+, ER− and ER±, and did not attempt to use quantitative values. For this report we have omitted 12 patients whose tumors were designated ER±. The 366 patients were treated in 8 cities in the United States and in Europe (see footnote). All cases were reviewed by Drs. Mary Sears and George Escher in order that uniform criteria of tumor response

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Participants in this study were as follows: E. Engelsman, C. B. Korsten, Netherlands Cancer Institute, Amsterdam, The Netherlands; J. C. Heuson, G. Leclerq, Institut Jules Bordet, Brussels, Belgium; E. V. Jensen, Ben May Laboratory for Cancer Research, University of Chicago, Chicago, Illinois, U.S.A.; A. Singhakowinta, S. C. Brooks, Wayne State University School of Medicine, Detroit, Michigan, U.S.A.; H. Maass, H. Nowakowski, G. Trams, University of Hamburg, Hamburg, Germany; Hannelore Braunsberg, C. W. Jamieson, St. Mary's Hospital Medical School and St. Thomas' Hospital, London, England; W. S. Fletcher, H. S. Moseley, B. S. Leung, University of Oregon Medical School, Portland, Oregon, U.S.A.; E. D. Savlov, J. L. Wittliff, University of Rochester School of Medicine, Rochester, New York, U.S.A.

could be applied. They used the criteria described in "Estrogen Receptors in Human Breast Cancer" [2] and recently printed in more detail [3]. There were 296 patients who had a single endrocrine treatment, 57 who had two courses, 11 who had three courses, and 2 who had four courses of endocrine therapy. Pertinent data were abstracted from the clinical charts for each of the patients and sent to the Clinical and Diagnostic Trials Section, National Cancer Institute, for statistical analysis.

Since some patients in our study material had more than one ER assay, a patient was treated as ER+ in these analyses if any one of multiple determinations was considered positive. Likewise, for patients who had several evaluable endocrine therapies, the patient will in some parts of the analysis be counted as having a favorable response if any of these treatments led to objective tumor regression. This will be referred to in both tables and text as "overall response".

Sometimes the estrogen receptor determinations were made on the primary tumor (74 cases), but more often they were made on tissue taken from sites of metastases or the source of material was unknown to us. Preliminary analysis showed that the response to treatment of ER+ tumors did not depend on the site of the tissue used for the ER determination (Table 1) nor on the time from diagnosis when the ER determination was performed. For this reason, both these variables have been ignored in the analysis.

The statistical methods used in this report are those of standard contingency table analysis for studying cross-classified data and logistic regression analysis for simultaneously evaluating the effects of several variables on an all-or-none response (here, regression of disease after endocrine therapy). Logistic regression is closely related to ordinary multiple regression vs failure in patients treated for study of all-or-none variables such as tumor regression versus failure in patients treated for advanced cancer. The logit (log odds) of the probability of regression, p_i, for the i^{th} patient, $i = 1, 2, \ldots, n$, is related to the regressor variables by the equation:

$$\ln(p^i/(1-p^i)) = B_0 + B_1X_{i1} + B_2X_{i2} + \ldots + B_kX_{ik}$$

where the X_{ij} represents the values of the j^{th} regressor variable for the i^{th} patient, $j = 0, 1, \ldots, k$, and the B_j are regression coefficients estimated by the method of maximum likelihood. Statistical tests allow us to determine how many regressor variables are needed to predict response and to judge their relative importance.

RESULTS

Summary data concerning the relationship between the estrogen receptor value and response to endocrine therapy for each of the eight hospitals are shown in Table 2. A convenient measure of association for data presented in such 2×2 tables is the odds ratio. An odds is the ratio of the probability of a regression to the probability of failure; an odds ratio is the ratio of two such odds. In this setting if the ER assay provided no information about the probability of tumor regression we expect the odds ratio to be 1.0. Values greater than 1.0 would indicate that patients with ER+ tumors were more likely to respond to endocrine treatment. For the eight hospitals studied in this report, the odds ratios were all greater than 1.0, ranging from 3.82 to 51.0 (the odds ratio in one hospital could not be estimated since there were no

Table 1. Site of ER determination vs % responding by ER result

Source of specimen	Number (% Responding) ER−	Number (% Responding) ER+	Total patients
Primary tumor	37 (5)	37 (59)	74
Lymph node	20 (20)	26 (50)	46
Skin nodule	51 (4)	47 (66)	98
Liver	3 (0)	3 (33)	6
Bone	4 (0)	6 (17)	10
Adrenal gland	3 (33)	9 (55)	12
Other	6 (17)	6 (50)	12
Unknown	60 (15)	48 (67)	108
Total	184 (10)	182 (59)	366

$\chi^2_2 = 9.18$, $P = 0.24$.

Table 2. Estrogen receptor vs overall response by hospital

Hospital location	Response	Estrogen Receptor Negative	Positive	Total	Odds Ratios	Chi-Square	P(R/ER −)†	P(R/ER +)‡	P(R)§
Amsterdam	Failure	46	6	52					
	Regression	9	30	39	25.56	37.16 ($P \ll 0.00001$)	0.16	0.83	0.43
	Total	55	36	91					
Brussels	Failure	14	12	26					
	Regression	1	5	6	5.83	1.42 (N.S.)*	0.07	0.29	0.19
	Total	15	17	32					
Chicago	Failure	31	12	43					
	Regression	1	19	20	49.08	21.97 ($P \ll 0.00001$)	0.03	0.61	0.32
	Total	32	31	63					
Detroit	Failure	15	5	20					
	Regression	1	17	18	51.00	16.00 ($P < 0.00006$)	0.06	0.77	0.47
	Total	16	22	38					
Hamburg	Failure	29	10	39					
	Regression	3	11	14	10.63	9.95 ($P < 0.002$)	0.09	0.52	0.26
	Total	32	21	53					
London	Failure	7	11	18					
	Regression	1	6	7	3.82	0.50 (N.S.)	0.13	0.35	0.28
	Total	8	17	25					
Portland	Failure	12	11	23					
	Regression	3	16	19	5.82	4.52 ($P < 0.05$)	0.20	0.59	0.45
	Total	15	27	42					
Rochester	Failure	11	7	18					
	Regression	0	4	4	∞	2.75 (N.S.)	0.00	0.36	0.18
	Total	11	11	22					
Grand total		184	182	366			0.10	0.59	0.35

Pooled odds ratio = 12.67 ($\chi_1^2 = 94.86$, $P \ll 0.00001$).
Adjusted odds ratio 15.47 ($\chi_1^2 = 100.05$, $P \ll 0.00001$).
*N.S. = Not significant.
†Probability of regression for ER − patients.
‡Probability of regression for ER + patients.
§Probability of regression for all patients, ignoring ER result.

regressions in ER− patients). The significance of a deviation from 1.0 for an odds ratio may be tested by a one-degree of freedom chi-square statistic. For these data, 5 of the 8 hospitals showed a significant association between the ER result and tumor regression; the three hospitals in which the odds ratio was not significant were those with the smallest total numbers of patients.

There are various ways that the data from several centers may be combined. The simplest one is to pool the data ignoring hospitals. This procedure, while intuitively appealing, is not recommended by statisticians because in some circumstances it can lead to serious misinterpretations of the data. Nevertheless, in this instance if we pool the data, we obtain an estimated odds ratio of 12.67 associated with a highly significant chi-square, 94.86 with one degree of freedom. A more proper way to combine the data is to use a procedure such as the Mantel–Haenszel technique [4]. Preliminary to employing this technique, a test should be done to see if the separate odds ratios differ only by chance [5]. The preliminary test was performed yielding a chi-square with 7 degrees of freedom equal to 7.73 ($p=0.36$), indicating that the Mantel–Haenszel procedure for combining data across various centers is appropriate. The summary estimate of the odds ratio by this method is 15.47 associated with a highly significant chi-square with one degree of freedom equal to 100.05 ($P \ll 0.00001$). this latter estimate of the odds ratio may be regarded as adjusted for the different regression rates in the various hospitals. Notice that the overall regression rates in these hospitals vary from 18 to 47%, suggesting that different kinds of patients are seen in the various hospitals. For these data the unadjusted estimate of 12.67 differs somewhat from the adjusted estimate of 15.47, indicating that some confounding occurs by simply pooling the data. The overall response rate for all hospitals combined was 35% (10% for ER− patients and 59% for ER+ patients).

Since hospital location affected the response rates, the distributions of patients by hospital for years post-menopausal, disease free interval, dominant site and visceral site are shown in Tables 3–6. Thirty-one per cent of the patients were either pre-menopausal or within 1 yr post-menopausal, 38% were between 1 and 10 yr post-menopausal and the remaining 30% were more than 10 yr post-menopausal (Table 2). Ignoring the unknowns, highly significant variation among hospitals is present ($\chi^2_{21}=72.3$, $P<0.0001$). Significant variation in the distribution of disease free interval by hospital was also noted (Table 4). Here the unknowns were treated as a separate category ($\chi^2_{21}=33.57$, $P=0.04$). The dominant site of metastasis was about equally divided between the three major sites, that is, soft part, bone, and visceral (Table 5), but significant differences between the hospitals were not detected ($\chi^2_{14}=16.64$, $P=0.28$). Only 113 of the 366 patients (31%) had visceral metastases. About two-thirds occurred in the lung, about one-fourth in the liver, and the rest in other or unknown sites (Table 6). Ignoring other and unknown sites because of the low frequencies, no significant differences between hospitals were detected for the proportions having liver or lung metastases ($\chi^2_7=4.21$, $P=0.76$). The metastases in the 7 patients coded as having "other" sites

Table 3. Distribution of years post-menopause for individual centers

Hospital location	Years post menopause*†					
	<1 and Premenopausal	1–5	6–10	>10	Unknown	Total
Amsterdam	29 (32)	8 (9)	6 (7)	48 (53)	0	91
Brussels	10 (31)	4 (13)	2 (6)	16 (50)	0	32
Chicago	25 (40)	20 (32)	13 (21)	3 (5)	2 (3)	63
Detroit	5 (13)	9 (24)	10 (26)	14 (37)	0	38
Hamburg	19 (36)	13 (25)	10 (19)	11 (21)	0	53
London	8 (32)	9 (36)	6 (24)	2 (8)	0	25
Portland	13 (31)	12 (29)	7 (17)	10 (24)	0	42
Rochester	6 (27)	6 (27)	3 (14)	7 (32)	0	22
Total	115 (31)	81 (22)	57 (16)	111 (30)	2 (1)	366

*Whether natural or artificial.
†Percentages shown in parentheses.

Table 4. Distribution of disease free interval for individual centers

Hospital location	Disease free interval (months)*				
	0–9	10–19	>19	Unknown	Total
Amsterdam	16 (18)	14 (15)	39 (43)	22 (24)	91
Brussels	6 (19)	7 (22)	13 (41)	6 (19)	32
Chicago	12 (19)	14 (22)	19 (30)	18 (29)	63
Detroit	3 (8)	11 (29)	17 (45)	7 (18)	38
Hamburg	9 (17)	15 (28)	22 (42)	7 (13)	53
London	8 (32)	7 (28)	5 (20)	5 (20)	25
Portland	9 (21)	13 (31)	18 (43)	2 (5)	42
Rochester	10 (46)	4 (18)	5 (23)	3 (14)	22
Total	73 (20)	85 (23)	138 (38)	70 (19)	366

*Percentages shown in parentheses.

Table 5. Distribution of dominant site for individual centers

Hospital location	Dominant site*			
	Soft tissue	Bone	Visceral	Total
Amsterdam	36 (40)	32 (35)	23 (25)	91
Brussels	8 (25)	13 (41)	11 (34)	32
Chicago	25 (40)	23 (37)	15 (24)	63
Detroit	15 (40)	13 (34)	10 (26)	38
Hamburg	16 (30)	18 (34)	19 (36)	53
London	7 (28)	12 (48)	6 (24)	25
Portland	10 (24)	13 (31)	19 (45)	42
Rochester	9 (41)	3 (14)	10 (46)	22
Total	126 (34)	127 (35)	113 (31)	366

*Percentages shown in parentheses.

Table 6. Distribution of visceral sites by individual centers

Hospital location	Visceral Site*				
	Liver	Lung	Other	Unknown	Total
Amsterdam	6 (26)	14 (61)	0	3 (13)	23
Brussels	3 (27)	8 (73)	0	0	11
Chicago	4 (27)	8 (53)	3 (20)	0	15
Detroit	3 (30)	6 (60)	1 (10)	0	10
Hamburg	3 (16)	15 (79)	1 (5)	0	19
London	1 (17)	4 (67)	1 (17)	0	6
Portland	8 (42)	10 (53)	1 (5)	0	19
Rochester	2 (20)	8 (80)	0	0	10
Total	30 (27)	73 (65)	7 (6)	3 (3)	113

*Percentages shown in parentheses

were designated as "central nervous system", brain, "intra-abdominal" and gastrointestinal tract.

The relationship of these four clinical variables to the response to endocrine treatment is shown in Table 7. For menopausal status the probability of tumor regression increased with the number of years since menopause; there was little difference between tumor regression rates for pre-menopausal women or women in

Table 7. Relationship of clinical information to percentage failure or regression based on overall responses

	Failure number (%)	Regression number (%)	Total number
Menopausal status			
Pre-menopausal or			
<1 yr post menopausal	75 (65)	40 (35)	116
1–5 yr post menopausal	57 (70)	24 (30)	81
6–10 yr post menopausal	40 (70)	17 (30)	57
>10 yr post menopausal	66 (59)	45 (41)	111
Unknown menopausal status	1 (50)	1 (50)	2
Disease free interval			
0–9 months	61 (84)	12 (16)	73
10–19 months	60 (71)	25 (29)	85
>19 months	80 (58)	58 (42)	138
Unknown	38 (54)	32 (46)	70
Dominant site			
Soft part	88 (70)	38 (30)	126
Bone	78 (61)	49 (39)	127
Visceral	73 (65)	40 (35)	113
Visceral Site			
Liver	23 (77)	7 (23)	30
Lung	43 (59)	30 (41)	73
Other	6 (86)	1 (14)	7
Unknown	1 (33)	2 (67)	3
No visceral site	166 (66)	87 (34)	253
All patients	239 (65)	127 (35)	366

the first 10 yr post-menopause, but for women more than 10 yr post-menopausal there was an increase in regression rate. The regression rate was more markedly affected by the length of the disease free interval, being greater the longer the interval. For this variable no data were available for an appreciable number (19%) of patients. In our analyses unknown disease free interval was combined with >19 months since tumor regression rates were similar in the two categories. The dominant site of metastasis did not show any relationship to regression rate in these data. However, for women with visceral metastases regression rates were lower for patients with dire sites of metastasis, that is, liver or other (see above).

The treatments used in the various hospitals differed markedly (Table 8). Estrogens were the most common form of treatment, followed in frequency by castration and adrenalectomy. Androgens and anti-estrogens were also fairly common, but only 18 patients were treated by hypophysectomy. Despite this variety of forms of endocrine treatment, the regression rates for ER− and ER+ patients showed surprising consistency (Table 9). If we confine our attention to categories in which there are at least 10 patients, we notice that for ER− tumors the regression rates vary from 7 to 19%, while for the ER+ tumors the regression rates vary from 38 to 70%. The rates for all treatment courses combined are 9% for ER− tumors and 51% for ER+ tumors, comparing closely to the regression rates for overall response (Table 2), 10 and 59% respectively for ER− and ER+ tumors.

The relationship between overall response, ER assay, and the other clinical variable was investigated using the logistic regression model. Variables were treated as follows: ER− =0, ER+ =1; hospitals with low regression rates (Brussels and Rochester)=0, hospitals with medium regression rates (Chicago, Hamburg, London)=2, hospitals with high regression rates (Amsterdam, Detroit, Portland)=5; disease free interval less than 10 months=0, disease free interval greater than or equal to 10 months or unknown=1; dire visceral site of metastasis (liver and other)=0, not dire sites (lung, unknown or no visceral

Table 8. Treatments used by individual centers*

Treatment	Hospital location								All hospitals
	Amsterdam	Brussels	Chicago	Detroit	Hamburg	London	Portland	Rochester	
Adrenalectomy	0	10	17	8	0	3	34	5	77
Castration	30	8	22	5	18	5	3	5	96
Hypophysectomy	0	0	10	1	5	1	1	0	18
Androgens	12	2	11	7	8	8	0	6	54
Estrogens	36	10	11	26	15	8	1	12	119
Anti-estrogens	19	15	4	0	9	0	0	0	47
Andrenalectomy and castration	0	0	15	1	0	2	4	0	22
Other	0	0	11	0	2	3	0	2	18
All treatments	97	45	101	48	57	30	43	30	451

*Each treatment course is entered separately when patients had more than one treatment.

sites) = 1. The variables used in this model are those suggested by the analysis in Table 7 and thus the dominant site was not included. Menopausal status was initially included but statistical tests showed that it was not needed in the equation.

With this system of coding, all 4 regressor variables were significant in predicting tumor response, but ER was easily the most important, followed in order by hospital, visceral site, and disease free interval. The predicted percentage regressing based on this model agreed quite well with the observed percentage regressing for the cells containing 10 or more patients (Table 10). When these predicted percentages were multiplied by the number of patients in each category, the predicted number regressing disagreed from the observed number regressing by 2 in only 1 category, by 1 in 12 categories, and agreed exactly with the observed number in 11 categories. Note that for both ER− and ER+ patients a gradation of probability of tumor regression can be observed depending on the clinical data and that for categories containing at least 10 patients the observed tumor regression rates for ER− patients varied from 5.0 to 19.6% while for ER+ patients the rates varied from 25.0 to 78.9%.

Before the advent of estrogen receptor measurements the response to previous endocrine therapy was used to predict response to a second course of endocrine therapy. For these data, the response to the first and second treatment was the same in 72% of the cases (Table 11). A chi-square test of independence of the two responses showed that the first response is useful in predicting the second response ($\chi_1^2 = 3.45$, $P = 0.032$, one-tailed), but the ER assay was even more highly associated with second response ($\chi^2 = 5.05$, $P = 0.012$, one-tailed). When both responses to the first course of endocrine therapy and the ER result were used as variables in a logistic regression analysis to predict response to second treatment, we found that the ER assay was a more powerful predictor than the first response, but the two variables are strongly correlated. Fifty per cent of patients who had ER+ tumors which regressed after a first course of endocrine therapy also showed regression after a second course, but only 30% of patients with ER+ tumors showed regression after a second course of endocrine therapy if they showed no regression following the first course.

DISCUSSION

This analysis shows that certain clinical variables increase our ability to predict response to endocrine therapy when added to that provided by the ER assay. However, for predicting response to endocrine therapy, the ER test was easily the most important variable. The clinical variables available in this analysis permitted only a partial explanation of the failure of some patients with ER+ tumors to respond to endocrine therapy. Note that in the category with all favourable clini-

Table 9. Relationship between treatment, estrogen receptor status and response*

Treatment	ER − Tumors Number of Regressions divided by total (%)	ER + Tumors Number of regressions divided by total (%)	All Tumors Number of regressions divided by total (%)
Adrenalectomy	3/27 (19)	19/50 (38)	22/77 (29)
Castration	4/60 (7)	22/36 (61)	26/96 (27)
Hypophysectomy	0/9 (0)	2/9 (22)	2/18 (11)
Total	7/96 (11)	43/95 (45)	50/191 (26)
Androgen	2/26 (8)	12/28 (43)	14/54 (26)
Estrogen	5/58 (9)	35/61 (57)	40/119 (34)
Anti-estrogen	4/26 (15)	9/21 (43)	13/47 (28)
Total	11/110 (10)	56/110 (51)	67/220 (30)
Other	0/2 (0)	0/1 (0)	0/3 (0)
Combinations of above	1/10 (10)	19/27 (70)	20/37 (54)
Total	1/12 (8)	19/28 (68)	20/40 (50)
All treatments	19/218 (9)	118/233 (51)	137/451 (30)

*Each treatment course is entered separately when patient had more than one treatment.

cal variables, the overall response rate was 79 vs 59% for all ER + patients. When predicting the response to a second course of endocrine therapy, the response to the first course of endocrine therapy improved predictions based on the ER assay alone.

Perhaps the most disappointing aspect of this analysis from the point of view of predicting response to endocrine therapy is that a variable had to be included to indicate whether the patient was treated at a hospital with a high, medium, or low regression rate. Various explanations could be put forth to explain the differences in regression rates between the hospitals. First of all the treatments used differed markedly from hospital to hospital. However, the data in Table 9 suggest that differences in the treatments used are insufficient to explain the differences in regression rates since the regression rates for ER − and ER + tumors are quite similar regardless of the particular form of endocrine manipulation employed. We also noted that hospitals differed with respect to some characteristics of the patients, specifically with regard to menopausal status, length of disease free intervals, but not with respect to proportions having liver or lung metastasis. Despite these differences, the fact that both length of disease free interval and site of visceral metastasis were retained in the regression equation along with the variable for hospital indicates that these variables are required in addition to the hospital variable and therefore, they are not sufficient to explain the differences observed in the hospitals.

Some other explanations come to mind. In some hospitals patients were treated with chemotherapy in addition to hormonal manipulations, but these patients were excluded from this study, even if they responded, since they were not evaluable from the point of view of attributing any observed tumor regression to hormonal treatment. Possibly the exclusion of these patients has resulted in selective biases in some hospitals, making their regression rates appear either lower or higher than they otherwise would have been, depending upon which kinds of patients were treated with chemotherapy. Another possibility is that the definition of ER − and ER + tumors varied among hospitals. However, one can calculate from the data in Table 2 that the percentage ER + varied only between 40 and 68% (the average was 53%) and there appeared to be no relationship between the percentage ER + and whether the hospitals' overall regression rates were categorized as high, medium, or low. Of course the percentage ER + is really not very meaningful in absence of an outside standard. Despite these observations, what is truly remarkable is that

Table 10. *Observed and predicted response rates for various categories of patients*

Estrogen receptor	Hospital	Visceral site	Disease free internal	Number of patients	Observed number regressing	Predicted number regressing*	Observed % regressing†	Predicted % regressing*
−	low	dire	< 10 months	1	0	0		0.7
−	low	dire	≥ 10 months	0	0	0		1.4
−	low	not dire	< 10 months	9	0	0		2.1
−	low	not dire	≥ 10 months	16	1	1	6.3	4.4
−	medium	dire	< 10 months	2	0	0		1.3
−	medium	dire	≥ 10 months	4	0	0		2.7
−	medium	not dire	< 10 months	15	2	1	13.3	3.9
−	medium	not dire	≥ 10 months	51	3	4	5.9	8.1
−	high	dire	< 10 months	2	1	0		3.4
−	high	dire	≥ 10 months	8	0	1		7.0
−	high	not dire	< 10 months	20	1	2	5.0	9.8
−	high	not dire	≥ 10 months	56	11	11	19.6	19.1
+	low	dire	< 10 months	2	0	0		9.2
+	low	dire	≥ 10 months	2	1	0		18.1
+	low	not dire	< 10 months	4	1	1		24.2
+	low	not dire	≥ 10 months	20	7	8	35.0	40.9
+	medium	dire	< 10 months	0	0	0		16.4
+	medium	dire	≥ 10 months	7	3	2		29.8
+	medium	not dire	< 10 months	12	3	5	25.0	38.0
+	medium	not dire	≥ 10 months	50	30	29	60.0	57.1
+	high	dire	< 10 months	1	0	0		34.4
+	high	dire	≥ 10 months	8	3	4		53.2
+	high	not dire	< 10 months	5	4	3		62.2
+	high	not dire	≥ 10 months	71	56	55	78.9	78.1
				366	127	127	34.7	

*Based on the logic regression model. The prediction equation was $\ln[p/(1-p)] = -5.0 + 2.72\ X_1 + 0.33\ X_2 + 1.14\ X_3 + 0.77\ X_4$ where X_1 = ER status, X_2 = hospital category, X_3 = visceral metastasis, and X_4 = disease free interval. See text for description of how the variables were coded. Predicted number of regressions was rounded to the nearest integer. Predicted % regressing is the solution for p in the prediction equation × 100.
†Observed % regressing was not calculated if the number of patients was < 10.

in all 8 centers there is evidence that ER+ tumors are more likely to respond to hormonal therapy than ER− ones. The test for heterogeneity of this effect did not reveal significant variation among hospitals. The variation in overall regression rates by the hospitals most probably reflects selection of patients too subtle to be accounted for by the variables measured in this study.

The observation that site of visceral metastasis was important in predicting response to hormonal therapy is supported by a recent report of Puga *et al.* [6] who confirmed the findings of others that lesions in liver and brain were associated with a poor prognosis whereas metastatic diseases of bone, lung and lymph nodes more often responded to oophorectomy. Estrogen receptors were not measured

Table 11. Relationship between ER assay and responses to first and second courses of endocrine therapy

ER result	Response to first course of treatment	Number of patients	Number (%) of regressions after second course of treatment
−	failure	27	3 (11.1%)
−	regression	1	0 (0.0%)
+	failure	23	7 (30.4%)
+	regression	16	8 (50.0%)
All patients		67	18 (26.9%)

in their study since it was based on patients treated between 1960 and 1964.

In the last few years an increasing number of articles has appeared concerning estrogen receptor measurements in patients with breast cancer [7–13], all of which indicate that tumor regression following hormonal therapy is more common in ER+ patients. Additional areas of concern are the details of measurement of estrogen receptor protein, the relationship between the measurements made on the primary tumor and those made on recurrent disease, the possible significance of the absolute amount of estrogen receptor protein present, and the relationship of the estrogen receptor assay to other variables known to affect the response to therapy of survival. Heuson *et al.* [14] analysed 34 cases (some of which are included in this report) using the quantitative ER value. Among 12 variables of known prognostic value the estrogen receptor concentration was the most significant in relation to therapeutic, in agreement with the findings presented here. In addition they found that the probability of tumor regression was related to the presence of bone involvement and age. Their method of analysis was the same as that used here, the logistic regression model.

One of the more exciting new developments in the field of hormone receptors concerns the study of progesterone receptors (PgR). McGuire *et al.* [15] have recently summarized work in this area. The central idea in this work is that PgR can be used as a marker for estrogen action in breast tumors. In an analysis of 521 cases they found that PgR were present in 74% of 392 ER+ specimens, but in ER− specimens, they were present in only 9% of 129 specimens. It has been suggested that the failure of ER+ patients to respond to endocrine therapy might be explained by the absence of PgR. Experiments have been performed which indicate that estrogen is required for PgR synthesis [15]. Thus estrogen may not be biologically active in ER+ but PgR− tumors. Other workers [16–18] have measured both PgR and ER and their findings are in general in agreement with those of McGuire *et al.* that PgR are much more often found in ER+ tumors than in ER− ones. McGuire *et al.* also present data on response to endocrine therapy in 54 patients as a function of the two hormone receptors. Thirteen of 16 patients with ER+, PgR+ metastatic tumors responded favorably to endocrine therapy, compared to only 7 of 17 patients with ER+, PgR− tumors. In the other studies insufficient time has elapsed to obtain the clinical correlations; however, measurement of PgR along with ER promises to provide increased accuracy in predicting responses to endocrine therapy.

Other theories besides the use of PgR as a marker for estrogen activity have been proposed to explain why not all ER+ tumors regress after endocrine therapy. One of these is that some tumors may have cytoplasmic ER but may lack nuclear ER. Laing *et al.* [19] have studied 209 tumors for both nuclear and cytoplasmic receptors and found that 36 of 105 tumors (34%) positive for cytoplasmic receptors lacked nuclear receptors. Their clinical correlations were based on only 32 patients, but 18 of 22 patients (82%) positive for both cytoplasmic and nuclear receptors responded to endocrine therapy.

Another theory used to explain the failure of some ER+ tumors to regress following endocrine therapy is that tumors may be composed of several populations of cells, some of which may be hormone dependent and others which are not. Leclercq and Heuson [20] in a review of the therapeutic significance of hormone receptors in breast cancer have discussed this multiclonal theory and suggest that preliminary data support this idea.

Wittliff *et al.* [13] have proposed yet another explanation of why not all ER+ tumors

respond to endocrine therapy. Since the sucrose gradiant method reveals both 8S and 4S species of ER, they postulate that the physiologically active ER is composed of subunits which must be synthesized and combine properly for estrogen to enter the nucleus and affect cell growth. They believe that ER+ but hormone unresponsive tumors may contain only a single ER subunit of the 4S species which would nevertheless be classified as ER+ by the dextran-coated charcoal assay. They noted no response to endocrine therapy among 9 ER+ patients who had only the 4S species present and recommend that separation procedures such as sucrose gradient centrifugation be used until possible differences in the molecular behavior of estrogen receptors in human breast carcinomas have been elucidated.

Whether clinical variables such as those identified by Heuson *et al.* [14] and by us in this study will continue to be important predictors of response of breast cancer to hormone therapy as we learn more about the cellular biology of hormones is uncertain. Only future studies can answer that question.

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