Europ. J. Cancer Vol. 16, pp. 323–331
Pergamon Press Ltd. 1980 Printed in Great Britain

Estrogen Receptor Status: an Important Variable in Predicting Response to Endocrine Therapy in Metastatic Breast Cancer

JOSEPH C. ALLEGRA,* MARC E. LIPPMAN,* E. BRAD THOMPSON,† RICHARD SIMON,‡ AUDREY BARLOCK,* LINDA GREEN,§ KAREN K. HUFF,* HOAN MY T. DO,* SUSAN C. AITKEN* and ROBERT WARREN*

*Medicine Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD 20014, U.S.A.
†Laboratory of Biochemistry, National Cancer Institute, National Institutes of Health, Bethesda, MD 20014, U.S.A.
‡Biometrics Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD 20014, U.S.A.
§Department of Oncology, Howard University, Washington, D.C., U.S.A.

Abstract—*The influence of estrogen receptor status on response rate to endocrine therapy in 85 patients with metastatic breast cancer was determined in a retrospective study. The specific purpose of this study was to assess the role of estrogen receptor determinations in the light of a host of clinical variables known or suspected to influence response rates to endocrine therapy. Thirty-four of 52 patients whose tumors contained significant amounts of estrogen receptor (>10 fmole/mg cytoplasmic protein) had objective responses to endocrine therapy while only 3/33 patients whose tumors did not possess estrogen receptor (<10 fmole/mg cytoplasmic protein) responded (P <0.0001). A quantitative relationship was found between the amount of estrogen receptor and response rate. The quantity of estrogen receptor was not associated with the duration of response. The predictive value of the estrogen receptor assay was not associated with the receptor dissociation constant. Prior treatment with endocrine or chemotherapy did not diminish the ability of estrogen receptor determinations to predict response to subsequent endocrine therapy. Response rate in estrogen receptor positive tumors was not affected by extent of disease, site of involvement with metastatic tumor, or prior therapy. We conclude that these negative prognostic factors are less important in predicting response to endocrine therapy than estrogen receptor values.*

INTRODUCTION

ESTROGEN receptor positivity (>10 fmole/mg cytoplasmic protein) is associated with approximately 50% of breast tumor specimens [1]. The presence of estrogen receptor in a tumor specimen is associated with a response rate of about 60% to endocrine therapy while its absence greatly decreases the likelihood of response to endocrine therapy [1, 2].

The present study describes response rate to endocrine therapy as a function of estrogen receptor positivity or negativity in a large series of patients. We show a quantitative relationship between the amount of estrogen receptor and response rate. Furthermore this report is concerned with a detailed analysis of the association between estrogen receptor and a variety of clinical, pathological, and biochemical variables including response rate as a function of extent of disease, sites of involvement with metastatic tumor, the receptor dissociation constant, and the effect of prior chemotherapy or endocrine therapy. This is of particular importance in that while the correlation between the presence of estrogen receptor and objective response to endocrine therapy is well established, there is little information available which explores the usefulness of this test in the context of other clinical variables [1]. We will show that estrogen receptor positivity is an important variable in predicting response to endocrine therapy.

Accepted 8 May 1979.
Address all correspondence to: Dr. Lippman 10/6B02, Medicine Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD 20014, U.S.A.

MATERIALS AND METHODS

Receptor assays

Biopsies of metastatic or inoperable localized breast cancer were trimmed of excess fat

and non-tumorous tissue and divided with a portion submitted for confirming pathology in all cases. Samples for estrogen receptor assay were kept on ice and then frozen in liquid nitrogen within 20 min. Estrogen receptor assays were performed as previously described [3]. When sufficient sample permitted, Scatchard analyses were performed to quantify the number of binding sites; otherwise assays were performed in duplicate at one or two concentrations of estradiol chosen to exceed several times the expected equilibrium dissociation constant. Scatchard analyses were performed at a minimum of four concentrations of steroid and none were accepted as consistent with high affinity binding unless linear correlation coefficients in excess of 0.9 were obtained. Data were analyzed using computer assisted methods [4]. A positive estrogen receptor assay was taken to be equal to or greater than 10 fmole of [^{3}H] estradiol binding per mg of cytoplasmic protein. This value was selected arbitrarily before analysis of results was begun. No adjustment of this value for menopausal status was used.

Patients

Patients with metastatic or surgically unresectable primary breast cancer who had estrogen receptor assays performed on a specimen obtained *immediately prior* to the institution of an endocrine therapy regimen were included in this study. There were 85 patients in this category and all were evaluable. In all cases, assessment of response was performed using standardized response criteria [5]. In brief, complete response required the disappearance of all measurable disease including healing of all bone lesions and a return of the patient to a premorbid performance status. Partial response required a shrinkage of at least 50% in all measurable disease. Though a given lesion might not regress to this extent, regression averaged over all lesions had to be equal or greater than 50%. No new lesions could appear and no growth could be observed in a pre-existent lesion. For purposes of this study, no patient was classified as partial response unless improvement was maintained for 2 months or more. Only patients with complete or partial responses are termed objective responders. Any patient not achieving this degree of improvement (at least 50% tumor shrinkage) was termed a non-responder. These criteria differ from the UICC criteria [6] which define a 'no-change' group. In our criteria stable disease would be defined as a failure. All patient records were examined and assessed by individuals (A.B., J.A., R.W., L.G.) unaware of estrogen receptor results. Ninety-five additional patients in whom Scatchard analyses were prepared on estrogen receptor binding studies (but in whom endocrine trials were not conducted) are included in the analysis of binding affinity.

Statistical analyses

Comparisons of proportions were performed by the contingency chi-square test with continuity correction. Comparison of continuous or ordered polychotomous distributions was performed by the Wilcoxon rank–sum test adjusted for ties [7]. This latter test requires no distributional assumptions of the data, as would a *t*-test. All significance levels correspond to two-sided statistical tests.

RESULTS

All 85 patients were considered evaluable in this study. To be evaluable a biopsy and an adequate estrogen receptor assay performed immediately prior to therapy combined with an endocrine therapy trial were required. Some characteristics of these patients are shown in Table 1. The estrogen receptor positive and negative groups are essentially identical with respect to age, menopausal status, Karnofsky performance index, disease free interval, number of sites involved with metastatic tumor and prior therapy. It is important to note that both groups of patients have received considerable amounts of prior therapy with greater than 50% of patients receiving either prior endocrine or chemotherapy. The mean estrogen receptor value expressed as fmole/mg of cytoplasmic protein is 80.6 for the estrogen receptor positive patients and 1.4 for the estrogen receptor negative group.

Sites of involvement by metastatic breast cancer for estrogen receptor positive and negative patients are shown in Table 2. Estrogen receptor analysis was not performed on every site of involvement in a given patient but tissue was obtained from the most surgically accessable site. Frequency of involvement for all sites is similar; however, it should be noted that in some groups the numbers of patients are small.

Treatment regimens for receptor positive and negative patients are shown in Table 3. A wide variety of endocrine therapies were employed in both groups. The proportion of

Table 1. Characteristics of the patients treated with endocrine therapy as a function of estrogen receptor status

	Estrogen receptor positive	Estrogen receptor negative
No. of patients	52	33
Mean estrogen receptor (fmole/mg cytoplasmic protein)	80.6	1.4
Age (mean ± S.E.M.)	49 ± 7	52 ± 7
Menopausal status		
Pre	25%	24%
Post	75%	76%
Karnofsky index (mean ± S.E.M.)	91 ± 7	85 ± 9
Disease free interval [median (months)]	18	14
No. of sites involved		
1	13 (25%)	7 (21%)
2	16 (31%)	7 (21%)
≧3	23 (44%)	19 (58%)
Prior therapy		
Endocrine	15 (28%)	6 (18%)
Chemotherapy	21 (40%)	19 (57%)
Total	27 (51%)	21 (63%)

Table 2. Sites of involvement by metastatic breast cancer as a function of estrogen receptor status

	Estrogen receptor positive	Estrogen receptor negative	*P* value (ER + vs ER −)
Skin	36/52 (69%)	20/33 (60%)	>0.1
Soft tissue	19/52 (36%)	14/33 (42%)	>0.1
Node	21/52 (40%)	14/33 (42%)	>0.1
Lung	16/52 (30%)	11/33 (33%)	>0.1
Pleura	1/52 (2%)	6/33 (18%)	>0.1
Ascites	0/52 (0%)	4/33 (12%)	>0.1
Brain	1/52 (2%)	1/33 (3%)	>0.1
Liver	9/52 (17%)	10/33 (30%)	>0.1
Bone	30/52 (57%)	19/33 (57%)	>0.1
Bone marrow	6/52 (11%)	6/33 (18%)	>0.1

patients in each group receiving a specific therapy was similar and any given therapy was administered equivalently to estrogen receptor positive and negative patients.

The response rate to endocrine therapy as a function of estrogen receptor values is shown in Fig. 1. Overall, 34/52 patients (65%) whose tumors were estrogen receptor positive achieved an objective response compared to 3/33 patients (9%) in the estrogen receptor negative group ($P<0.0001$). As the amount of estrogen receptor increases, the likelihood of response also appears to increase. This quantitative relationship between the amount of estrogen receptor and response rate is shown in greater detail in Table 4. The response rate between 0 and 10 fmole (estrogen receptor negative group) is only 9%. This increases to 30% between 10 and 20 fmole. Between 20 and 50 fmole, 63% of patients have an objective response and 77% of patients whose tumors contained greater than 50 fmole of estrogen receptor per mg of cytoplasmic protein responded. Also, in the estrogen receptor positive group, the distribution of estrogen receptor values for responders was significantly different than for non-responders ($P<0.05$).

Since response rate to endocrine therapy was associated with the quantitative amount

Table 3. Endocrine therapy employed in evaluating response as a function of estrogen receptor status

Therapy	Estrogen receptor positive (N=52)	Estrogen receptor negative (N=33)
Estrogen*	10 (19%)	4 (12%)
Tamoxifen†	19 (37%)	7 (21%)
Halotestin‡	1 (2%)	2 (6%)
Tamoxifen and halotestin§	7 (13%)	7 (21%)
Medical adrenalectomy‖	0 (0%)	1 (3%)
Tamoxifen and medical adrenalectomy¶	2 (4%)	4 (12%)
Surgical adrenalectomy	3 (6%)	4 (12%)
Oophorectomy	10 (19%)	4 (12%)

*Diethylstilboestrol 5 mg p.o., t.i.d.
†Tamoxifen 2–100 mg/m^2 p.o., b.i.d.
‡Halotestin 7 mg/m^2 p.o., b.i.d.
§Tamoxifen 2–100 mg/m^2 p.o., b.i.d. plus halotestin 7 mg/m^2 p.o., b.i.d.
‖Aminoglutethemide 500 p.o., q.i.d. plus hydrocortisone 10 mg p.o., q.i.d.
¶Tamoxifen 10 mg/m^2 p.o., b.i.d. plus aminoglutethemide 500 mg p.o., q.i.d. plus hydrocortisone 10 mg p.o., q.i.d.

Table 4. Objective response rate to endocrine therapy as a function of the amount of estrogen receptor

Estrogen receptor (fmole/mg cytoplasmic protein)	Response rate			
$0 \leqq ER < 10$	3/33 (9%)	$P > 0.05$	$P < 0.001$	$P < 0.00001$
$10 \leqq ER \leqq 20$	3/10 (30%)			
$20 < ER < 50$	7/11 (63%)			
$ER \geqq 50$	24/31 (77%)			

of estrogen receptor, we next examined the possibility of an association between the amount of receptor and response duration. This is illustrated in Fig. 2. In this chart the percentage of patients in remission is plotted vs the duration of remission. The patients are divided into 2 groups. One group contains all patients who achieved a remission and had greater than 50 fmole of estrogen receptor and the other group is composed of patients with less than 50 fmole. Because patients with greater than 50 fmole of estrogen receptor had the highest response rate, the 50 fmole level was used to separate the patients into 2 groups for illustration only. Statistical analysis, however, used the individual receptor concentrations. There is no significant correlation between duration of remission and the amount of estrogen receptor.

One criterion sometimes employed to ensure that radiolabeled binding be to estrogen receptor, is that the binding affinity for the putative receptor be higher than some arbitrary cutoff. Figure 3 lists estrogen receptor values as a function of the receptor dissociation constant for a series of 116 patients (21 of whom had endocrine therapy trials and are included in the present study). Seventy-two percent of patients had dissociation constants for [^{3}H] 17β-estradiol which were less than 2 nM. There were some patients with considerably higher values. As shown, there is no significant association between the amount of estrogen receptor and the receptor dissociation constant.

The relationship between binding affinity of the receptor and response rate was next examined. We expected that patients with larger binding constants would be less likely to respond. As seen in Fig. 4, there was a large range of dissociation constants among both responder and non-responders in the estrogen receptor positive group. Of note is the fact that two patients with large dissociation con-

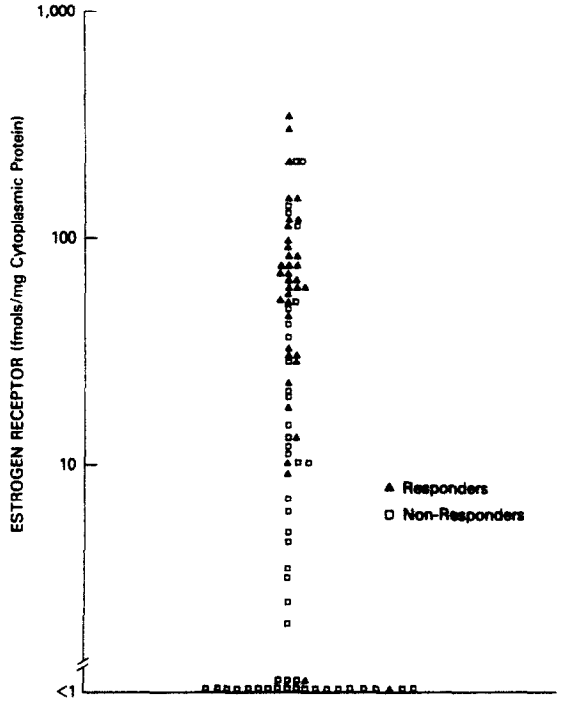

Fig. 1. Objective response rate to endocrine therapy as a function of estrogen receptor status. Objective response is the sum of complete and partial response. ▲ = Responders; □ = non-responders.

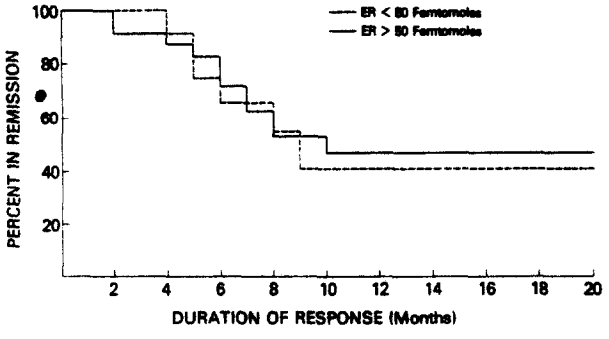

Fig. 2. Duration of response to endocrine therapy as a function of the amount of estrogen receptor. (———) E.R. > 50 fmole; (- - -) E.R. < 50 fmole. Objective response is the sum of complete and partial response.

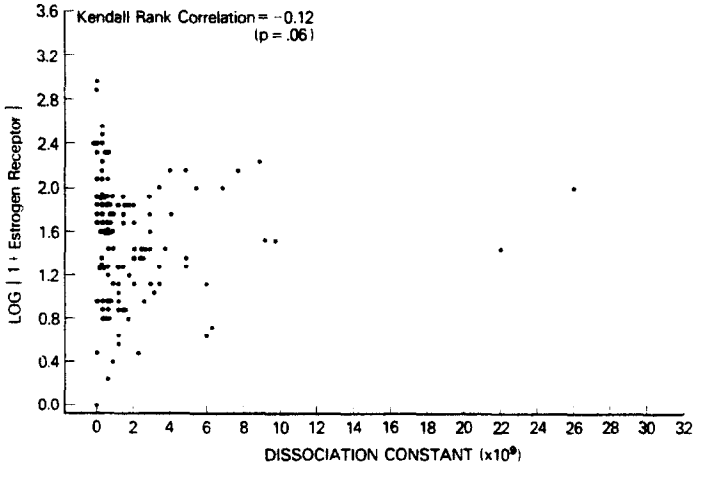

Fig. 3. Estrogen receptor values as a function of the receptor dissociation constant.

stants (10 and 25 nM) responded to endocrine therapy. This is a surprising result. Clearly there must be either a broader range of binding affinities for true estrogen receptor than heretofore suspected, or unappreciated methodologic variables may confound the value of dissociation constant determinations.

The real value of estrogen receptor determinations lies in their ability to predict response independently of clinical variables renown to influence response rate. Responses to endocrine therapy as a function of estrogen receptor are assessed by the site of metastasis in Table 5. While some sites are involved in insufficient numbers of patients for valid statistical analysis, in general, metastatic tumors are more likely to respond to endocrine therapy regardless of disease site in patients whose tumors are estrogen receptor positive. Although not all of these sites were biopsied, it appears that the estrogen receptor value at any site predicts, with a high degree of probability, response at other sites of involvement. The high rate of response of liver and lung disease in estrogen receptor positive patients is particularly noteworthy. In receptor positive patients, bone marrow, bone, lung, and liver respond as often as skin and soft tissue disease.

Responses in patients with or without visceral (lung and liver) involvement are summarized in Table 6. Patients whose tumors are estrogen receptor positive responded to endocrine therapy at a very high rate, regardless of visceral involvement with tumor (61 and 64%). Also, patients with visceral involvement had a somewhat lower percentage of estrogen receptor positive tumors compared to patients without visceral metastasis (53 vs 69%). These data imply that the lower response rates of these sites are more likely due

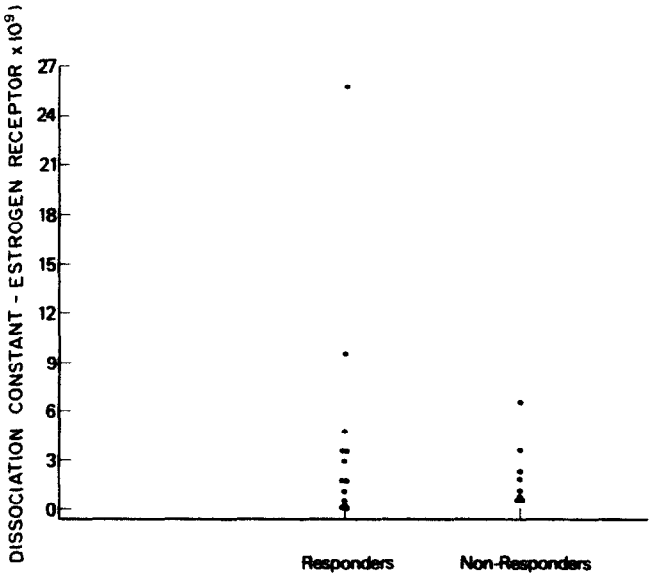

Fig. 4. The receptor dissociation constant in patients treated with endocrine therapy as a function of response. All patients are estrogen receptor positive.

Table 5. Objective response rate to endocrine therapy as a function of site of involvement and estrogen receptor status

	Estrogen receptor positive	Estrogen receptor negative	*P* value (ER + vs ER −)
Skin	19/36 (52%)	1/20 (5%)	<0.01
Soft tissue	11/19 (57%)	1/14 (7%)	<0.01
Node	13/21 (61%)	0/14 (0%)	<0.01
Lung	10/16 (62%)	2/11 (18%)	=0.06
Pleura	0/1 (0%)	0/6 (0%)	—
Ascites	—	0/4 (0%)	—
Brain	0/1 (0%)	0/1 (0%)	—
Liver	5/9 (55%)	0/10 (0%)	<0.05
Bone	15/30 (50%)	2/19 (10%)	<0.05
Bone marrow	4/6 (67%)	0/6 (0%)	=0.06

Table 6. Objective response rate to endocrine therapy as a function of visceral disease and estrogen receptor status

	Visceral disease	Without visceral disease
Estrogen receptor positive	13/21 (61%)	20/31 (64%)
Estrogen receptor negative	2/19 (10%)	1/14 (7%)
	$P<0.01$	$P<0.01$

to more frequent involvement by estrogen receptor negative tumors, than to intrinsic hormone unresponsiveness.

Table 7 summarizes the objective response rate to endocrine therapy as a function of number of sites involved with metastatic disease and estrogen receptor status. Patients whose tumors are estrogen receptor positive respond to endocrine therapy at a very high rate regardless of extent of disease.

Finally, we examined the effect of prior therapy on endocrine responsiveness. As noted in Table 1, 40/85 patients received prior chemotherapy. Twenty-one of 40 (52%) were estrogen receptor positive. Of the 45 patients who did not receive prior chemotherapy, 69% were estrogen receptor positive, but this difference does not approach statistical significance.

The overall frequency of estrogen receptor positivity in the 85 patients treated with endocrine therapy in this study was 52/85 or 61%. This does not differ significantly from our previously published frequency of estrogen receptor positivity of 52% of 329 patients in our breast cancer population [8]. Furthermore, the mean estrogen receptor value in patients who received prior chemotherapy is 31.5 vs 46.1 in patients who had

Table 7. Objective response rate to endocrine therapy as a function of number of sites involved with metastatic disease and estrogen receptor status

	Response rate		
	1 Site	2 Sites	≧3 Sites
Estrogen receptor positive	11/13 (84%)	11/16 (68%)	12/23 (52%)
Estrogen receptor negative	1/7 (14%)	1/7 (14%)	1/19 (5%)
	$P<0.01$	$P=0.05$	$P<0.01$

not received prior chemotherapy ($P>0.1$). Of the 21 patients in the estrogen receptor positive group who received prior chemotherapy 14 had an objective response to endocrine therapy (67%) compared to a response rate of 20/31 (64%) in those estrogen receptor positive patients who had not had prior treatment with chemotherapy. Prior treatment with chemotherapy did not alter the low response rate in estrogen receptor negative tumors. Thus prior chemotherapy did not significantly alter the incidence of estrogen receptor positivity or the predictive index of this test.

With respect to prior endocrine therapy, 15 patients in the estrogen receptor positive group and 6 patients in the estrogen receptor negative group had received prior treatment. Of the 15 patients in the estrogen receptor positive group, 8 (53%) responded to prior therapy while only 1/6 in the estrogen receptor negative group responded to prior endocrine therapy. In this present trial, of the 8 patients in the estrogen receptor positive group who responded to prior therapy, 6 responded to endocrine therapy. Of the 7 non-responders to prior therapy in the estrogen receptor positive group, 2 responded in this trial. Although 2/7 is not significantly different from the 3/33 rate in our estrogen receptor negative group in this trial, there may be a trend towards a higher response rate in estrogen receptor positive tumors which have failed prior endocrine therapy. This suggests that failure to respond to endocrine therapy in estrogen receptor positive tumors may be a function of the type of endocrine therapy. That is, the receptor positivity does predict endocrine dependence but the therapy employed does not adequately alter hormone levels. Eight of the 15 estrogen receptor positive patients responded and none of 6 of the estrogen receptor negative patients responded to endocrine therapy. The response rates of this subset of patients who had received prior therapy is not different from that of the group without prior endocrine therapy. Thus, prior endocrine therapy did not significantly alter the predictive index of the estrogen receptor assay.

DISCUSSION

The response rate to endocrine therapy in patients with metastatic breast cancer is approximately 30%. In 1971, Jensen *et al.* [9] found estrogen receptor in human breast cancer tissues and they suggested that estrogen receptor status might be useful in predicting tumor regression after endocrine manipulation. Over the past 7 yr there has been a proliferation of reports correlating endocrine response with estrogen receptor status. In 1974 these were summarized at an international workshop [1]. These collected data show that patients whose tumors possess estrogen receptor have a response rate of 50–60% while those tumors which lack estrogen receptor have a response rate of less than 10%. Our data are in agreement with these results. We report a 65% response rate in our estrogen receptor positive group and a response rate of only 9% in our estrogen receptor negative group.

Many complex biochemical tests are eventually felt to be of little value in that they fail to provide information not strongly suggested by clinical findings. In our series we found no differences between the estrogen receptor positive and negative with regard to age, menopausal status, Karnofsky performance index, disease free interval, number of sites involved with metastatic tumor, or prior therapy which could explain the difference in response rate other than the estrogen receptor status of their tumors. Thus it appears that

estrogen receptor status predicts response to endocrine manipulation independently of other prognostic factors. This fact deserves especial emphasis since it points out that effective therapy may be withheld from patients who may experience appreciable benefit if less accurate clinical shibboleth are relied upon.

The fact that a quantitative relationship exists between the amount of estrogen receptor and response rate to endocrine therapy is interesting. Our results show that as estrogen receptor values increase, the likelihood of objective response also increases. Patients whose tumors possessed greater than 50 fmole of estrogen receptor had an extremely high response rate of 77%. This relationship between the quantitative amount of estrogen receptor and response rate to endocrine therapy has been suggested by Heuson *et al.* [10] in a small series of patients. Furthermore McGuire *et al.* [11] have recently shown that the amount of estrogen receptor permits identification of patient subgroups having low (<3 fmole/mg protein), intermediate (3–100 fmole/mg protein) or very high (>100 fmole/mg protein) response rates. In their study the response rate is 6, 46 and 80% in these three subgroups.

It is also important to note that prior chemotherapy did not alter the incidence of receptor positivity in our patients and of more importance that prior chemotherapy or endocrine therapy does not alter the predictive index of the estrogen receptor. These data are in agreement with those of Kiang *et al.* [12, 13].

Although the quantitative amount of estrogen receptor correlates with response rate, it does not correlate with remission duration. This may not be too surprising since the amount of estrogen receptor (and subsequent response rate) is probably correlated with the number of cells which contain estrogen receptor, while response duration is a fraction of the number of hormone independent cells and their corresponding growth rate. Thus knowing that a large number of cells are hormone dependent provides little information as to whether a few thousand or few million cells are hormone independent.

Under identical circumstances steroid hormone receptors are uniformly of high affinity and limited binding capacity whereas a host of poorly characterized 'nonspecific' or low affinity binders may be present in a tumor sample. For this reason it would obviously appear reasonable to use an affinity criterion for differentiating receptor binding from association of ligand with other sites. Our data do not support this notion. We show that at least some patients whose tumors contain receptor with relatively low apparent binding affinity (>10 nM) respond to endocrine therapy. These data are similar to the data of Crabtree *et al.* [14]. In their study, the dissociation constant of glucocorticoid receptors showed considerable variation among individual patients with leukemia and lymphoma. These low affinity receptors may represent true affinity mutants in breast cancer cells. Alternatively, a variety of either biologically relevant or artifactual substances may significantly alter receptor affinity. Further study of this point is obviously required.

Our data also show that response rates are high in estrogen receptor positive tumors regardless of site of involvement with metastatic disease. Indeed lung and liver metastasis respond as well as skin, soft tissue or nodal disease. This differs from the traditional viewpoint which states that visceral involvement is refractory to endocrine therapy but agrees with recently published data of Manni *et al.* [15]. It appears that estrogen receptor status has an overwhelming influence on response rate and that the relative insensitivity of visceral metastasis to endocrine therapy reflects the distribution of estrogen receptor positive and negative tumors at these sites. Furthermore, the extent of disease is also not a factor in the ability of estrogen receptor positive tumors to respond to endocrine therapy. Patients with tumor involvement at one, two or three or more sites had very high response rates if their tumors were estrogen receptor positive compared to estrogen receptor negative tumors.

In summary, estrogen receptor status predicts response to endocrine therapy and there is a quantitative relationship between the amount of estrogen receptor and the likelihood of response. Prior chemotherapy or endocrine therapy does not effect the predictive index of the estrogen receptor. Neither extent of disease nor visceral involvement effects the response rate of estrogen receptor positive tumors.

Acknowledgements—We wish to thank the many collaborating physicians who submitted clinical material for analysis and allowed examination of their patient's records including: Drs. Alford, Blom, Borssuck, Camalier, Casey, Egan, Funderburk, Gold, Hiltabidle, Isaacson, Jonas, Jones, Kiernan, Kim, Kirson, Kison, Kleinberg, MacDonald, Mitchell, Moore, Palmer,

Perlin, Schein, Scully, Thistlethwaite, Tsangaris, Watkins and Wherry.

We would also like to thank C. Baughman and V. Tinley for their assistance in reviewing patient records at the George Washington University Medical Center and M. Allegra for her assistance in reviewing the records at Georgetown University and P. De Steffano for assistance in data management and computerization.

We would also like to thank Dr. D. C. Tormey (formerly of the Medicine Branch) and Dr. R. C. Young and the members of the Medicine Branch, NCI for their assistance with this study.

REFERENCES

1. W. L. McGuire, P. P. Carbone, M. E. Sears and G. C. Escher, Estrogen receptors in human breast cancer: an overview. In *Estrogen receptors in Human Breast Cancer.* (Edited by W. L. McGuire, P. P. Carbone and E. P. Volmer) p. 1. Raven Press, New York (1975).
2. W. L. McGuire, K. B. Horwitz, O. H. Pearson and A. Segaloff, Current status of estrogen and progesterone receptors in breast cancer. *Cancer (Philad.)* **39,** 2934 (1977).
3. M. E. Lippman and K. K. Huff, A demonstration of androgen and estrogen receptors in a human breast cancer using a new protamine sulfate assay. *Cancer (Philad.)* **38,** 868 (1976).
4. S. Aitken and M. E. Lippman, A simple computer program for quantitation and scatchard analysis of steroid receptor proteins. *J. Steroid Biochem.* **8,** 77 (1977).
5. Breast Cancer Task Force Treatment Committee, National Cancer Institute, Bethesda, Md. *Breast Cancer: Suggested Protocol Guidelines for Combination Chemotherapy Trials and for Combined Modality Trials.* U.S. Department of Health, Education and Welfare Publication No. (NIH) 77-1192.
6. J. L. Hayward, P. P. Carbone, J. C. Heuson, S. Kumaoka, A. Segaloff and R. D. Rubens, Assessment of response to therapy in advanced breast cancer. *Cancer (Philad.)* **39,** 1289 (1977).
7. E. H. Lehmann, *Non-Parametrics: Statistical Methods based on Ranks*, p. 208. Holden-Day, San Francisco (1975).
8. J. C. Allegra, M. E. Lippman, E. B. Thompson, R. Simon, A. Barlock, L. Green, D. Huff, M. Do and R. Warren, Steroid hormone receptors in human breast cancer. *Proc. Amer. Soc. clin. Oncol.* **19,** 336 (1978).
9. E. V. Jensen, G. E. Block, S. Smith, K. Kyser and E. R. De Sombre, Estrogen receptors and breast cancer response to adrenalectomy. *Nat. Cancer Inst. Monogr.* **34,** 55 (1971).
10. J. C. Heuson, E. Longeval, W. H. Mattheiem, M. C. Deboel, R. J. Sylvester and G. Leclercq. Significance of qualitative assessment of estrogen receptors for endocrine therapy in advanced breast cancer. *Cancer (Philad.)* **39,** 1971 (1977).
11. W. L. McGuire, Steroid receptors in human breast cancer. *Cancer Res.* **38,** 4289 (1978).
12. D. T. Kiang, M. D. Frenning, A. I. Goldman, V. F. Ascensao and B. J. Kennedy, Estrogen receptors and responses to chemotherapy and hormonal therapy in advanced breast tumor. *New Engl. J. Med.* **299,** 1330 (1978).
13. D. T. Kiang and B. J. Kennedy, Factors affecting estrogen receptors in breast cancer. *Cancer (Philad.)* **40,** 1571 (1977).
14. G. R. Crabtree, K. A. Smith and A. Munck, Glucocorticoid receptor and sensitivity of isolated human leukemia and lymphoma cells. *Cancer Res.* **38,** 4268 (1978).
15. A. Manni, J. E. Trujillo, J. S. Marshall, J. Brodkey and O. H. Pearson, Antihormone treatment of stage IV breast cancer. *Cancer (Philad.)* **43,** 440 (1979).