Introduction

It is now well established that determination of estrogen receptors (3, 6, 8, 15, 21) and PGR (7, 14, 18) in mammary cancers may be useful in predicting the response to hormonal treatments. Recently, it has also been shown that the presence of progesterone receptors is associated with a favorable prognosis in 98 patients with primary breast cancer. The occurrence of metastases was 3.6 times less probable in patients with progesterone receptor-positive tumors than in patients with progesterone receptor-negative tumors. There was also an inverse relationship between the concentration of progesterone receptor and the frequency of metastases. However, there was no statistical correlation between frequency of local recurrences and progesterone receptor content of the tumor.

In patients displaying clinical or histological criteria of gravity, the presence of progesterone receptors allowed us to define subgroups with good prognosis. Thus, in women with progesterone receptor-positive cancers, metastases had occurred at 18 months, in only 5% of the 39 Grade III cancers and in none of the 25 cases with invaded axillary nodes.

Measurement of estradiol receptor (105 patients including the previous 98 patients) was found to be less effective for guiding the prognosis of early breast cancer. Combined evaluation of estradiol and progesterone receptors did not provide any more information than did the determination of progesterone receptor alone.

Materials and Methods

Patients. The data reported are from 105 female patients treated at the Centre René Huguenin (St. Cloud, France) between January 1975 and April 1979. Their ages varied between 35 and 88 years (mean, 60.3 years). In all cases, the diagnosis, treatment, and follow-up were performed by the physicians of the Centre. Pseudo inflammatory, bilateral, or multiple cancers were excluded from the study. The stage of the disease was classified according to the TNM (tumors-nodes-metastasis) system (19).

Treatment consisted of either modified partial mastectomy (16) with ablation of the axillary nodes or partial mastectomy with low axillary dissection (Levels 1 and 2 of Berg), followed by postsurgical radiotherapy.

The patients were examined systematically 1 month after surgery, then every 3 months over a period of 2 years, and finally once a year. Chest X-ray examinations were performed at 3-month intervals during the first 2 years. Every year, liver scintigraphy, mammography, and thermography were done for each patient.

Among the 105 patients, 9 had adjuvant chemotherapy. 5-Fluorouracil (500 mg), methotrexate (15 mg), and cyclophosphamide (500 mg) were given weekly over a period of 3 months and then every 2 weeks for the following 18 months. Vincristine sulfate (1 mg) was given in the first 4 infusions and thereafter in every fourth infusion.

Pathology. Tumors were graded according to the classification of Bloom et al. (1), and local recurrences were confirmed by biopsy.

PGR and Estrogen Receptor Determinations. Determinations were performed as described previously (18). Tumors were considered receptor positive (PGR positive or ER positive) if they contained ≥10 fmol of specific binding sites per mg cytosolic protein.

Statistical Analysis. Graphs were derived from the life table analysis. Data were analyzed separately on each day. The comparison between groups was by the log rank test, and the χ² test was used to assess the statistical significance of differences (9, 10, 17).

Results

Clinical Data

Data on clinical characteristics and recurrences in relation to the presence of PGR and estrogen receptors in primary tumors are summarized in Tables 1 and 2.

PGR as a Prognostic Factor in Early Breast Cancer

Chart 1 shows the marked difference in the disease-free interval between PGR-positive and PGR-negative patients (risk multiplication factor, 2.5). However, this analysis covers 2 types of recurrences (metastases and local recurrences) which do not show the same relationship to the presence of PGR.

The occurrence of metastases was 3.6 times more probable in patients bearing PGR-negative tumors than in patients with PGR-positive cancers (Chart 2). However, there was no differ-
Table 1
Clinical characteristics and recurrence as a function of the presence of PGR and estrogen receptors in primary tumors

<table>
<thead>
<tr>
<th>Clinical characteristics (no. of patients)</th>
<th>Results of follow-up studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menopause</td>
<td>Invasion of lymph nodes</td>
</tr>
<tr>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td>PGR positive (n = 54)</td>
<td>16</td>
</tr>
<tr>
<td>PGR negative (n = 44)</td>
<td>11</td>
</tr>
<tr>
<td>ER positive (n = 94)</td>
<td>25</td>
</tr>
<tr>
<td>ER negative (n = 11)</td>
<td>2</td>
</tr>
</tbody>
</table>

* Of the 9 patients who had adjuvant chemotherapy, all were ER positive and 5 of 8 were PGR positive. In the latter group, metastases did not occur in any case and local recurrence occurred in one case. In the 3 PGR-negative patients, there was one case of metastases and one case of local recurrence.

* Natural menopauses only. Six patients (2 PGR positive and 5 ER positive) had X-ray castration.

* Medullar and colloid carcinomas were excluded.

* Overall recurrences observed were: PGR-positive patients, 6; PGR-negative patients, 16; ER-positive patients, 21; ER-negative patients, 5.

Table 2
Stage of the disease and receptor content of the tumors

| No. of patients |
|-----------------|-----------------|-----------------|-----------------|
| Stage I | Stage II | Stage IIIa | Stage IIIb | Stage IV |
| PGR positive (n = 54) | 4 | 36 | 6 | 8 | 0 |
| PGR negative (n = 44) | 5 | 22 | 10 | 7 | 0 |
| ER positive (n = 94) | 9 | 57 | 12 | 16 | 0 |
| ER negative (n = 11) | 0 | 6 | 4 | 1 | 0 |

Table 3
Occurrence of metastases as a function of the concentration of PGR in primary breast cancer

<table>
<thead>
<tr>
<th>PGR (fmol/mg protein)</th>
<th>No. of patients developing metastases</th>
<th>Risk multiplicity factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>42</td>
<td>12</td>
</tr>
<tr>
<td>1-9</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>10-99</td>
<td>26</td>
<td>2</td>
</tr>
<tr>
<td>100-199</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>&gt;200</td>
<td>17</td>
<td>0</td>
</tr>
</tbody>
</table>

* Could not be calculated because of the absence of events. Factor is very low.

positive and PGR-negative patients in both pre- and post-menopausal groups.

PGR as a Prognostic Factor in Relation to Lymph Node Invasion and Histological Grading

The presence of tumor cells in axillary lymphatic nodes and histological grading of breast cancers are well established prognostic factors in these cancers. It was, therefore, important to determine whether PGR measurements could provide supplementary information in patient subgroups defined by those criteria.

PGR in N+ Patients. In the N+ group, clear differences were observed when considering the occurrence of metastases in relation to PGR (Chart 4). At 18 months, no case of metastasis was observed in the PGR-positive group (25 patients), whereas 5 of 15 (33%) of the PGR-negative patients had metastatic spreading.

Again, no significant differences in relation to the presence...
of PGR were observed in local recurrences in N+ patients. When data from both types of events were pooled and disease-free intervals were considered, a statistically significant difference ($\rho = 0.006$) was obtained between PGR-positive and PGR-negative patients. When examining either metastatic occurrence or local recurrences in the group of patients without invaded axillary nodes, no significant differences were observed between PGR-positive and PGR-negative subgroups.

**PGR and Histological Grading of the Tumor.** There was no recurrence in any of the patients with Grade I cancers. In Grade II tumors, there was no statistically significant difference in the prognosis of PGR-positive and PGR-negative patients. For Grade III tumors (39 patients, of whom 23 were N+), the probability of metastases was 4 times higher for PGR-negative than for PGR-positive patients (Chart 5), and no statistically significant differences were observed for local recurrences as a function of PGR presence in these patients.

**Combined Estrogen Receptor and PGR Determination as a Prognostic Factor in Early Breast Cancer**

Two questions were asked. (1) How does the prognostic value of estrogen receptor compare with that of PGR? (2) Does the combination of PGR and estrogen receptor measurements provide more valuable information for the prognosis than that obtained from determination of PGR alone?

Establishment of a prognosis based only on the determination of the estradiol receptor was less evident because of the low proportion of ER-negative patients (10%) in this study (see "Discussion").

This may explain why, when considering the patients independently of their menopausal status, no statistically significant difference in disease-free interval was observed between ER-positive and ER-negative cancers. The difference was evident only in the postmenopausal patients ($\rho = 0.02$) with a risk multiplication factor of 2.7 for ER-negative patients.

Among the PGR-positive patients, the proportion of ER-negative subjects was too low ($n = 2$) to give any significant differences in disease-free interval from the ER-positive cancers ($n = 52$). The group of PGR-negative patients was large enough to allow statistical analysis. In this group, the disease-free interval was compared between ER-negative ($n = 8$) and ER-positive ($n = 36$) patients. The difference was statistically nonsignificant ($\rho = 0.68$). Thus, the prognosis in PGR-negative patients is not modified by the presence or absence of estrogen receptors in the tumors.

**DISCUSSION**

The presence of PGR in primary breast cancers was found to be associated with a favorable early prognosis if the occurrence of metastases, but not the frequency of local recurrences, is considered. This dissociation is not surprising, since local evolution is related to the efficiency of local treatment, whereas frequency of metastases is a function of the ability of the tumor to disseminate. The presence of PGR allows for the division of patients into subgroups. Despite the existence of well-known determinants of unfavorable prognosis, the occurrence of metastases is very rare in the PGR-positive group. Among the 25 PGR-positive patients with invaded axillary nodes, there was no metastatic spreading during an average follow-up period of 28.5 months. Only 5% of the PGR-positive patients with Grade III tumors ($n = 20$) showed metastases after an average follow-up of 25 months.

The results presented here on estrogen receptor and early prognosis in breast cancer are somewhat different from 2 previously published reports (5, 11). The absence of statistically significant differences between ER-positive and ER-negative patients is probably due to the fact that, in our study, 90% of the patients were ER positive, whereas the proportion was only 56% in the study of Maynard et al. (11), with positivity established at 5 fmol/mg protein, and 63% in the study of Knight et al. (5). The proportion of patients having ER-positive tumors varies considerably from one laboratory to another. Leclercq and Heuson (6) reviewed this problem and found a range of 35 to 85%. These authors showed that in many cases the proportion increased steadily as the study progressed, and they ascribed these progressive changes to the improvement of techniques. In their laboratory in 1977, about 85% of all breast cancers (primary and metastatic) were shown to contain estrogen receptors. The population of ER-positive tumors was higher in primary breast cancers. Our results are in agreement with these findings. We find 85.9% ER-positive cancers in the overall population and 90% in the present study, which includes only primary breast cancers. The population of ER-negative patients is relatively small and does not permit detection of small variations in frequency. Differences between ER-negative and ER-positive patients in the disease-free interval have been shown to be relatively small by Maynard et al. (11). At 18 months, about 18% of ER-positive patients relapsed compared to 27% among ER-negative patients. With our distribution of estrogen receptor, a small difference would be

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* M-F. Pichon, unpublished results.
difficult to discern in a group of approximately 100 patients. In postmenopausal subjects, this difference is clearer and thus is statistically significant in our study. We also examined the possibility that prognostic prediction might be improved by using different cutoff points for defining ER-positive tumors. However, taking patient distributions in which 70% or 50% of the population was in the ER-positive group (distributions similar to those in Refs. 5 and 11) did not give any statistically significant difference from the ER-negative group. However, this marker may give clearer results in some subgroups of patients, such as those previously described (2, 5, 11). Moreover, in our study, the determination of estrogen receptor added to that of PGR did not improve the prognostic value of the latter.

Of the 105 patients studied, only 9 had received adjuvant chemotherapy. If these patients are disregarded, there are no modifications in the conclusions reached. The probability of occurrence of metastases in PGR-negative patients is still 3.02 times higher than in PGR-positive subjects. No significant differences were observed between the 2 groups when considering the occurrence of local recurrences ($p = 0.5$). At 18 months, metastatic spreading in patients not receiving chemotherapy and with PGR-positive tumors occurred in only 6% of the 35 cases of Grade III and in none of the 20 cases with invaded axillary nodes.

The relationship between the presence of steroid receptors and early prognosis in breast cancer is not clear. It is possible to ascribe this correlation to a property of either the host or the tumor. The first hypothesis attributes the presence of the receptors and the absence of diffusion of the tumor to the same (unknown) characteristic of the host, perhaps some particularity of the hormonal status. The second, and perhaps more likely, explanation is that receptors are markers of tumor differentiation and therefore are related to the evolution.

In conclusion, the presence of PGR in primary breast cancers is associated with a markedly lower frequency of metastases, particularly among patients having invaded axillary nodes or Grade III tumors.

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**REFERENCES**


Relationship of Presence of Progesterone Receptors to Prognosis in Early Breast Cancer

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