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Prognostic Value of Progesterone Receptor After Long-term Follow-up in Primary Breast Cancer

M.F. Pichon, C. Pallud, K. Hacene and E. Milgrom

In a previous study of a series of 105 patients with primary breast cancer we found that the progesterone receptor (PgR) status was an important prognostic factor for early recurrences. 95 patients from the same series were followed-up for a median of 9.5 years and reassessed for the prognostic value of PgR status by univariate and multivariate statistical methods. In univariate analysis, the disease-free interval was only related to the lymph-node status. For overall survival, PgR and combined PgR–ER (oestradiol receptor) status had a prognostic value ($P = 0.035$ and 0.05, respectively). Moreover, PgR status was found to be discriminant for the survival of the node-negative patients ($P = 0.017$). In multivariate analysis, ER and PgR status were not significant, indicating that receptor status is not a powerful predictor of the course of breast cancer.
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INTRODUCTION

In 1980, we published a study of 105 patients with primary breast cancer, followed-up for an average duration of 2 years showing that progesterone receptor was a potent indicator of prognosis in these tumours [1]. Other studies subsequently published have either concurred with this result [2–9] or presented opposite conclusions [10–13]. One of the reasons for such discrepancies might have been the variable time of observation of the patients. Moreover, recent studies of prognosis in breast cancer have been complicated by the use of adjuvant chemotherapy.

It thus appeared interesting to re-examine the outcome of this cohort of patients, of whom only 10 dropped out of the study, who have now been followed-up for an average of 9.15 years, received no adjuvant therapy and in whom the natural history of the disease could be observed.

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PATIENTS AND METHODS

Patients

From the initial series of 105 patients, 95 were retained in this study. They were treated and followed-up at the Centre René Huguenin (Saint Cloud, France) between January 1975

Table 1. Clinical characteristics of our series of 95 breast cancers

	Menopause		Stage				Invaded lymph nodes*		Grade of tumours†		
	Pre	Post	I	II	IIIa	IIIb	Yes	No	I	II	III
ER (+), n = 88	25	60	11	50	16	11	43	44	5	40	37
ER (−), n = 7	2	5	1	3	3	0	2	5	0	0	5
PgR (+), n = 54	16	36	6	32	10	6	28	25	4	29	19
PgR (−), n = 37	11	25	6	18	9	4	15	22	0	10	21

*Based on pathological record. For 1 patient operated without axillary dissection staging was based on clinical record (No).
†8 tumours were not graded: 2 comedocarcinomas, 1 intracystic carcinoma, 1 cylindroma, 1 sarcoma. 3 carcinomas were not graded for technical reasons.

and October 1989. Their mean age at first diagnosis was 64.5 years (range 35–86). All the patients were diagnosed, treated and followed up by the physicians of the Centre. 10 patients were initially treated by tumorectomy with low axillary dissection and radiotherapy, the remaining 85 had modified mastectomy (Patey's type). Only 9 patients received adjuvant chemotheraphy {vincristine, cyclophosphamide, methotrexate, 5-fluorouracil (VCMF) [1]}.

The overall clinical characteristics are summarised in Table 1 and the results of follow-up in Table 2. The minimum length of observation was 271 days, the maximum 4595 days and the median 3340 days (9.15 years).

The treatment after first recurrence was local therapy with surgery alone or with radiotherapy, or chemotherapy for cutaneous metastases (n = 9) or local recurrences (n = 6). Bone metastases (n = 17) were treated by radiotherapy and endocrine therapy. Soft tissue metastases (n = 20) and lymph nodes metastases (n = 4) were treated by chemotherapy. At the end of the present study, 67.4% of the patients are still alive.

Methods

Oestradiol and progesterone receptor determinations were performed on primary tumours by radioligand binding assays [14]. The threshold of receptor positivity was 10 fmol/mg cytosol protein for both receptors.

Histopathology. Tumours were graded according to the classification of Bloom *et al.* [15].

Statistical analysis. Disease-free survival and overall survival rates were computed by the method of Kaplan and Meier [17] and compared by the logrank test [16]. Multivariate analysis based upon the Cox proportional hazards model [18] was performed to identify, in a stepwise manner, whether or not ER or PgR status had additional prognostic values once the other factors had been considered. Only deaths from breast cancer were taken into account in the statistical analysis.

RESULTS

Disease-free interval (DFI)

First relapse (local recurrence or metastases) was observed in 31/91 patients with known PgR with a median of 796 days (26.5 months). The minimum interval was 148 days and the maximum 3905 days. Apart from the lymph-node status, which was highly significant (P = 0.0007) in the prediction of subsequent events, no other clinical or biological characteristics (size and grade of tumour, hormonal status, receptors status) displayed significant differences in DFI by univariate analysis.

Overall survival

As expected, significant differences were obtained in survival of the patients according to their nodal status (P = 0.02) and

Table 2. Results of follow-up

		Metastases					
Deaths*	Local recurrences	All sites	Bone	Lung	Liver	Lymph nodes	Skin
ER (+)	6 28	29	17	9	9	4	8
ER (−)	0 3	2	0	2	0	0	1
PgR (+)	4 12	13	7	2	3	3	5
PgR (−)	2 17	16	8	8	5	1	4

*From breast cancer only.

Table 3. Long-term prognostic value of ER and PgR, (logrank test)

	No. of deaths/ total	P-value*
ER (+)	28/88	
ER (−)	3/7	ns
PgR (+)	12/54	
PgR (−)	17/37	0.035
ER (−) PgR (−)	3/5	
ER (−) PgR (+)	0/1	
ER (+) PgR (−)	14/32	0.05
ER (+) PgR (+)	12/53	

*Limit of significance ≤ 0.05.

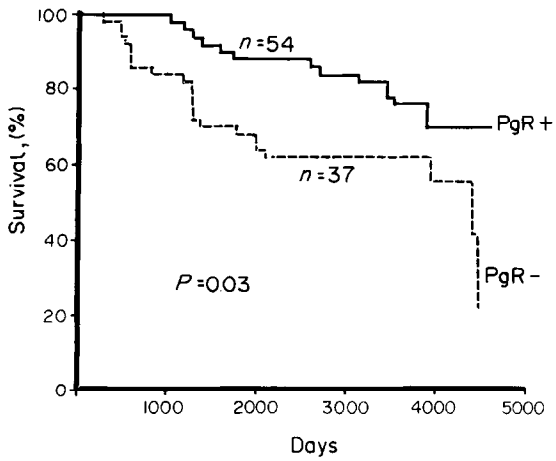

Fig. 1. Overall survival among PgR-negative and PgR-positive primary breast cancer.

histological grading of the tumours ($P = 0.01$). ER status of the primary tumour was found at the limit of significance ($P = 0.06$, Table 3) whereas PgR status (Fig. 1) and combined receptors status led to statistically significant differences between groups (Table 3).

PgR and survival in the node-negative group

Table 4 shows the results of the comparisons based on the lymph-node status of the patients. In the node-negative group,

Table 4. Prognostic value of ER and PgR among patients with (N+) or without (N−) invasion of lymph nodes (logrank test)

	N(−)		N(+)	
	No. of deaths/ total	P-value	No. of deaths/ total	P-value*
ER (+)	8/44		20/43	
ER (−)	2/5	0.06	1/2	ns
PgR (+)	1/25		11/28	
PgR (−)	9/22	0.017	8/15	ns
ER (−) PgR (−)	2/3		1/2	
ER (−) PgR (+)	0/1		—	
ER (+) PgR (−)	7/19	0.0006	7/13	ns
ER (+) PgR (+)	1/24		11/28	

*Limit of significance ≤ 0.05.

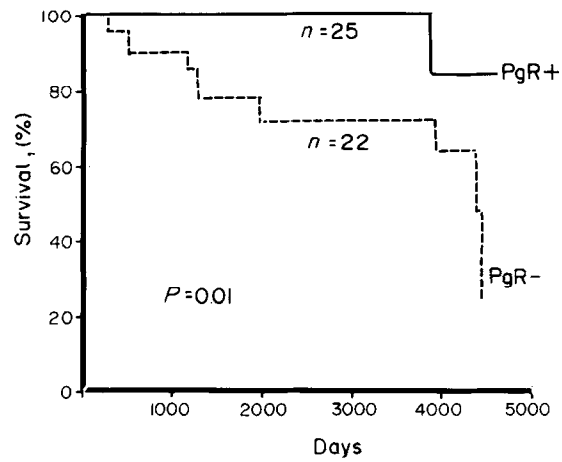

Fig. 2. Overall survival according to PgR status of the primary tumour among patients without invaded axillary nodes.

PgR is a powerful discriminant of the probability of survival (Fig. 2). The presence of PgR is associated with a longer survival ($P = 0.017$). The probability of survival is also significantly different among the four categories of ER–PgR status ($P = 0.0006$).

Multivariate analysis

We have tested the relative significance of nine variables: size of the primary tumours, lymph-node status, hormonal status, histological grading and its three components (nuclear pleomorphism, number of mitoses and architectural differentiation) and ER and PgR. Regarding the DFI, only the histological grading displayed a statistical significance ($P = 0.016$).

Cox's analysis of overall survival results in only two significant parameters for this series of patients: nuclear pleomorphism for the first rank ($P = 0.010$) followed by lymph-node status ($P = 0.039$). If the nuclear pleomorphism is excluded, the histological grading becomes the most important feature ($P = 0.013$). The next variable is ER status, but this is beyond the limit of significance ($P = 0.064$). PgR status has no significance in this analysis.

DISCUSSION

The originality of this study is due to the long-term follow-up of almost the same cohort of patients previously studied during the first 2 years of evolution of their primary breast cancer.

Our original analysis showed that the probability of developing metastases was 3.6 times smaller in the PgR-positive group, and that the prognosis of patients with grade III or node-positive tumours was better if PgR were present rather than absent. Our current study confirms the prognostic value of PgR regarding the overall survival, but leads to different conclusions when stratifying patients into subgroups. We verified that the composition of the group of patients or the existence of intervening therapies could not introduce an important bias in the results.

This series of patients includes 13% stage I, 56% stage II, 32% stage III; percentages similar to the average annual proportions of the different stages recorded at the Centre René Huguenin during the last 5 years (stage I 18%, stage II 60%, stage III 22%).

Adjuvant treatment (vincristine + CMF) was given to only 9 patients. The first study showed no statistical differences when these patients were excluded from the analysis. Moreover, it is now well established that more intensive chemotherapy regimens

including doxorubicin are necessary to achieve significant improvements in recurrence rates of high-risk patients [19].

In the estimation of the DFI, only the lymph-node status has a prognostic value in the present study. The median DFI (26.5 months) exceeds the average observation period of the previous work (23 months) and this difference might explain why we do not reach the same conclusions regarding the prognostic value of PgR in early breast cancer.

Long-term follow-up shows statistically significant differences in the length of survival according to the PgR status of the primary tumour (Fig. 1). PgR-positive tumours are characterised by a constant trend of death rate (approximately 2.4% per year) after a 'silent period' of approximately 1000 days. PgR-negative tumours display two apparent periods of high risk, the first from initial diagnosis to 1000 days and a late one starting at 4000 days.

The differences in overall survival between PgR-positive and -negative tumours are mainly due to the late recurrences in the PgR-negative group. It was observed in an extended series of 1262 patients treated at the same centre that only 42% of total relapses and distant metastases occur during the first 5 years of follow-up of patients with breast cancer [20].

For the patients presenting criteria of bad prognosis (grade III tumours or invaded lymph nodes) the rates of death are not significantly different between PgR-positive and -negative tumours. After an initial difference in the probability of deaths, the actuarial curves of the grade III group tend to join each other at 3.7 years (data not shown), and the proportion of deaths was similar: 9/21 (43%) in the PgR positive group vs. 8/19 (42%) in the opposite group. For the node-positive group, the actuarial curves diverge after 540 days and follow a parallel slope down (not shown). 53% of deaths were observed in the node-positive PgR-negative group vs. 39% in the opposite group (not significant).

20–35% of patients without axillary metastases will have recurrence of disease after mastectomy [21]. There is a need to find new prognostic factors that will facilitate the detection of high-risk subpopulations among the node-negative group. Among the classical factors the size of the tumour is a predictor of recurrence in some studies, but it is closely related to lymph-node status. In our analysis, we found no statistically significant differences in overall survival according to the three categories of size tested (< 15, 15–29 and >29 mm in diameter).

The histological grade was significant ($P = 0.01$) in predicting overall survival, while ER status had no statistical value. On the contrary, PgR status enables the discrimination of high-risk patients among the node-negative group. Another study of 807 node-negative patients by Thorpe *et al.* found similar results by univariate analysis [22]. Furthermore, with criteria of the proliferative activity of the tumours: S-phase fraction, ploidy [23] or Ki67 immunostaining [24]; PgR status could contribute to a powerful prognostic index for these patients.

Multivariate analysis of the prognostic factors in our series shows that ER and PgR status are not powerful predictors of recurrence and survival. Reviewing risk factors by multistage Cox analyses of 1022 patients with operable breast cancer, Hacene *et al.* [25] showed that only some of them (tumour size, top axilla nodal status, mitotic index and nuclear pleomorphism) had a constant and independent predictive value of metastasis-free survival. The other factors have either a temporal prognostic value at one or several stages, or are not independent prognostic factors. This might help to explain why conflicting reports have been published concerning the prognostic value of steroid receptors in breast cancer.

In conclusion, PgR status of the primary tumour appears by univariate analysis as an individual prognostic factor in survival. This has been shown with shorter follow-up by several other studies [2–9, 22]. Among subgroups of patients presenting well-established criteria of bad prognosis, PgR adds no prognostic value and appears only to be linked to a delayed development of the tumour. For patients without axillary metastases, the absence of PgR in the primary tumour could contribute to the decision of treatment by adjuvant chemotherapy.

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The Assessment of Sexual Function in Cancer Patients

Ann M. Cull

The sexual function of cancer patients may be compromised by their disease or treatment. This is infrequently assessed as an outcome variable and methodological differences between reported studies make comparison difficult. Where sexual function is being assessed as one dimension of a more comprehensive assessment of quality of life, a single item concerned with frequency of intercourse or satisfaction may be sufficient, but many studies require more detailed information. Methods developed for clinical assessment of sexual dysfunction are generally too long and detailed for this purpose. The best developed scales for cancer patients are embedded in lengthy and expensive questionnaires. A pool of items can be identified from which a scale could be derived to assess the relevant aspects of sexual experience. The development of an appropriate and psychometrically sound scale is now required to encourage greater consideration of the impact of disease and treatment on cancer patients' sexual function.
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INTRODUCTION

QUALITY OF LIFE measures generally take account of the impact of cancer and its treatment on the physical, functional, emotional and social aspects of patients' lives. Sexual relationships make a significant contribution to the quality of life for many people and may be compromised by disease and treatment, yet sexual function is rarely assessed as a treatment outcome.

Many patients feel reticent about volunteering sexual concerns in the face of cancer and doctors are often reluctant to ask about sexual problems. Clinical estimates are therefore likely to underrepresent the prevalence of sexual difficulties.

The nature and frequency of sexual problems will vary with disease site and treatment. Disruption of sexual function may be anticipated following genital malignancy or radical therapy within the pelvis. However, decrease in the frequency and range of sexual behaviour and dysfunctions of the sexual response cycle have been reported across all disease sites and following all therapeutic modalities. Currently available estimates of the prevalence of sexual morbidity associated with cancers of the breast, bowel, female genital tract, bladder, prostate and testis are discussed in Andersen's review [1]. The treatment of disease at body sites of less obvious sexual significance may also have sexual repercussions. For example, Devlen *et al.* [2] found that 20% of lymphoma patients, disease-free and off treatment, reported a persistent loss of libido which the authors interpreted as a side-effect of chemotherapy. Sugarbaker *et al.* [3] found no difference between limb-spared sarcoma patients and amputees with respect to pain, mobility or treatment trauma, but sexual functioning was more impaired in the conservatively treated group. Sexual morbidity in oncology is therefore a common problem. Indeed Andersen [4] concludes that the majority of previously sexually active cancer patients will experience significant sexual disruption as a result of their disease and treatment.

Clearly the selection of the least disruptive treatment for the same medical endpoint is an important strategy for reducing sexual as for any other morbidity, but even where sexual outcome is assessed it is often difficult to compare results because of substantial methodological differences between studies. For example there is a lack of sound data to support the assumption of an improved psychosexual outcome following breast-conserving therapy [5].

More systematic assessment is required not only for clinical trials but to inform patient choice. A recent study using the time trade-off technique [6] showed that some men will choose treatment with a poorer chance of survival in order to increase their chance of remaining sexually potent.

Psychological and behavioural interventions to reduce the incidence and severity of problems can be most effective if delivered early, making the case for more systematic screening

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