Prognostic significance of steroid hormone receptors (ER and PR) in primary operable breast cancer

KEYWORDS: Breast Neoplasms; Prognosis; Receptors; Estrogen;

INTRODUCTION

Prognostic factor is indicative of the inherent biological aggressiveness of a tumor, reflecting natural history of the disease after local therapy. It is, therefore, most accurately assessed in systematically untreated patients.

For this purpose, we attempted to evaluate the prognostic significance of estrogen (ER) and progesterone (PR) receptors in 267 node-negative breast cancer patients in terms of relapse-free interval, treated with locoregional therapy only.

Biological behavior of breast cancer supports the assumption that patients without spreading of malignant cells to axillary lymph nodes (ANN) can be classified into several subgroups in keeping with the different aggressiveness (1). According to the Consensus statement of St. Gallen (2), a large group of node-negative breast cancer patients are treated with no expected benefit. Therefore, it is important to determine the subgroup of patients who are at high risk for recurrence and should, with no doubt, receive more aggressive adjuvant therapy than subgroups of patients who are at intermediate/low risk.

PROGNOSTIC VALUE OF ER AND PR IN A QUANTITATIVE MANNER

Our retrospective study was of short-term outcome of ANN breast cancer patients (median follow up time was 45 months), the aim of which was to define the patients at high risk of recurrence, using first-line generation (clinico-pathological) parameters. Considering steroid receptor content, measured by biochemical dextran-coated charcoal method recommended by the EORTC (3), we observed that only in middle-aged postmenopausal patients subset bearing pT2 tumors, the lowest tested cut-off value of 5 fmol/mg for both receptors showed prognostic significance (Figure 1).

Breast carcinomas with steroid receptor content lower than 5 fmol/mg in these patients defined high risk-related subgroup (relapse-free interval probability were calculated according to Kaplan and Meier with Cox-Mantel test for comparing survival functions and p values (0.05 were considered significantly).

\begin{table}[h]
\centering
\begin{tabular}{|l|l|l|l|}
\hline
Parameter & Rank of Influence & β & p* & RR \\
\hline
The entire node-negative & 1 & Tumor size & 0.7358 & 0.001 & 2.09 \hline
2 & Tumor grade & 0.7101 & 0.020 & 2.03 \hline
3 & Age & -0.0301 & 0.040 & 0.97 \hline
Younger patients & 1 & Age & -0.2017 & 0.005 & 0.82 \hline
Middle aged patients & 1 & Tumor size & 0.7165 & 0.040 & 2.05 \hline
2 & Tumor grade & 2.4515 & 0.020 & 11.61 \hline
Older-aged patients & 1 & Tumor size & 1.9102 & 0.033 & 7.68 \hline
2 & Tumor grade & 2.4515 & 0.020 & 11.61 \hline
3 & Tumor type & -1.5218 & 0.040 & 0.52 \hline
\end{tabular}
\caption{Multivariate analysis of the entire node-negative breast cancer patients and age- and menopausal-related subgroups; younger, middle-aged and older patients}
\end{table}

Obviously, steroid hormone receptors (ER and PR) considered as continuous variables did not reach statistical significance to become independent variable, i.e. they did not add any further information about prognosis (biological course of disease and appearance of relapse) in analyzed group of ANN breast cancer patients. Tumor size and grade, age and histological type showed that they were different predictors of relapse across thus forming the age- and menopausal related patients' subgroups. It is well known that results of multivariate analysis obscure differences among the biologically different subgroups. Our result that ER and PR well-defined small subset of patients with different prognosis (middle-aged postmenopausal patients bearing pT2 tumors) overcomes bias cited above and provides clinically useful model. Also, it is possible that prognostic information concerning importance of ER and PR expression could have been overlooked i.e. underestimated when considering the entire node-negative breast cancer population. In that context, it is understandable why the results of prognostic value of ER and PR in natural course of node-negative breast cancer were controversial (4, 5). It is unre-

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure1.png}
\caption{Steroid hormone receptor status-related disease free probability (p) of node negative postmenopausal middle-aged breast cancer patients with pT2 tumors}
\end{figure}

This result was attained by gradual examination of the distribution of clinicopathological variables within five years increments of patients' age as well as prognostic power of particular variable. Our first goal in this study was to form patients' subgroups based on the pronounced mutual relationship between conventional parameters. Forming the age- and menopausal-related subgroups satisfied this requirement: the group of patients of age up to 44 - "younger" (n=54) was mostly premenopausal. Patients aged over 59 - "older" (n=75) were postmenopausal except one with perimenopausal status. Within age 45 and 59, i.e. "middle aged" (n=168), there were pre-, peri-, and postmenopausal women with nearly same frequency.

The results of multivariate analysis for all node-negative breast cancer patients, as well as for younger up to 45, middle-aged 45-58 and older above 59 years patients, are shown in Table 1. (Stepwise methods using the Cox regression model on a computer using BMDP-2L program).

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alistic and overly simplistic to expect that any individual biomarker alone will be prognostically powerful enough to be clinically useful.

PROGNOSTIC VALUE ER AND PR IN QUALITATIVE MANNER

The other way to analyze prognostic power of ER and PR could be during biological course of breast cancer as related to their phenotypes, i.e. using predetermined cut-off value for both receptor content.

Both steroid hormone receptors are estrogen-regulated proteins (6). Provided that ER is present, PR is synthesized in tissue, implying a functioning ER pathway (7). Consequently, three biological types of steroid hormone receptor-related carcinomas should appear as: breast carcinoma with functional ER "ER+ PR+" or without functional ER "ER- PR-" and breast tumors without both receptors "ER- PR-". Although breast tumors that lack ER but contain PR should not exist, studies have repeatedly found a small percentage of such carcinomas, with an incidence of up to 5%. The biological significance of these types of breast carcinomas is not clear.

Distribution of ER and PR receptor phenotypes (with cut-off values of 10 fmol/mg and 20 fmol/mg, respectively) and observed recurrence events within each phenotype are shown in Table 2.

Table 2. Observed breast cancer recurrence related events relative to steroid hormone receptor phenotypes

<table>
<thead>
<tr>
<th>Steroid hormone receptor phenotype</th>
<th>No of patients (%)</th>
<th>No of recurred (%)</th>
</tr>
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<tbody>
<tr>
<td>ER+PR+</td>
<td>117 (39%)</td>
<td>27 (23%)</td>
</tr>
<tr>
<td>ER+PR-</td>
<td>73 (25%)</td>
<td>19 (26%)</td>
</tr>
<tr>
<td>ER-PR+</td>
<td>95 (32%)</td>
<td>19 (20%)</td>
</tr>
<tr>
<td>ER-PR-</td>
<td>12 (4%)</td>
<td>5 (42%)</td>
</tr>
</tbody>
</table>

Twelve (4%) carcinomas displayed negative ER but positive PR status. Approximately twice as high recurrence rate in ER-PR+ subgroup of patients was noted, compared with the other steroid hormone receptor phenotype subgroups. Relapse-free probability for each of the four receptor phenotype subgroups is shown in Figure 2.

Figure 2. Relapse-free probability of survival in node-negative breast cancer patients according to the steroid hormone receptor phenotypes

There was a significantly lower disease-free probability of survival for patients ER-PR+ carcinomas than any of the other three steroid hormone receptor phenotypes (p>0.05 > 1.64). There was no difference in relapse-free probability between any couple of ER+PR+ and ER+PR- and ER-PR- subgroups (p>0.05 < 1.64).

Considering the distribution of obtained independent prognostic parameters of entire node-negative breast cancer patients, within subgroups of patients in relation to ER, PR phenotypes, we did not find statistical difference in tumor size and grade (2 test) or in age (Mann-Whitney U test) between ER-PR+ subgroup and any other receptor subgroups (p>0.05). As homogeneity was striking in distribution of independent prognostic parameters (age of patients, tumor size and grade) among the examined groups, the question is whether the worse outcome in ER-PR+ is due to intrinsic biological aggressiveness (8). This is difficult to explain.

Three possible explanations for the existence of breast carcinomas that lack ER but contain PR may be following: first, the ER may be present but masked in binding assay because of endogenously bind estrogens (9). ER assay in these cases would be "false-negative". However, this explanation has not been widely accepted so far (10). Second, an abnormal ER may be present, which does not bind estrogen but can bind to DNA and activate transcription (11). The third explanation, which suggests that ER is truly absent and that estrogen does not regulate PR synthesis i.e. presence of a PR gene with abnormal regulation that function in a constitutive manner, is therefore plausible. Accordingly research of association between no estrogen regulated PR synthesis and aggressiveness of breast carcinomas is intriguing for future studies.

In summary, one may rightly wonder whether there is a need for new prognostic markers before we have learnt how to optimally use the currently available ones.

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