THE PROGNOSTIC SIGNIFICANCE OF RECEPTOR STATUS IN PATIENTS WITH EARLY BREAST CANCER

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© **I.V. Kolyadina,** PhD, Tutor, the Oncology Department[1]; Oncologist, Surgeon[2];
I.V. Poddubnaya, D.Med.Sc., Professor, Corresponding Member of of Russian Academy of Medical Science, Head of Oncology Department[1, 2];
G.A. Frank, D.Med.Sc., Professor, Head of the Department of Tumor Pathological Anatomy[3];
D.V. Komov, D.Med.Sc., Professor, Head of the Surgical Department of Tumor Diagnostics[2];
A.S. Ozhereliev, D.Med.Sc., Professor, Leading Research Worker, the Surgical Department of Tumor Diagnostics[2];
A.I. Karseladze, D.Med.Sc., Professor, Head of the Department of Tumor Pathological Anatomy[2];
V.D. Ermilova, D.Med.Sc., Leading Research Worker, the Department of Tumor Pathological Anatomy[2];
Y.V. Vishnevskaya, PhD, Research Worker, the Department of Tumor Pathological Anatomy[2];
N.P. Makarenko, PhD, Associate Professor, the Oncology Department[1, 2];
R.A. Kerimov, D.Med.Sc., Leading Research Worker, the Surgical Department of Tumor Diagnostics[2];
K.A. Teterin, Head of Radiology Department of the Clinic[1];
S.M. Banov, PhD, Oncologist of the Clinic[1]

[1]Russian Medical Academy for Postgraduate Education, Barikadnaya St., 2/1, Moscow, Russian Federation, 123995;
[2]N.N. Blokhin Russian Cancer Research Center of Russian Academy of Medical Science, Kashirskoe shosse, 24, Moscow, Russian Federation, 115478;
[3]Moscow Research Oncological Institute named after P.A. Gertsen, 2nd Botkinsky pereulok, 3, Moscow, Russian Federation, 125284

The aim of the investigation is to study prognostic value of tumor receptor status in early breast cancer (I stage).

Materials and Methods. There was performed retrospective analysis of case histories of 1036 patients with early breast cancer ($T_1N_0M_0$-stage), who were treated in N.N. Blokhin Russian Cancer Research Center and the Clinic of Russian Medical Academy for Postgraduate Education from 1985 till 2009. There was studied the prognostic significance of estrogen receptor (ER), progesterone receptor (PR) and HER2, as well as prognostic value of HER2 hyperexpression in early breast cancer both in independent form, and in combination with the receptors of steroid hormones.

Results. Based on the combination of receptors there were distinguished immunohistochemical subtypes of breast cancer: luminal A and B, triple-negative cancer and cancer with HER2 overexpressoin. The presence or absence of receptors of steroid hormones ER and PR was stated to have no independent prognostic significance in early breast cancer. HER2 hyperexpression shows no prognostic value in the analysis of overall survival, but it is an unfavourable factor for recurrence free survival both as an independent form, and in combination with the steroid hormone receptors.

Key words: breast cancer; ER PR HER2 receptor status; immunohistochemical subtypes of breast cancer.

Recently, the concept of biological action of breast cancer has undergone considerable changes [1, 2]. The implementation of a modern immunohistochemical analysis into practice has enabled to determine not only tumor histological type and anaplasia degree, but also the presence of a number of receptors that can predict the course of the disease and elaborate the most optimal therapeutic regimen for each clinical setting [3–5]. There are many reports devoted to the study of different receptor combinations, and on their basis there have been distinguished immunohistochemical tumor subtypes, and shown the association of tumor immunophenotype with stage and course of the disease [6, 7]. However, prognostic value of receptor status in early breast cancer is as yet little understood, though this is precisely clinical setting the unfavourable course of which is not due to a tumor large size or regional lymph nodes involvement, but biological action of the tumor itself.

The aim of the investigation was to study prognostic value of morphological factors in early breast cancer and distinguish most unfavourable immunohistochemical subtypes that require individual therapy.

Materials and Methods. We studied morphological characteristics of tumors in 1036 female patients with early breast cancer ($T_1N_0M_0$-stage) who received treatment in N.N. Blokhin Russian Cancer Research Center and the Clinic of Russian Medical Academy for Postgraduate Education from 1985 till 2009. The patients' age was from 21 to 88 years (Table 1). Tumor histological size did not exceed 2 cm (T_1), the examination of the operative material did not reveal regional lymph nodes invasion (N_0), and there were no signs of distant metastasis on examination

For contacts: Kolyadina Irina Vladimirovna, tel. +7 906-792-66-94; e-mail: irinakolyadina@yandex.com

Table 1

Characteristic of female patients (n=1036) and tumors included in the study

Factors	Absolute number	%
Patients' age, years:	21–88	
mean	52	
median	51	
<40	140	13.5
40–50	375	36.2
50–60	271	26.2
>60	250	24.1
Tumor histological type (n=872):		
noninvasive cancer	9	1
invasive ductal carcinoma	594	68.1
invasive lobular carcinoma	132	15.1
other invasive carcinomas	137	15.7
Tumor anaplasia degree (n=733):		
G1	94	12.8
G2	572	78.0
G3	67	9.2
Estrogen receptors in tumor (n=911):		
negative	285	31.3
positive	626	68.7
Progesterone receptors in tumor (n=824):		
negative	275	33.4
positive	549	66.6
Tumor HER2-status (n=294):		
no hyperexpression	261	88.8
hyperexpression	33	11.2

(M_0). All patients underwent radical surgery: mastectomy — 480 cases (46.3%), or partial mastectomy — 556 cases (53.7%); adjuvant radiotherapy — 595 (57.4%); adjuvant systemic medication (chemotherapy, hormonal treatment, or both methods) — 565 (54.5%). The observation period was from 7 to 312 months (median — 82 months). Further progression of the disease (local, regional, distant recurrences) was found in 241 patients (23.3%), time to disease progression was from 6 to 228 months (median — 36 months).

We studied tumor morphological characteristics and the relationship of tumor receptor status with long-term treatment results. Based on the analysis there were distinguished the most unfavourable morphological criteria significantly correlating with therapeutic failures.

Tumor histological type of 872 female patients was studied: prevailing type was invasive ductal carcinoma (68.1%), lobular carcinoma was revealed in 15.1% of cases, other histological types (medullary, tubular, mixed, mucinous) were revealed in 15.7% of cases.

Anaplasia degree was studied in 733 cases: most tumors (78%) had II tumor grade (G2). Estrogen receptor (ER) status was examined in 911 tumors, progesterone receptor (PR) — in 824 tumors, moreover, in 31.3% of cases there was no ER expression (ER-negative cancers), and in 33.4% of cases there was no progesterone receptor expression (PR-negative cancers).

Immunohistochemical analysis to determine HER2 hyperexpression was performed in 294 patients, before 2004 — retrospectively in 34 women, and since 2005 — in 260 women on routine analyses of operative material. HER2+++ hyperexpression revealed in immunihistochemical analysis, and/or gene amplification revealed in FISH-reaction were found in 11.2% of cases.

The data were statistically processed using SPSS 16.0 program, the values were considered statistically significant when $p<0.05$, overall and recurrence-free survival was determined by Kaplan-Meier method.

Results and Discussion. In accordance with the analysis results of receptor combinations ER, PR and HER2-status we distinguished 4 immunohistochemical cancer subtypes: luminal, A and B types, triple negative cancer, and HER2-positive cancer (Table 2).

High-differentiated tumors with the presence of ER expression, ± PR expression, and no HER2 hyperexpression are generally thought to refer to *luminal type A* [8, 9]. In our study luminal A-subtype was found in most female patients (200 from 294 cases; 68.1%).

Luminal B type currently includes two tumor types: tumors with immunophenotype ER+ PR± HER2+ (HER2+ luminal B) and low differentiated carcinomas with ER+ PR± HER2– (HER2– luminal B). Luminal B-subtype is less common than luminal A and characterized as more malignant [10]. In our analysis luminal B-subtype was revealed in 24 cases (8.2%): 11 patients had HER2+ luminal B-subtype, and 13 patients — HER2– subtype.

Triple negative cancer was revealed in 52 cases (7.7%). These tumors have no ER, PR and HER2 expression. Moreover, triple negative cancer group includes not only basal-like variants with unfavourable course with immunohistochemical characteristics (ductal tumor type, G2-3-degree of anaplasia, frequently: HER1 and cytokeratin 5/6 expression), but also favourable variants of medullary, mucinous, and tubular carcinomas characterized by the absence of any receptors expression [11, 12]. To distinguish true basal-like variant of triple negative cancer, more detailed immunohistochemical analysis is needed [13].

Tumors with no steroid receptor expression but HER2 hyperexpression reveled by immunohistochemistry (HER2+++) or FISH-reactions (+) are referred to HER+ cancer subtype (ER– PR– HER2+). In our study *HER2+ immunohistochemical cancer subtype* was revealed in 15 cases (5.2%).

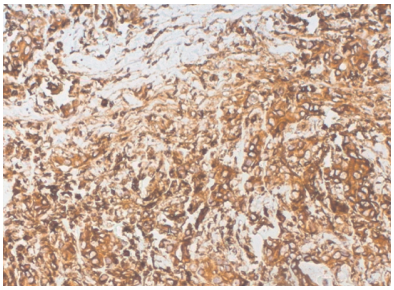
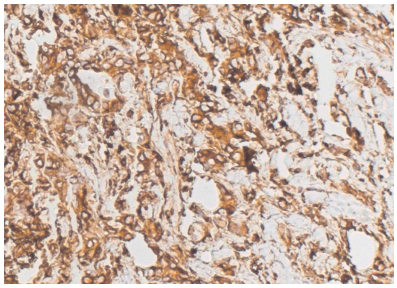
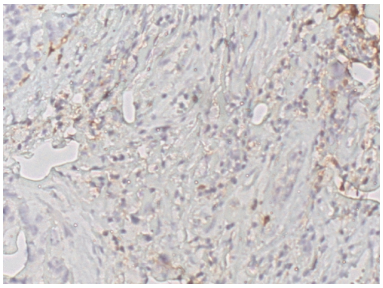
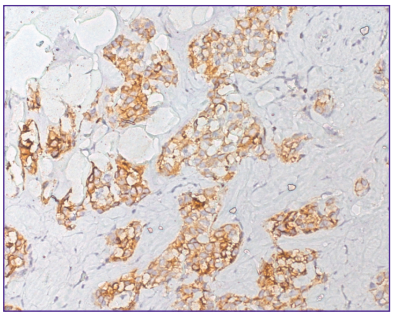
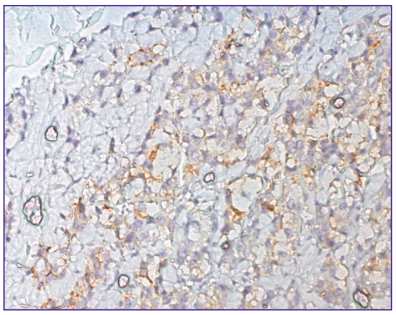
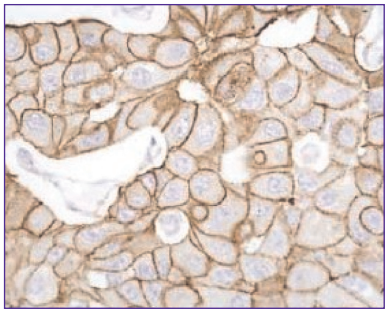
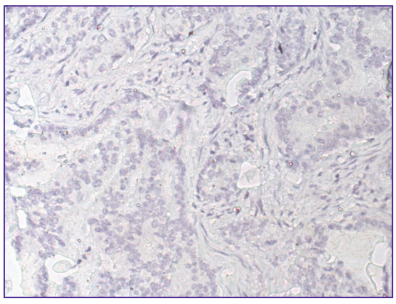
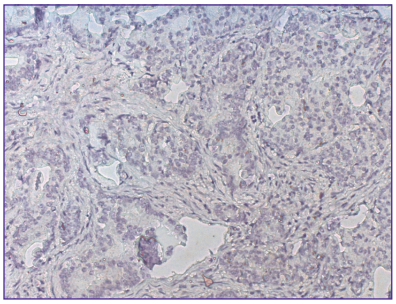
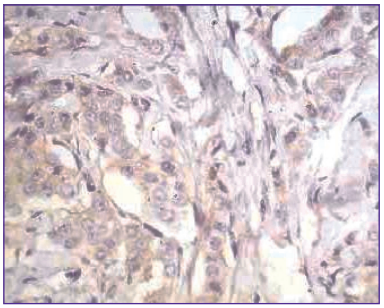
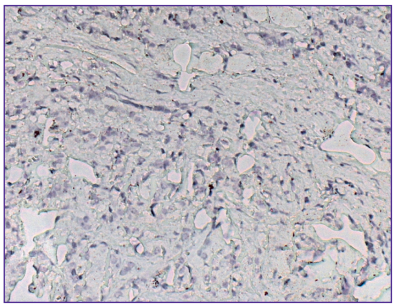
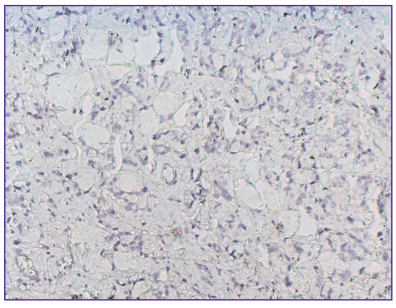
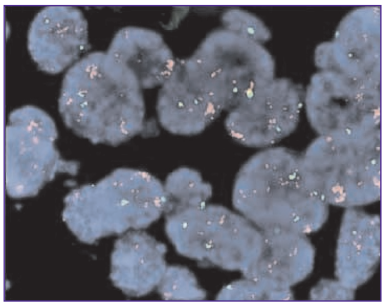
241 patients (23.3%) had recurrences of the disease, observation median being 82 months. Time to disease progression was from 6 to 228 months (median — 36 months). We analyzed prognostic value and survival indices in different receptor status of tumors. The monoanalysis of ER (expression/no expression), PR (expression/no expression), HER2 (hyperexpression/no hyperexpression) indices showed only tumor HER2-status to have prognostic value for recurrence risk. Thus, in the presence of HER2 hyperexpression there was observed more than double increase in recurrence rate (21.9%) compared to that in the absence of HER2 hyperexpression (9.9%), $p=0.04$.

The analysis of tumor ER PR-status showed no statistical significance of any combination ($p>0.05$).

The most interesting data were obtained when analyzing

Table 2

Immunohistochemical characteristics of breast cancer subtypes

Luminal A type: high differentiated carcinomas ER+ PR± HER2–		
 ER+	 PR+	 HER2–
Luminal B type: 1) ER+PR±HER2+ (in immunohistochemical analysis (HER2+++) or FISH-reaction (–)) 2) low differentiated carcinomas ER+ PR± HER2–		
 ER+	 PR+	 HER2+ (immunohistochemical analysis)
Triple negative cancer: ER– PR– HER2–		
 ER–	 PR–	 HER2–
HER2+ cancer: ER– PR– HER2+. Hyperexpression HER2 revealed in immunohistochemical analysis (HER2+++) or FISH-reaction (–)		
 ER–	 PR–	 HER2+ (FISH+)

immunohistochemical cancer subtypes (ER PR HER2 combinations).

Thus, in luminal A-subtype, the number of progressive disease patients is considerably lower (8.0%) than in luminal B-subtype (HER2– variant — 15.4%, HER2+ variant — 20%). Progression of the disease in triple negative cancer

Table 3

Prognostic value of the presence of expression of receptors and their combinations for disease recurrence, %

Receptors	Progressive cancer patients	Patients with no progressive cancer	p
Monoanalysis			
ER+	21.9	78.1	0.2
ER–	23.9	76.1	
PR+	21.3	78.7	0.3
PR–	20.0	80.0	
HER2+	21.9	78.1	0.04
HER2–	9.9	90.1	
ER PR combination analysis			
ER+ PR+	20.5	79.5	0.4
ER+ PR–	17.9	82.1	
ER– PR+	29.8	70.2	
ER– PR–	20.9	79.1	
Immunohistochemical subtypes of ER PR HER2 cancer			
Luminal, A type	8.0	92.0	<0.01
Luminal, B type, HER–	15.4	84.6	
Luminal, B type, HER+	20.0	80	
Triple negative cancer	13.5	86.5	
ER– PR– HER2+ cancer	33.3	66.7	

Table 4

Overall survival indices in different receptor status of tumor (monoanalysis and analysis of combinations), %

	Overall survival indices					p
	3-year	5-year	7-year	10-year	15-year	
Monoanalysis						
ER–	94.6	89.0	84.8	79.8	67.5	0.4
ER+	95.0	90.4	84.5	81.6	72.4	
PR–	96.3	91.5	88.0	81.4	69.5	0.2
PR+	95.2	91.2	88.5	84.9	69.0	
HER2–	96.5	90.8	–	–	–	0.5
HER2+	93.9	89.5				
Analysis of ER PR combination						
ER+ PR+	95.8	92.2	86.1	81.9	69.4	0.4
ER+ PR–	96.1	89.7	87.7	81.0	63.6	
ER– PR+	93.7	87.3	79.4	76.2	69.5	
ER– PR–	96.4	91.8	86.6	81.6	65.7	
Immunohistochemical subtypes of ER PR HER2 cancer						
Luminal, A type	96.4	91.6	–	–	–	0.8
Luminal, B type, HER–	91.7	90.2	–	–	–	
Luminal, B type, HER+	90.9	84.0				
Triple negative cancer	95.1	90.6	–	–	–	
ER0 PR0 HER2+ cancer	93.3	86.2	–	–	–	

was observed in 13.5% of patients. ER– PR– HER2+ variant turned out to be the most unfavourable cancer subtype (recurrence rate — 33.3%), p<0.01 (Table 3).

The comparison of overall survival indices showed no statistically significant prognostic value of any receptor: the indices of ER, PR and HER2 in monoanalysis and the analysis of different receptor combinations were identical (p>0.05) (Table 4). Since HER2-status of tumor was started to be determined after 2004, HER expression prognostic value both in monoanalysis, and in the analysis of combinations with steroid hormone receptors is analyzed for 1–5-year overall survival and recurrence-free survival (RFS).

The comparison of RFS indices showed the presence or absence of ER and PR receptor expression to have no independent prognostic value (Table 5) in contrast to tumor HER2-status that has prognostic value both in monoanalysis, and in the analysis of combinations with

Table 5

Recurrence-free survival indices in different steroid hormone receptor status in tumor, %

	Recurrence-free survival indices					p
	3-year	5-year	7-year	10-year	15-year	
			Monoanalysis			
ER–	87.6	87.6	77.6	72.3	56.1	0.8
ER+	89.2	89.2	78.3	74.5	57.4	
PR–	88.2	83.4	81.5	75.7	56.1	0.5
PR+	88.3	83.0	80.6	76.4	59.7	
			Analysis of ER PR combinations			
ER+ PR+	88.9	83.6	80.4	76.7	48.9	0.4
ER+ PR–	84.1	82.4	79.9	74.2	49.2	
ER– PR+	82.5	79.8	73.4	74.7	45.0	
ER– PR–	89.9	83.6	81.1	75.6	47.6	

Table 6

Indices of 1–5-year recurrence-free survival in different HER2-status of tumor (monoanalysis and analysis of immunohistochemical types), %

	Recurrence-free survival indices					p
	1-year	2-year	3-year	4-year	5-year	
			Monoanalysis			
HER2–	97.3	96.4	92.6	89.2	87.4	0.04
HER2+	93.8	90.6	82.9	76.7	73.4	
			Analysis of ER PR HER2 combinations			
Luminal, A type	98.1	95.5	93.9	93.2	90.0	0.03
Luminal, B type, HER2+	80.0	80.0	80.0	80.0	80.0	
Luminal, B type, HER2–	96.3	92.3	82.2	82.2	67.5	
Triple negative cancer	94.2	90.4	87.8	87.8	85.0	
ER0 PR0 HER2+ cancer	93.3	93.3	86.0	86.0	65.0	

steroid hormone receptors in tumor. Moreover, the difference in RFS indices was observed beginning from the first follow up year (Table 6) confirming literature data on unfavourable course of HER-positive breast cancer and the tendency of this cancer for early recurrence.

Thus, HER2 hyperexpression does not show prognostic value in overall survival analysis, though HER2 is an unfavourable factor for RFS both independently, and in combinations with receptors of steroid hormones.

Relatively favourable indices of recurrence rate and survival rate of female patients in triple negative cancer (recurrence rate — 13.5%; 5-year RFS — 85%) are likely to be explained by heterogeneity of the group. The group of triple negative cancer included not only unfavourable variants of invasive ductal carcinoma, but also favourable variants of medullary and tubular carcinomas characterized by the absence of expression of any receptors. To distinguish true basal-like variant of triple negative cancer that has immunohistochemical characteristics (ductal type of tumor, G2-3-degree of anaplasia, frequently: expression of HER1 and cytokeratins 5/6), more detailed immunohistochemical analysis is required.

Conclusion. The presence or absence of the receptors of steroid hormones ER (estrogen) PR (progesterone) in tumor has no independent prognostic value in early breast cancer, in contrast to HER2 hyperexpression that is an unfavourable prognostic factor both for recurrence risk, and for further survival of female patients. Disease recurrence risk in HER2+ cancer is double increased (21.9%; in patients with HER2– cancer: 9.9%; $p<0.05$), and recurrences are reported starting with the first follow up year. 5-year recurrence-free indices in HER+ are considerably lower than those in HER2– cancer (73.4 and 87.4%; $p<0.05$). ER– PR– HER2+ variant of cancer appeared to be the most unfavourable subtype of breast cancer, as one in three women with this cancer type has recurrence of the disease (33.3%; $p<0.01$), and 5-year recurrence-free survival rate is 65% ($p<0.03$). Relatively favourable course of the disease in triple negative cancer in our study (recurrence rate — 13.5%; 5-year recurrence-free survival rate is 85%) is most probably explained by the heterogeneity of female patients of this group.

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