

RECEPTOR STATUS OF TUMOR AS PROGNOSTIC FACTOR IN PATIENTS WITH BILATERAL BREAST CANCER

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Aim: To determine the receptor status of tumors as prognostic factor in development of bilateral breast cancer (BBC) and factor of prognosis of disease. **Patients and Methods:** 272 cases of BBC during the period from 1995 to 2011 in different oncological institutions of Ukraine have been analyzed. **Results:** Patients with metachronous BBC with positive status of hormone receptors (HR) of tumors have significantly better indices of overall and progression-free survival (three-years — 95%, five-years — 72%), than patients with HR-negative status (among them nobody has survived over 5 years). In patients with synchronous BBC, the receptor status of tumors has similar influence on the prognosis of survival. Nevertheless, indices of overall survival (65%) and progression-free survival (66%) in HR-positive patients were lower than that at metachronous BBC (overall survival and progression-free survival — 72%). **Conclusions:** Synchronous breast cancer has more aggressive clinical course than metachronous one. It was determined significant influence of receptor status of tumors on the overall survival and progression-free survival in patients with BBC.

Key Words: bilateral breast cancer, synchronous, metachronous, hormone receptors status.

Over the last decades the morbidity of bilateral breast cancer (BBC) has increased [1–4], that is explained by influence of etiological factors, increase of morbidity of unilateral breast cancer and improvement of opportunities of diagnostics of contralateral neoplasms and system of their registration. Researchers of problems of bilateral involvements of mammary gland have been tried to determine reliable risk factors of BBC development for timely diagnostics of second tumor and adequate treatment to improve the overall survival and quality of life of patients. However, up to now no reliable clinical-morphological factors, which would allow to prognosticate probability of BBC, were not proposed [2–5].

Hartman et al. [3] and Chen et al. [5] have stated that one of the factors, which influence the prognosis of BBC, is receptor status of tumor. McGuire [6] has marked that the first molecular factor of prognosis and hormone-sensitivity of breast cancer is status of estrogen receptors (ER). Several years later, the determination of level of progesterone receptors (PR) expression was also added to risk factors [7]. McGuire [6] and Horwitz et al. [7] have noted, that presence of both kinds of steroid receptors in tumor is the evidence of relatively favorable prognosis of clinical outcome of breast cancer and sensitivity to the hormonal therapy.

Kurian et al. [8] have stated, for patients, whose primary tumor had positive hormone receptors (HR), the risk of involvement of contralateral mammary gland is higher compared with overall population. Risk of BBC in women with negative HR status of primary tumor is statistically reliably higher than in women, whose primary tumor had positive HR.

Balleine et al. [9] have observed that absence of expression of PR in the first tumor is associated with

worse prognosis of disease outcome. Authors also observed significant decrease of PR expression in the second tumor in women in post-menopause compared with the first tumor by conditions that the first tumor developed in pre-menopause. In case of synchronous BBC, the receptor status of both tumors is almost the same.

Comparing the receptor status of synchronous and metachronous tumors, Soo Jung Gong et al. [10] have detected that in synchronous tumors the expression of ER is congruent in 71%, and expression of PR — in 86% of cases. At metachronous tumors both levels of ER and PR coincided in 52% of cases. It was also detected the age dependence of levels of expression of ER at synchronous variant of BBC. HR-positive synchronous tumors are much more often (71%) to be found in women, who are older than 50 years ($p=0.02$). At metachronous BBC the statistically significant difference between two age groups was not detected.

Swain et al. [11] have studied the dependence of BBC development on receptor status of primary tumor of mammary gland and treatment and shown that patients with positive ER have increased risk of metachronous BBC by conditions that the hormonal therapy was not been applied in treatment of primary disease. In contrast, patients with HR-positive status, who received tamoxifen or any other variant of hormonal therapy, were associated with decrease of risk of involvement of contralateral gland.

The same results have been obtained by Kurian et al. [8]. They have compared two groups of patients with HR-positive status, in one of groups patients were treated with, in another one — placebo. Authors have observed the tenfold increase of risk of development of metachronous BBC in women with HR-negative status and reliable decrease of survival in this group of patients.

The aim of our work was to determine the receptor status of tumors as prognostic factor in development of BBC and factor of prognosis of disease outcome in these patients.

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Abbreviations used: BBC — bilateral breast cancer; ER — estrogen receptors; HR — hormone receptors; PR — progesterone receptors.

PATIENTS AND METHODS

We have carried out retrospective analysis of data of 272 patients with BBC, who have been observed and treated in oncological institutions of Zakarpattia, Lviv, Volyn, Ivano-Frankivsk, Kyiv and Donetsk regions during 1995–2011. The study was approved by the local ethics committee.

Synchronous bilateral cancer is defined as simultaneous detection of mammary gland tumors with time interval up to 6 months between the first and the second tumor. Cancer of both mammary glands with interval between diagnosis of tumors more than 6 months is evaluated as metachronous bilateral cancer. Part of synchronous tumors was constituted 28.31% ($n = 77$), and metachronous — 71.69% ($n = 195$). We have conducted the evaluation and analysis of receptor status of tumors of both mammary glands and its impact on prognosis of disease outcome.

For some patients, in time of verification of diagnosis of the first tumor of mammary gland, was no technical opportunity to determine the receptor status of tumor. However, on the moment of detection of the second tumor of metachronous BBC the opportunities of morphological diagnostics were significantly better, therefore data on the receptor status were available for significantly larger number of patients. The distribution of patients into the first and the second breast cancer in accordance with presence of HR in tumor is presented in Table 1.

Table 1. Distribution of patients with metachronous BBC in accordance with the status of HR in tumors

Receptor status of tumor	First tumor		Second tumor	
	Number of patients	%	Number of patients	%
Negative HR	5	26.3	23	33.3
Positive HR	14	73.7	46	66.7
Total	19	100.0	69	100.0

Concerning the synchronous BBC, the receptor status of tumor was determined almost in half of patients. The distribution of patients in accordance with the presence of HR in tumors of both mammary glands is presented in Table 2.

Table 2. Distribution of patients with synchronous BBC according to the status of HR in tumors

Receptor status of tumor	Number of patients	%
Negative HR	11	32.4
Positive HR	23	67.6
Total	34	100.0

Overall survival is defined as interval between beginning of special treatment and death of patient (non-censored data) or date of the last information that patient is alive (censored data). If death of patient was occurred in consequence of another causes (i.e., not cause of breast cancer), such data were also considered to be censored.

Progression-free survival is defined as interval between date of beginning of special treatment of patient and date of the first detection of metastases or recurrence (non-censored data) or the last information about absence of generalization of process (censored data).

Expression of ER and PRs was evaluated by radiological and immunohistochemical methods.

Statistical processing has been carried out by program R-v2.15.0 with additional package “survival”. Significance of difference between groups has been evaluated by the Student’s *t*-criterion in Welch modification and by Wilkinson criterion. Statistical processing of overall survival and progression-free survival was performed with the help of Cox Regression.

RESULTS

In patients with full information about HR status of the first and the second tumor of bilateral metachronous cancer the full symmetry of indices of receptor status was observed. Tumors were differed from each other only in the level of HR expression. It was detected that middle age of patients with positive HR status of the second tumor was 57.01 ± 2.28 years/in patients with negative HR — 52.06 ± 7.25 years ($p = 0.120$).

The impact of HR status of the first tumor on the risk of development of BBC was determined. We have shown that the time before detection of the second tumor was 7.95 ± 0.81 years in patients with metachronous BBC with HR-positive first tumor, while in patients with negative HR status this interval was 6.21 ± 2.08 years ($p = 0.7753$).

In group of synchronous BBC with HR-positive status of tumor the middle age of patients was 58.40 ± 6.12 years, in patients with HR-negative status — 48.85 ± 8.39 years ($p = 0.02559$). Among patients of this group in 94.45% ($n = 34$) of cases tumors of right and left mammary glands coincided with each other in respect to HR. Only in two patients (5.55%) tumors of right and left mammary glands have demonstrated the difference in receptor status.

We have detected that receptor status of tumor in group of patients with metachronous breast cancer had essential impact on the overall survival ($p = 0.0333$). Among patients with metachronous BBC with positive HR $94.60 \pm 4.71\%$ and $72.53 \pm 8.24\%$ of patients have survived three and five years, respectively. It was observed that among patients with negative HR, three-years have survived $92.50 \pm 4.26\%$ of patients, and no patients have lived more than five years ($p = 0.0333$).

The impact of receptor status of tumor on the progression-free survival was determined. In patients with positive HR the progression-free survival was the same as overall survival (three-years — $92.20 \pm 4.56\%$, and five-years — $71.03 \pm 8.57\%$). Three years without progression with negative HR have lived $69.24 \pm 9.11\%$ of patients, and no patient have lived more than five years. Difference between these groups was also statistically significant ($p = 0.0212$).

We have also analyzed the impact of receptor status on the overall survival of patients with synchronous BBC (Fig. 1). Among patients with synchronous breast cancer with positive HR for three years have lived $64.42 \pm 14.96\%$, and for five years — $48.20 \pm 17.87\%$ of patients. Among patients with negative HR three-

years overall survival was $44.32 \pm 22.20\%$, and five-years survival was not registered ($p = 0.211$).

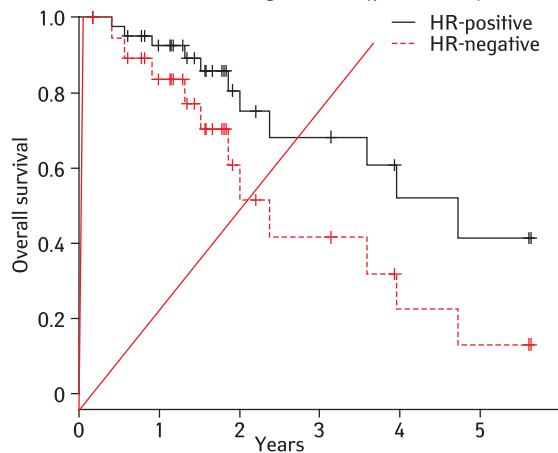


Fig. 1. Overall survival of the patients with synchronous BBC according to the HR status of tumors (Cox Regression, $p = 0.1683$)

The same tendency was observed by analyzing of progression-free survival of patients with synchronous BBC (Fig. 2). Among patients with positive HR both three-years and five-years progression-free survival was $65.80 \pm 12.96\%$. Among HR-negative patients no one has lived for five years without progression, and three-years was $44.40 \pm 22.20\%$ for patients with synchronous BBC ($p = 0.116$).

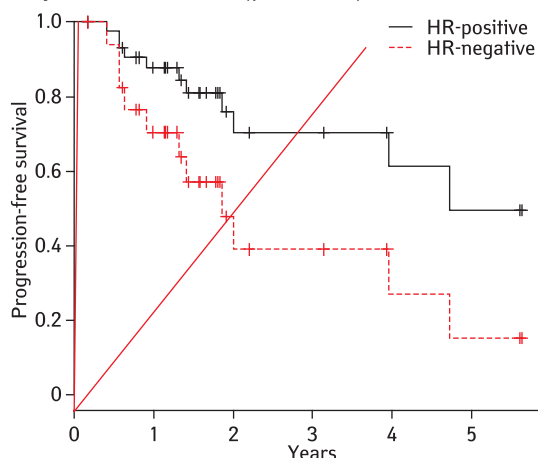


Fig. 2. Progression-free survival of the patients with synchronous BBC according to the HR status of tumors (Cox Regression, $p = 0.106$)

DISCUSSION

The impact of HR status of the first tumor on the risk of development of BBC was not statistically significant ($p = 0.7753$). Nevertheless, we have obtained almost two-years difference between two groups of patients, that may suggest that metachronous tumor develops faster in patients with negative receptor status of steroid hormones.

It was shown that HR status essentially influences the overall survival of patients ($p = 0.0333$). Thus, among patients with positive HR 95% of them have lived for three years and 73% of them have lived for five years. Among patients with negative HR three-years overall survival was 92%, and no patient with metachronous BBC has lived more than five years.

Moreover, we have determined that the progression-free survival in patients with positive HR was the same as overall survival (three-years — 95%, and five-years — 73%). Seventy six percent of patients with metachronous BBC, who had negative HR, have lived three years without progression. Difference between these groups was also statistically significant ($p=0.0212$) that can indicate the essential impact of HR status on the progression-free survival.

Analyzing levels of three-years and five-years overall survival of patients with synchronous BBC with different receptor status of tumor, we have determined that among patients with positive HR these indices were 64% and 48%, respectively, while in patients with negative HR status — 44% and 0%. The observation that overall survival is increased at positivity of receptor status of tumor was not statistically significant ($p=0.211$).

The same results were obtained in the study of progression-free survival in accordance with the status of receptor of steroid hormones in synchronous BBC. Among patients with positive HR both three-years and five-years progression-free survival was 66%, while among patients with negative HR the five-years boundary without progression no one has overcome, and three-years survival was 44%. It has to be noted that the dependence of progression-free survival in patients with synchronous BBC on receptor status of tumors was not statistically significant ($p=0.116$).

We have also noted that patients with bilateral cancer with HR-negative status, in average, are 10 years younger, than patients with positive status of HR. It was observed that among patients with synchronous BBC indices of overall survival and progression-free survival are worse, than in patients with metachronous BBC. In our opinion, it is the evidence that synchronous cancer, especially with negative HR of tumor, is characterized by greater aggressiveness.

In conclusion, for patients with breast cancer with negative HR the time between detection of the first and the second breast cancer was, in average, 6 years, in patients with positive HR — 8 years. In patients with metachronous BBC with HR-positive status of tumors the indices of overall survival and progression-free survival were significantly better (three-years — 95%, five-years — 72%), than in patients with HR-negative status, whose overall three-years and five-years survival were 92 and 0%, and progression-free survival — 76 and 0%, respectively.

In patients with synchronous BBC receptor status of tumors has the same influence on overall survival and progression-free survival. However, indices of overall five-year survival (65%) and progression-free survival (66%) in patients with positive HR are lower, than the similar indices at metachronous BBC. It may be suggested that it is the evidence of greater aggressiveness of synchronous variant of disease.

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