UDC № 618.19-00694

HORMONOTHERAPY IN PATIENTS WITH BILATERAL BREAST CANCER

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Summary. The incidence of bilateral breast cancer (BBC) is increasing all around the world. This leads to the definition of clear approaches towards these patients treating tactics, including hormonotherapy of bilateral breast cancer.

Methods. In the period from 1995 to 2011 totally 272 cases of bilateral breast cancer were analyzed in various cancer institutions of Ukraine compared to 92 cases of unilateral breast cancer.

Results. The use of hormonotherapy improves the 5-year overall survival and progression-free survival in patients with unilateral and bilateral breast cancer. Metachronous breast cancer (HT"+": OS – 93%, PFS – 89%; HT"–": OS – 80%, PFS – 70%) has worse survival rates than unilateral cancer (HT"+": OS – 94%, PFS – 92%; HT"–": OS – 81%, PFS – 78%). While synchronous BBC has poorer survival rates than metachronous one (HT"+": OS – 73%, PFS – 74%; HT"–": OS – 49%, PFS – 53%).

Conclusion. Bilateral breast cancer has a more aggressive disease course than unilateral one. Synchronous breast cancer has a more aggressive disease course than metachronous one. The use of tamoxifen is not enough for hormonal therapy of BBC. These patients should be treated with the use of aromatase inhibitors.

Keywords: bilateral breast cancer, synchronous, metachronous, hormonotherapy..

Introduction. Determination of the principal positions in the choice of treatment strategy remains to be one of the important aspects of the problem of bilateral breast cancer. According to Bernstein J.L. et al. [1] this is primarily due to the increase in the proportion of such patients. As noted by Kurian AW et al. [2], a few decades ago, the second detection of malignant tumors usually had a contraindication to radical treatment planning.

To determin the treatment strategy of metachronously and synchronously detected tumors - the problem is much more complex and requires a more differentiated approach to each individual patient [3]. According to the authors, the factors that have an influence on the choice of treatment of BBC include the following: the nature of the breast lesion (synchronous, metachronous), location and stage of each tumor, histogenesis, prognosis of each of the detected tumors, age and somatic state of patients and disorders associated with the presence of tumors, the character of previous treatment, the state of menstrual function, etc. [4,5]. Stark A. et al. [6] and Brankovic-Magic M. et al. [7] assure that therapeutic tactics for patients with metachronous breast cancer should not differ from those for patients with unilateral cancer.

Gong S. J. et al. [8] believe that medical tactics must be based on the main prognostic factors - age, menstrual status, presence of a family history, the stage of each tumor. In addition, the scientists convinced that the treatment of the second tumor must differ by more radical means.

Many authors include patients with bilateral breast cancer in the group at high risk of cancer. That is why a greater radicalism is justified in the treatment of a bilateral breast cancer compared with unilateral breast cancer. However, Skowronek J. and Piotrowski T. [9] argue that the treatment of metahronous tumor should be similar to the treatment of the first tumor. Clinical management of patients with bilateral breast cancer should correspond to the stage of disease based on biological parameters of the tumor [9]. Li C.I. et al [10] believe that the indications for systemic chemotherapy, hormone therapy or radiation therapy in the treatment of the second tumor are the same as in the primary tumor.

Many researchers have determined the dependence of the risk of bilateral breast cancer , depending on the receptor status of the primary breast cancer and of presence of hormonotherapy in its treatment. However, only few researches devoted their studies towards the effect of hormonal therapy on survival rates in patients with bilateral breast cancer. History of hormonotherapy for breast cancer in Ukraine has its own characteristics . Drugs that block the action of estrogen took the powerhouse earlier than it was possible to routine determination of expression of estrogen and progesterone in breast tumors. Another feature applies to patients with bilateral breast cancer. Mostly in identifying the second tumor (synchronous or metahronous) receptor status was not determined whether it has been defined by morphological verification of the first tumor. Given to these nuances in those 90 years there was a widespread phenomenon when hormonal therapy was intended and was conducted with patients who had unknown hormone receptor status of the tumor. To present date there is no consensus regarding appropriate treatment strategy of BBC. Should it be the same as in unilateral breast cancer or more aggressive? What hormonal therapy is optimal for patients with bilateral breast cancer?

The purpose of the study

The purpose of this study is to evaluate the impact of hormonotherapy on overall survival and progression-free survival in the treatment of patients with synchronous and metachronous bilateral breast cancer compared with those of patients with unilateral breast cancer.

Materials and Methods

The study included 272 patients with bilateral breast cancer during the period from 1995 to 2011, which amounted to a total sample of patients with this pathology. The cohort of patients was carried out in oncological institutions of Transcarpathian, Lviv, Volyn, Ivano-Frankivsk, Kyiv, Rivne and Donetsk regions. The diagnosis of breast cancer for all the patients was confirmed histologically. Out of the 272 patients 195 patients were identified with metachronous BBC and 77 patients with synchronous BBC. Control group were the 92 patients with unilateral breast cancer.By synchronous bilateral tumor were classified as those that are identified simultaneously in both breasts or the interval between the first and second tumor is not more than 6 months.

By metahronous bilateral cancers were classified as those tumors that were detected in both breasts gradually after 6 months or more.

Receptor status of the first tumor of metahronous bilateral breast cancer is evaluated for 19 patients (Table 1). Such a small number of patients with known ER and PR-tumors statuses due to the fact that at the time of diagnosis was not possible to determine these parameters (70 - 90 years). The content of steroid receptors in the tumors was evaluated by radioligand and immunohistochemical methods.

Among the 34 patients with synchronous bilateral breast cancer receptor status was determined in both tumors. Status of steroid hormone receptors tumor of unilateral breast cancer was identified among 67 patients.

The distribution of patients with bilateral and unilateral breast cancer according to hormone receptor status in the first and second tumors is presented in Table 1

Distribution of patients with bilateral and unilateral breast cancer according to the presence or absence of hormonal therapy in their treatment are presented in Table 2.

The vast majority of patients in all three compared groups used tamoxifen for hormonal therapy.

In the group of synchronous BBC was not enough data to estimate the extent of 10-year survival. Considering the above, for comparative analysis of hormonotherapy among patients with metachronous, synchronous and unilateral breast cancer we used the 5-year overall survival and 5-year progression-free survival.

Statistical analysis of the material was carried out using R 2.15.1 [R Core Team (2012). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL: www.R-project.org]

Breast cancer		**HR-negative**		**HR-positive**		**Total**	
		n	**%**	**n**	**%**	**n**	**%**
Unilateral		21	31,34	46	68,66	**67**	**100,00**
Metachronous	**First tumor**	5	26,31	14	73,69	**19**	**100,00**
	Second tumor	23	33,33	46	66,67	**69**	**100,00**
Synchronous	**Left breast**	7	20,59	27	79,41	**34**	**100,00**
	Right breast	6	17,65	28	82,35	**34**	**100,00**

Table 1. Distribution of patients with bilateral and unilateral breast cancer according to the hormone receptors status of tumors.

Breast cancer		Hormonotherapy " + "*		Hormonotherapy " – "		Total	
		n	%	n	%	n	%
Unilateral		49	53,26	43	46,74	**92**	**100,00**
Metachronous	First tumor	58	29,74	137	70,26	**195**	**100,00**
	Second tumor	75	38,46	120	61,54	**195**	**100,00**
Synchronous		36	46,75	41	53,25	**77**	**100,00**

Table 2. Distribution of patients with bilateral and unilateral breast cancer according to the presence or absence of hormonal therapy in their treatment.

* – all patients who received any hormonotherapy variant were combined into one group.

Using an additional package for the analysis of survival "survival" [Terry Therneau (2012). A Package for Survival Analysis in S. R package version 2.36-14.]. Significance of difference between groups has been evaluated by 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 and discussion

In determining receptor status of tumors depending on the age of the patients with bilateral breast cancer and unilateral breast cancer, we found that the average age of the patients did not differ significantly in the three study groups ($p > 0.05$). In general, patients with metahronous, synchronous or unilateral breast cancer with negative receptors were younger than patients with positive tumor steroid hormone receptors status (Table 3). Therefore, in our opinion, bilateral breast cancer does not differ from unilateral disease according to the age parameter.

Average age	HR-negative (years)	HR-positive (years)
Unilateral BC	51,34 ± 7,11	56,53 ± 5,39
Metachronous BBC	52,06 ± 7,25	57,01 ± 2,28
Synchronous BBC	48,85 ± 8,39	58,40 ± 6,12

Table 3. The average age of patients with bilateral breast cancer and unilateral depending on the receptor status of tumors.

The study of 5-year overall survival of patients with metachronous, synchronous and unilateral breast cancer depending on the availability of hormonotherapy in the complex treatment has allowed us to establish the following results (Table 4). Among patients with breast cancer unilateral 5-year overall survival rate amounted to 94,20 ± 4,01% among patients who underwent hormone therapy. Among patients with breast cancer unilateral who did not receive hormone therapy survived 5 years 81,03 ± 8,24% of patients.

As can be seen from this data, 5-year overall survival among patients with metahronnyy BBC receiving hormone made 92,70 ± 4,17% of patients and among patients without a history of hormonal therapy survived 5 years 80,34 ± 5,32% of women.

5-year overall survival	Hormonotherapy «+» (%)	Hormonotherapy «–» (%)
Unilateral BC (p>0.05)	94,20 ± 4,01	81,03 ± 8,24
Metachronous BBC (p>0.05)	92,70 ± 4,17	80,34 ± 5,32
Synchronous BBC (p>0.05)	72,70 ± 12,40	48,90 ± 16,65

Table 4
5-year overall survival among patients with bilateral and unilateral breast cancer depending on the presence of hormonotherapy in the treatment complex

Among patients with synchronous disease treated with hormonotherapy 5-year overall survival rate amounted to 72,70 ± 12,40% of people. Among those patients with synchronous BBC who did not receive hormone therapy for five years survived 48,90 ± 16,65% of patients. Our results did not achieve statistical significance in any of the three studied groups. However, despite the statistical unreliability, we observed a marked clinical benefit from the use of hormonotherapy among patients with bilateral and unilateral breast cancer.

Similar results are obtained as a result of study of the effect hormonotherapy on 5-year progression-free survival (Table 5). Among patients with unilateral breast cancer who underwent hormone therapy 92,36 ± 4,42% of women lived 5 years without progression. For those patients treated with hormonotherapy we found that 5-year progression-free survival amounted to 78,02 ± 5,21% of patients.

In the group of metahronous BBC among patients who underwent hormone therapy for five years without progression lived 89,10 ± 5,07% of women, and among those patients who were treated without hormone therapy 5-year progression-free survival amounted to 70,20 ± 5 22% of patients. A clear dependence of progression-free survival due to presence of hormonotherapy in complex of treatment of metahronous bilateral breast cancer gets its graphical representation in Figure 1. As seen in this Figure 1 and Tables 4 and 5, the use of hormone therapy in the treatment of metahronous BBC significantly improves the survival of patients.

Taking into consideration the results comparing the effectiveness of treatment of synchronous, metahronous and unilateral breast cancer using hormonotherapy we can notify next positions. Synchronous breast cancer differs by the most aggressive course of the disease as the 5-year overall survival and progression-free survival are the worst.

5-year progression-free survival	Hormonotherapy «+» (%)	Hormonotherapy «–» (%)
Unilateral BC (p<0.05)	92,36 ± 4,42	78,02 ± 5,21
Metachronous BBC (p<0.05)	89,10 ± 5,07	70,20 ± 5,22
Synchronous BBC (p>0.05)	73,80 ± 10,25	52,70 ± 15,20

Table 5
5-year progression-free survival in patients with bilateral and unilateral breast cancer depending on the presence of hormonotherapy in the treatment complex.

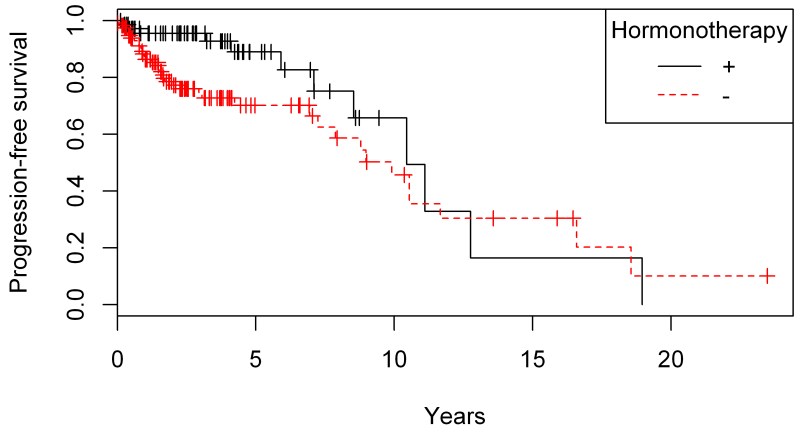

Fig. 1. Progression-free survival of patients with metachronous bilateral breast cancer, depending on the presence of hormonotherapy in treatment (Cox regression, p=0,0499).

This also applies to those patients who received hormone therapy (OS - 73 %, PFS - 74%) and those treated without the use of hormone therapy (OS - 49 %, PFS - 53%). Patients with metachronous breast cancer have a more favorable course of the disease than patients with synchronous breast cancer. Nevertheless, 5-year survival of patients with metachronous breast cancer with hormone therapy in a history of treatment (OS - 93 %, PFS - 89%) or without hormonal therapy (OS - 80 %, PFS - 70%) is worse than in patients with unilateral breast cancer (HT "+": OS - 73 %, PFS - 74 %; HT "-": OS - 49 %, PFS - 53%). Based on the results it can be assumed that the approach to hormone therapy of bilateral breast cancer may not be such as at unilateral breast cancer and should vary more aggressive with modern drugs including aromatase inhibitors.

Conclusions

1. Status of steroid hormone receptors and tumor of unilateral and bilateral breast cancer does not depend on the age parameter.
2. The use of hormonotherapy improves the 5-year overall survival and progression-free survival among patients with unilateral and bilateral breast cancer.
3. Metahronous breast cancer (HT "+": OS - 93%, PFS - 89%; HT "-": OS - 80%, PFS - 70%) has a more aggressive disease course than unilateral cancer (HT "+": OS - 94%, PFS - 92%; HT "-": OS - 81%, PFS - 78%). While synchronous breast cancer is more aggressive than metachronous (HT"+": OS – 73%, PFS – 74%; HT"–": OS – 49%, PFS – 53%).
4. For a better survival rates of patients with bilateral breast cancer the tamoxifen use is not sufficient. Therefore, it is necessary to use more modern drugs for this group of patients including aromatase inhibitors.

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