BILATERAL BREAST CANCER: DIAGNOSIS AND PROGNOSIS

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BILATERAL BREAST CANCER: DIAGNOSIS AND PROGNOSIS (Abstract): Aim: To assess bilateral breast cancer patients, initially diagnosed with stage II unilateral breast cancer. Material and Methods: 113 patients with stage 0-II breast cancer diagnosed between 1983 and 2011 were assessed. Of these, 8 patients had bilateral breast cancer: 7 patients with metachronous bilateral breast cancer and 1 patient with synchronous breast cancer. Breast ultrasound, mammography, computed tomography and magnetic resonance imaging were used to diagnose recurrence, loco regional and distant metastasis. Results: Age at diagnosis ranged from 37 to 59 years, with a maximum age incidence in the 4th decade (age between: 31-40 years). The average time interval between the two breast cancers was 8.125 years. The most common histological type was invasive ductal carcinoma. All eight patients with bilateral breast cancer had at least one type of recurrence/metastasis, mostly in the liver, and statistically the pleuro-pulmonary and liver metastases were the most frequent causes of death. Conclusions: Patients in the 4th decade diagnosed with unilateral breast cancer are at risk of developing bilateral breast cancer. In metachronous breast cancer, the time interval between the detection of the second breast cancer and death is directly proportional to the time interval between the two breast cancers. Keywords: BILATERAL BREAST CANCER, METASTASES, DEATH.

Primary bilateral breast cancer is rare, with a reported incidence ranging between 0.5 – 12% (1, 2). Synchronous form is less common than the metachronous one, with a ratio of 1:4 (3). The second breast cancer in the contralateral breast is more frequently diagnosed today than in the past due to the implementation of the national follow-up protocol after surgical treatment.

Bilateral breast cancer is a particular type characterized most often by a genetic component, occurs in a hormonal context and is characterized by an aggressive development (1, 4, 5).

MATERIAL AND METHODS
We retrospectively analyzed 113 patients with stage 0-II breast cancer, treated with radical or breast-conserving surgery. They were diagnosed with mammary neoplasia between January 1983 - December 2011, and deaths from breast cancer were recorded between January 2005 - December 2012. After diagnosis, patients were referred to the
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Oncology Clinics of the Iasi „Sf. Spiridon” University Hospital or Iasi Regional Cancer Institute, where they were assessed according to the national follow-up protocols. The imaging tools included standard mammography, breast ultrasound, computed tomography and magnetic resonance imaging, which allowed the detection of locoregional recurrences or distant metastases.

For statistical data analysis we used SPSS 16.00 for Windows to determine the frequency, multiple regression, enter method, regression coefficient, Pearson correlation (r), relative risk (RR) assessment, and odds ratio (OR), Chi-Square Tests, ANOVA test, test of significance (significant at \( p<0.05 \)) and confidence interval (CI).

RESULTS

Of the 113 cases included in the study, 8 (7%) patients had bilateral breast cancer. Of these 7 (87.5%) patients had metachronous bilateral breast cancer and 1 (12.5%) synchronous breast cancer. In patients with metachronous breast cancer the interval between the two cancers was variable, as follows: 3 years in 1 patient, 5 years in 2 patients, 6 years in 2 patients, 15 years in 1 patient and 24 years in 1 patient.

In the study group the average time interval between the two breast cancers was 8.125 years (tab. I).

<table>
<thead>
<tr>
<th>Breast Cancer type</th>
<th>No. of cases</th>
<th>Minimum time interval between breast neoplasms (yrs.)</th>
<th>Maximum time interval between breast neoplasms (yrs.)</th>
<th>Average time interval between breast neoplasms (yrs.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilateral</td>
<td>8</td>
<td>0</td>
<td>24</td>
<td>8.125</td>
</tr>
</tbody>
</table>

Age at the time of diagnosis of the first breast cancer ranged from 37 to 59 years, with a maximum frequency in the 4th decade (4 cases) (fig. 1).

![Years](image)

**Fig. 1.** Case distribution according to age at the time of diagnosis of the first breast cancer.

All patients were initially diagnosed with stage II breast cancer in one breast. Contralateral breast cancer was diagnosed as:

- stage I, in 5 patients, (breast cancer in the second breast occurred during the first six years after the first diagnosis of cancer);
- stage II, in 2 two patients (breast cancer in the second breast occurred 15 to 24 years after the first diagnosis of cancer);
- stage II, in one patient with synchronous breast cancer.

Surgical procedures included bilateral radical mastectomy (3 patients), radical mastectomy in one breast and breast-conserving surgery in the other breast (3 patients), bilateral breast-conserving surgery (2 patients). Histopathology revealed that the most frequent type was invasive ductal carcinoma (5 cases), while intraduc-
tal carcinoma and invasive lobular carcinoma were found in one case each. One patient had invasive ductal carcinoma associated with ductal carcinoma in situ. It was noted that in a majority of cases (5 cases) the right and left breast tumors shared the same histological type, but in 3 cases the right and left breast tumors were of different histological types. Immunohistochemistry revealed that the tumors were in 5 (62.5%) patients’ hormone receptor-positive and Her-2/neu protein-negative, in 2 (25%) patients hormone receptor-negative and Her-2/neu protein-negative, and in 1 (12.5%) patient hormone receptor-positive and Her-2/neu protein-positive.

All 8 patients with bilateral breast cancer had at least one type of recurrence/metastasis. Three patients had only one type of metastasis; two patients had two types of metastasis; one patient presented three types of metastasis and two patients four types of metastasis. Liver metastases were the most common (5 patients) and pleural metastases the less common (1 patient) (tab. II).

<table>
<thead>
<tr>
<th>Metastasis</th>
<th>Local</th>
<th>Lymph nodes</th>
<th>Bone</th>
<th>Lung</th>
<th>Pleura</th>
<th>Liver</th>
<th>Skin</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases (%)</td>
<td>3 (37.5)</td>
<td>2 (25)</td>
<td>3 (37.5)</td>
<td>2 (25)</td>
<td>1 (12.5)</td>
<td>5 (62.5)</td>
<td>2 (25)</td>
</tr>
</tbody>
</table>

The relative risk and odds ratio (OR) of any metastasis to determine other types of metastasis were evaluated. When OR>1, the data are statistically significant. Although liver metastases were the most common, they were not a risk for the occurrence of other types of metastasis, being the sole type of metastasis in two patients. Only local recurrence and lymph node metastases presented a risk for the occurrence of other types of distant metastases. Significant associations were found between local recurrences and lymph node recurrence (OR = 15.333) and lymph node recurrence and skin metastases (OR = 7.636).

The time interval between first diagnosis and death was variable: 5 years (2 patients), 6 years (2 patients), 7 years (1 patient), 9 years (1 patient) and 25 years (1 patient).

The time interval between the diagnosis of the second cancer and death was: 1 year (2 patients), 2 years (2 patients), 3 years (1 patient), 4 years (1 patient), 5 years (1 patient) and 8 years (1 patient).

In our study group, all 8 patients had bilateral breast cancer and breast cancer as a cause of cancer death. The Pearson correlation coefficient (r) was calculated to detect the association between cause of death and bilateral breast cancer or type of secondary metastases that could cause death. Pearson correlation coefficient is used to measure the strength of a linear association between two variables, where the value r = 1 means a perfect positive correlation, value r = -1 means a perfect negative correlation, and 0 is no correlation.

In our case, it showed a significant negative correlation between cause of death and bilateral breast cancer (r = -0.246), between cause of death and lung metastasis (r = -0.562), pleural metastasis (r = -0.394) and liver metastasis (r = -0.506).

**DISCUSSION**

In our study the incidence of bilateral breast cancer was of 7%, similar to that reported in the literature (6), with the pre-
dominance of bilateral metachronous cancer.

A peculiarity of bilateral breast cancer in our study was the age at the first cancer diagnosis. While the literature shows an increased frequency of unilateral breast cancer in the fifth decade of life (51-60 years), in our study the patients had their first breast cancer diagnosed most commonly in the fourth decade (31-40 years) (7, 8). One particular aspect is that in most patients the breast cancer in the second breast was lower stage than in the first one (9). Thus, in all patients included in the study, the first malignancy was diagnosed in stage II and the second malignancy in stage I (5 cases). This was possible when all steps in the breast cancer imaging protocol were followed. This protocol provided a close follow-up of patients during the first 5 years after surgery: usually breast ultrasound at six months and annual mammograms. In the other two metachronous breast cancer cases, the contralateral cancer was diagnosed in stage II (more than 10 years after the first diagnosis). In these patients with stage II contralateral disease, the diagnosis was made during the annual breast cancer follow-up imaging. It is known that bilateral breast cancer at a young age can have a hereditary origin, and these patients may have a genetic predisposition for other type of cancer (10-14). Although our study group included patients who had another type of cancer (pancreas, stomach, colon, cervix, bladder, ovary, lymphoma, tongue), none of the patients with bilateral breast cancer had any other type of cancer.

Histology showed that invasive ductal carcinoma was the most common histologic type in both breast tumors, and combination histologies were uncommon (one case). Although the literature shows that the immunohistochemical characteristics of bilateral breast tumors are different (15), in our study the immunohistochemical data were similar for the two breast tumors.

Bilateral breast cancer patients had various types of single- or multiple-organ recurrences/metastases, but it was statistically demonstrated that liver, lung or pleural metastases are causes of death.

In most cases with metachronous bilateral breast cancer it was found that the time interval between the second breast cancer detection and death is directly proportional to the time interval between the two breast cancer diagnoses. Thus, it was noted that when bilateral breast cancer was diagnosed after a long time (10-15 years), patient death occurs after a longer time interval (4 to 5 years) as compared to the patients in which the time interval between the two cancers is shorter (1-5 years), when patient death occurs within less than 4 years after the second breast cancer was diagnosed. In patients with bilateral breast cancer, metastases from the second breast cancer were the major cause of death.

**CONCLUSIONS**

This study revealed that patients diagnosed with unilateral breast cancer during the fourth decade of life (31-40 years) are at risk of developing a contralateral breast cancer.

In patients with bilateral breast cancer, early diagnosis depends on breast imaging according to a well-established protocol during and after the first five postoperative years.

In metachronous breast cancer the time interval between the detection of the second breast cancer and death is directly proportional to the time between the two breast cancer diagnoses.
REFERENCES