The aim of the study was to analyze clinicopathological features in breast cancer patients with local recurrence (LR).

Material and methods. A retrospective analysis of database of breast cancer patients operated on in the Department of Surgical Oncology in Łódź from 1 January 2009 to 30 June 2013, identified 1080 women with primary breast cancer and 11 patients with LR.

Results. LR rate was 0.23% per year. True recurrence (TR) occurred more frequently in patients with luminal B molecular subtype, in HER-2 positive and in triple-negative subgroups. In one patient with luminal -A subtype new primary (triple negative) occurred. TR were noted predominantly in patients with axillary lymph nodes metastases and with luminal B subtype who did not receive adjuvant chemotherapy but were given only endocrine therapy. LR were observed more frequently in patients who did not receive adjuvant radiotherapy or this treatment was delayed. Minimal surgical margins in postoperative specimens measured by pathologist were 4-25 mm, mean 9.5 mm.

Conclusions. The LR rate in patients operated on breast cancer in the Department of Surgical Oncology between 2009 and 2013 was low. TR was diagnosed in patients with non- luminal A breast cancer despite wide surgical margins, especially if the patients did not receive optimal adjuvant systemic treatment or radiotherapy was delayed or omitted. Complete cancer excision followed by an immediate implementation of optimal adjuvant treatment seems to be crucial especially in patients with poor tumor biology.

Key words: breast cancer, local recurrence

According to the European Society of Mastology (EUSOMA) the optimal treatment of breast cancer patients is carried out in specialist breast units (1). One of the quality indicators is the rate of local recurrence (LR). The guidelines drawn up by the EUSOMA and ESMO (European Society of Medical Oncology) expert panelists accept the rate of LR in breast cancer patients less than 1% per year (2). In highly experienced institutions these figures usually do not exceed 0.5% per year thanks to close cooperation of multidisciplinary team (1, 2).

Ipsilateral LR are divided in two different categories: a true recurrence and new primary (3). The differences between both entities are summarized in tab. 1 (3, 4).

The aim of this study was to analyze clinicopathological features in breast cancer patients with LR.

MATERIAL AND METHODS

A retrospective analysis of database of breast cancer patients operated on in the Department of Surgical Oncology, Regional Cancer Center in Łódź from January 2nd 2009 to June 30th 2013, identified 1080 women with primary breast cancer and 11 patients with LR. The database of routine clinicopathological factors for the latter subgroup was created. Descriptive statistical analysis was performed using Excel 2013.
RESULTS

Clinicopathological characteristics of the analyzed patients with LR are presented in tab. 2.

The cumulative rate of LR in the analyzed group of 1080 patients was 1% (11 out of 1080) which means 0.23% per year. Recurrences were noted in the mastectomy scar, in the residual breast after BCS and in one case in the axilla. Axillary dissection was performed in 477 patients and sentinel node biopsy procedure was carried out in 603 patients. Only one recurrence was classified as the new primary cancer in a patient after BCS as it was located in another breast quadrant with different histological characteristics and grade. Ten recurrences were identified as true ones. Mean age of patients with local recurrence was 61.8 years, range 43-78 years. Recurrence appeared from one to 86 months after primary surgery, mean 25.9 months.

Histological characteristics of primary cancers were as follows: ductal carcinoma – in eight patients, lobular in two, mixed in one patient, grading G 1 – one, G2 – two, G3 – six patients. Tumors less than 2 cm (pT1) were resected in three and less than 5 cm (pT2) – in five patients. Three patients with locally advanced breast cancer (cT4) were given preoperative chemotherapy. In postoperative specimens in one patient cancer was classified as ypT2 and in two – as ypT3. Multifocality was described in 3 patients. Metastases to the axillary lymph nodes were found in eight patients, in two of them – micrometastases. In one patient initially with cN+, pathologic complete response in the axillary lymph nodes (ypN0) was confirmed after preoperative chemotherapy.

During axillary dissection from 5 to 21 axillary lymph nodes were harvested, mean 11. In one patient sentinel node biopsy was performed. According to the St. Gallen 2011 classification the surrogates of molecular subtypes were: luminal A – in one (new primary), luminal B HER2 negative- in four patients, luminal B HER2 positive – in one patient, non-luminal HER2 positive – in two, triple negative – in three patients. Mastectomy was performed in eight patients, three patients underwent BCS. Minimal surgical margins measured by the pathologist in postoperative specimens ranged between 4 and 25 mm, mean 9.5 mm.

In patients with LR who primary underwent BCS, mastectomy was done. LR in the mastectomy scar were widely excised. Recurrence in the axillary region was deemed inoperable. Adjuvant chemotherapy was given to four patients, six patients received adjuvant endocrine treatment. Three patients were given neoadjuvant chemotherapy. One patient treated with tamoxifen interrupted her therapy after 2 months on her own. In one patient taxane was discontinued after one cycle due to unacceptable toxicity. Two patients with HER2 positive tumors received trastuzumab in the adjuvant setting in standard doses. Patient
Table 2. Clinicopathological features in breast cancer patients with local recurrence

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Histological Type</th>
<th>pT</th>
<th>pN</th>
<th>Multifocality</th>
<th>Margins (mm)</th>
<th>Type of surgery</th>
<th>Sentinel Lymph node biopsy</th>
<th>Chemotherapy</th>
<th>Trastuzumab</th>
<th>Endocrine therapy</th>
<th>Radiotherapy</th>
<th>Local recurrence – months after operation</th>
<th>Dissemination of cancer after local recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pt1</td>
<td>78</td>
<td>lobular</td>
<td>T2</td>
<td>N1 (macromets in one lymph node)</td>
<td>-</td>
<td>Lum-BHER2(+)</td>
<td>yes 25</td>
<td>mastectomy</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>19</td>
</tr>
<tr>
<td>Pt2</td>
<td>52</td>
<td>ductal</td>
<td>T2</td>
<td>N2 (macromets in five lymph nodes)</td>
<td>5</td>
<td>HER2</td>
<td>no 5</td>
<td>mastectomy</td>
<td>no</td>
<td>AC (unacceptable toxicity)</td>
<td>yes</td>
<td>no</td>
<td>delay</td>
<td>13</td>
</tr>
<tr>
<td>Pt3</td>
<td>59</td>
<td>ductal</td>
<td>T2</td>
<td>N1 (macromets in one lymph node, extracapsular invasion)</td>
<td>3</td>
<td>TN</td>
<td>yes 4</td>
<td>BCT</td>
<td>no</td>
<td>AC</td>
<td>no</td>
<td>no</td>
<td>delay</td>
<td>8</td>
</tr>
<tr>
<td>Pt4</td>
<td>68</td>
<td>ductal</td>
<td>T2</td>
<td>N0</td>
<td>3</td>
<td>Lum-BHER2(+)</td>
<td>no 8</td>
<td>mastectomy</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>Tam</td>
<td>no</td>
<td>17</td>
</tr>
<tr>
<td>Pt5</td>
<td>61</td>
<td>lobular</td>
<td>T1</td>
<td>N1mi (one lymph node)</td>
<td>1</td>
<td>Lum-BHER2(+)</td>
<td>no 5</td>
<td>mastectomy</td>
<td>no</td>
<td>AC</td>
<td>no</td>
<td>Tam</td>
<td>yes</td>
<td>16</td>
</tr>
<tr>
<td>Pt6</td>
<td>63</td>
<td>ductal</td>
<td>T1</td>
<td>N0</td>
<td>1</td>
<td>LumA</td>
<td>no 10</td>
<td>BCT</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>Tam→AI</td>
<td>delay</td>
<td>64 (new primary TN ductal pT1c)</td>
</tr>
<tr>
<td>Pt7</td>
<td>51</td>
<td>mixed</td>
<td>cT4→ypT2</td>
<td>cN1→ypN0</td>
<td>x</td>
<td>Lum-BHER2(+)</td>
<td>no 10</td>
<td>mastectomy</td>
<td>no</td>
<td>AC</td>
<td>no</td>
<td>Tam</td>
<td>no consent</td>
<td>86</td>
</tr>
<tr>
<td>Pt8</td>
<td>56</td>
<td>ductal</td>
<td>T1</td>
<td>N1mi (one micromet, vascular emboli)</td>
<td>2</td>
<td>Lum-BHER2(+)</td>
<td>no 6</td>
<td>BCT</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
<td>Tam→AI</td>
<td>yes</td>
<td>41</td>
</tr>
<tr>
<td>Pt9</td>
<td>69</td>
<td>ductal</td>
<td>cT4→ypT3</td>
<td>cN1→ypN1 (macromets in one lymph node)</td>
<td>2</td>
<td>HER2</td>
<td>no 10</td>
<td>mastectomy</td>
<td>no</td>
<td>AT</td>
<td>to schedule</td>
<td>no</td>
<td>to schedule</td>
<td>1</td>
</tr>
<tr>
<td>Pt10</td>
<td>60</td>
<td>ductal</td>
<td>T2</td>
<td>N2</td>
<td>3</td>
<td>TN</td>
<td>yes 12</td>
<td>mastectomy</td>
<td>no</td>
<td>AC+T</td>
<td>no</td>
<td>no</td>
<td>no consent</td>
<td>18</td>
</tr>
<tr>
<td>Pt11</td>
<td>72</td>
<td>ductal</td>
<td>T3</td>
<td>N3</td>
<td>3</td>
<td>TN</td>
<td>no 10</td>
<td>mastectomy</td>
<td>no</td>
<td>FEC</td>
<td>no</td>
<td>no</td>
<td>yes</td>
<td>2</td>
</tr>
</tbody>
</table>

Local recurrence rate in breast cancer patients

with cT4N1 and HER2 positive tumor, who did not receive trastuzumab in the neoadjuvant setting, was scheduled to postoperative treatment, however, a rapid and massive local relapse occurred one month after mastectomy.

Adjuvant radiotherapy was planned in 9 patients, two patients refused this treatment, in three patients radiotherapy was delayed due to non-medical reasons (non-compliance).

In summary:
1. LR rate in breast cancer patients treated in the Department of Surgical Oncology in Lodz was 0.23% per year.
2. True recurrence occurred more frequently in patients with luminal B molecular subtype (5 out of 11 patients), in HER2 positive (3 out of 11) and in triple-negative subgroups (3 out of 11). In one patient with luminal -A subtype new primary (triple negative) occurred.
3. True recurrences were noted predominantly in patients with axillary lymph nodes metastases (9 out of 11 patients).
4. True recurrence occurred in 3 out of 5 patients with luminal B subtype who did not receive adjuvant chemotherapy but were given only endocrine therapy.
5. LR were observed more frequently in patients who did not receive adjuvant radiotherapy (5 out of 9 patients) or this treatment was delayed.
6. Minimal surgical margins in postoperative specimens measured by pathologist were 4-25 mm, mean 9.5 mm

DISCUSSION

The surgical treatment of breast cancer has evolved over the past 40-50 years from the era of the Halstedian radical mastectomy with wide margins and major pectoral muscle dissection through quadrantectomy with 2-centimeter margins introduced by Veronesi in the seventies of the last century to local excision with margins free from cancer cells on the
inked border of the specimen (St. Gallen 2013) (5, 6, 7). At the same time, rates of LR have declined steadily (6). This phenomenon can be explained by better knowledge of tumor biology, implementation of novel radiation techniques and more effective systemic treatment delivered to patients in experienced and well equipped cancer centers (1, 2). Low recurrence rate at our institution (0.23% per year) is satisfactory. However, careful analysis of our patients indicates that some of them did not receive an optimal adjuvant treatment due to various reasons (see Results section). The importance of adjuvant treatment was shown in many clinical trials. In the NSABP B14 trial, in patients with ER positive breast cancer hormonal therapy with tamoxifen reduced LR rate more than three times in comparison with patients treated with placebo (5). In the NSABP B13 trial, adjuvant chemotherapy administered in ER negative breast cancer patients diminished LR rate five times (8). The addition of trastuzumab to chemotherapy in HER2 positive patients resulted in a 50% decrease of LR rate (9). New targeted therapies (mTOR, PI3K, PARP inhibitors, HER2 dual blockade) should further improve treatment results (10). A precise identification of patients who may benefit from new targeted therapies is mandatory.

In this paper we analyzed the relationship between LR rate and surrogates of molecular subtypes according to the St. Gallen 2011 classification (11). We have shown that true recurrence occurred more frequently in patients with luminal B subtype (5 out of 11 patients), in HER2 positive patients (3 out of 11 patients) and in triple negative subtypes (3 out of 11 patients). In patient with luminal A molecular subtype a new primary tumor occurred. Nguyen et al. have demonstrated that LR rate in patients after BCS differed between molecular subtypes, the lowest (0.8% within 5 years) was noted in luminal-A breast cancer, the highest in HER2 positive breast cancer patients especially without trastuzumab (12). In our analysis the highest LR rate was noted in luminal-B subtype patients, followed by HER2 positive and triple negative subgroups. These groups are, however, very small so any conclusions must be drawn with caution. Mazouni et al. have shown that patients with triple negative breast cancer had an increased rate of distant metastases, but LR appeared more frequently in luminal B subtype, as it was revealed in our analysis (13). Similar results were reported for luminal B patients with low or lack of expression of progesterone receptor (PR) (13). These results suggest that luminal B breast cancer should be carefully monitored as it may have different biology depending on co-expression of steroid and HER2 receptors and higher proliferation indices. Usually luminal B subtype is ranked between low risk luminal A cancers and HER2 positive and triple negative tumors with definitely poor prognosis. Some of our patients with luminal B subtype did not receive adjuvant chemotherapy (3 out of 5) but they were treated with endocrine therapy which in case of more aggressive tumors with higher proliferation rate could be suboptimal and could explain, at least in part, the high LR rate in this subgroup.

The question arises whether ER, PR and HER2 status should be taken into account when planning the extent of surgery. The investigators from the Danish Breast Cancer Group denied it showing the similar higher risk of recurrence in patients with ER negative or HER2 positive breast cancer, even if they were submitted to mastectomy (14). A multivariate analysis performed by Mamounas et al. has shown that predictive factors of recurrence was young age, high tumor grade and high score in Oncotype DX, but not the extent of surgery – BCS or mastectomy (15). In our analysis the majority of patients (8 out of 11) underwent total mastectomy, only in three patients BCS was done and surgical margins were ample, mean 9.5 mm. The majority of our patients have cancers with histological grade 3, but only one patient was younger than 50 years. Nine patients were qualified for adjuvant radiotherapy, after BCS or mastectomy. In three patients radiotherapy was delayed (two patients did not give their consent to this treatment, one had a rapid relapse one month after mastectomy).

Meta-analysis of 17 randomized clinical trials on 10,601 patients has shown that adjuvant radiotherapy after BCS halves the rate of LR (16). Our results and those published in the literature suggest that local control is the result of interactions between tumor burden, feasibility of its radical resection, receptor and molecular subtype, tumor biology and effectiveness of systemic and local treatment (5, 6, 17). Due to a small sample size, we plan a further multicenter trial on LR, and research on biomarker conversion and cancer dormancy molecular signature in this setting (18).
CONCLUSIONS

The LR rate in patients operated on breast cancer in the Department of Surgical Oncology between 2009 and 2013 was low. True recurrence was diagnosed in patients with non-luminal A breast cancer despite wide surgical margins, especially if the patients did not receive optimal adjuvant systemic treatment or radiotherapy was delayed or omitted. Complete cancer excision followed by an immediate implementation of optimal adjuvant treatment (systemic and local) seems to be crucial especially in patients with poor prognostic tumor biology.

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