Long-term results of combined treatment of patients with early breast cancer after conserving therapy

Odległe wyniki skojarzonego leczenia chorych z wczesnym rakiem piersi po leczeniu oszczędzającym

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Słowa kluczowe: rak piersi, efekt kosmetyczny, leczenie oszczędzające.

Abstract

Introduction: Mastectomy was the most frequently used method of surgical treatment of patients with breast cancer in the Kielce Region. With the opening of the Surgical Oncology Clinic and the Department of Radiotherapy in the Holycross Cancer Centre, a larger number of patients could undergo breast-conserving therapy.

Aim of the research: The objective of the study was evaluation of the remote outcome of treatment of patients with breast cancer after conserving therapy.

Material and methods: During the period 2001–2005, in the Holycross Cancer Centre, 65 women with early-stage breast cancer underwent breast-conserving therapy. The patients were subjected to combined treatment. The total period of observation was from 105 to 143 months; median 113 months. In statistical analysis the distribution of the investigated variables was examined using the Kolmogorov-Smirnov test and Lillefors test. The significance of the differences between the variables analysed was tested by means of the Mann-Whitney U test. The probability of survival without symptoms of the disease was estimated by the Kaplan-Meier method. The cosmetic outcome was evaluated based on individual medical observations and a questionnaire developed at the Department of Radiotherapy.

Results and conclusions: Relapse of the disease was noted in 5 (8%) patients. Local recurrence occurred in 2 (3%) patients. In the analysed group, the 2-, 3-, 5-, and 10-year survival rates without symptoms were 98.5%, 96.9%, 95.4%, and 95.4%, respectively. No statistically significant differences were found between the groups of patients with and without cancer. In the majority of patients, after many-year observation, the cosmetic outcome is good.
Introduction

Mastectomy was the most frequently used method of surgical treatment of patients with breast cancer in the Kielce Region. With the opening of the Surgical Oncology Clinic (2000) and the Department of Radiotherapy (1997) in the Holycross Cancer Centre, an increasingly large group of patients could undergo breast-conserving therapy. Many studies have confirmed that conserving therapy is equivalent to mastectomy with respect to local control and long-term survival, which provided an incentive for more frequent use of this method [1–6]. At that time, in accordance with the recommendations, in patients with early-stage breast cancer the conserving therapy consisted of resection of the tumour with a margin (lumpectomy or quadrantectomy) and dissection of the regional lymph nodes. After surgical treatment, the patients underwent irradiation in the breast area and, when metastases were diagnosed, also in the area of regional lymph nodes. In the case of indications for systemic therapy, radiotherapy was postponed until the completion of chemotherapy [7, 8]. The entire process of treatment was carried out in the Holycross Cancer Centre. The patients were qualified for this form of therapy very thoroughly, so the examined group is not very large.

Aim of the research

The objective of the study is evaluation of the outcomes of treatment by many-year observation of patients with early-stage breast cancer, who had undergone combined therapy in the Holycross Cancer Centre during the period 2001–2005.

Material and methods

The analysed group included 65 women with breast cancer, aged 46–91, mean age 63 years. Table 1 presents the clinical characteristics of patients and type of therapy applied. Based on the clinical assessment and imaging tests, stage I cancer was diagnosed in 58 (89%) patients and stage IIA in 7 (11%).

The patients were subjected to conserving therapy (quadrantectomy or lumpectomy, and axillary lymphadenectomy). Based on histopathological examination of the tissue material, the degree of pathological advancement of cancer stage IA was found in 48 (74%) patients, stage IIA in 16 (25%), and stage IIIA in 1 (1%) patient. In the majority of patients, microscopic examination confirmed ductal carcinoma (89%). In 88% of the women in the study no metastases were observed into the axillary lymph nodes, in the surgical material. After surgical treatment the patients were qualified for adjuvant therapy. The indications for systemic therapy were: metastases to the regional lymph nodes, tumour diameter of over 1 cm, high-grade malignancy (G2, G3), and negative steroid receptors. Chemotherapy according to the cyclophosphamide, methotrexate, fluorouracil (CMF) regimen was most frequently applied (35 patients). In the case of qualification for chemotherapy, radiotherapy was used after the completion of systemic therapy. Hormonal therapy was used in 68% of patients. Tamoxifen was most frequently applied: in 40% of patients, followed by tamoxifen and switching to an aromatase inhibitor – in 25% of patients. In four patients the HER2 was positive. Therapy with trastuzumab was not applied.

Conformal radiotherapy was used in 61 patients, 53 received breast irradiation, and eight patients, in addition to breast irradiation, underwent regional nodal irradiation due to metastases diagnosed in histopathological examination. Two dose-fractionation regimens were applied: 39 patients were irradiated in a shortened treatment time 42, 5 Gy/17 fractions, 22 with conventional dose-fractionation – 50 Gy/25 fractions. The conventional dose-fractionation was used in patients in whom, apart from the breast, the regional lymphatic system was also irradiated. An increased radiation dose to the tumour bed was applied in nearly all the irradiated patients (60). All patients completed radiotherapy within the planned time.

Patients who had undergone surgical treatment were trained in the prevention of swelling. The Department of Rehabilitation at the Holycross Cancer Centre carried out rehabilitation procedures in accordance with the valid recommendations.

Statistical analysis

In statistical analysis, basic statistics were calculated: arithmetic mean, standard deviation, median, as well as lower and upper quartiles. The distribution of the investigated variables was examined using the Kolmogorov-Smirnov test and Lillefors test. The significance of the differences between the variables analysed was tested by means of the Mann-Whitney U test.
P-value < 0.05 was considered statistically significant. This means that statistical difference was observed on the distinguished level of significance. The probability of survival without symptoms of the disease was estimated using the Kaplan-Meier method.

Based on individual, documented medical observations performed by the physicians from the Holycross Cancer Centre and the questionnaire developed at the Department of Radiotherapy, the intensity of late complications and the cosmetic outcome after treatment were assessed.

**Results**

The total observation time was from 105 to 143 months; median 113 months. Sixty-two (95%) patients remain alive. Three patients died due to the metastases within 3 years after treatment. Recurrence of the disease was observed in 5 (8%) patients. Distant metastases to the skeleton, lungs, and liver were the cause of death in 2 patients. In 1 case the cause of death was not defined.

In 2 patients, relapse occurred within the treated breast, which required the performance of a simple mastectomy. The patients who had undergone treatment due to local recurrence are alive. In one patient, cancer was diagnosed in the other breast. After surgical treatment (mastectomy) the patient is alive without recurrence. Based on the analysis of the Kaplan-Meier estimator of the survival function, it was found that the probability of 5-year survival without symptoms of the disease was 96.9%, whereas the probability of 10-year survival without symptoms of the disease was 95.3% (Figure 1). No significant differences were observed between the groups of patients with and without cancer recurrence, according to the location of the tumour, receptor status, degree of clinical advancement, application of systemic treatment, radiotherapy, and hormonal therapy. The difficulty in the de-

### Table 1. Clinical characteristics of 65 patients

| Parameter                        | Result                |
|----------------------------------|-----------------------|
| Patients                         | 65 (100%)             |
| Age [years]:                     |                       |
| Mean                             | 63                    |
| Min.                             | 58                    |
| Max.                             | 67                    |
| Breast:                          |                       |
| Right                            | 4 (37%)               |
| Left                             | 41 (63%)              |
| Tumour localisation:             |                       |
| Lateral                          | 40 (62%)              |
| Medial                           | 16 (25%)              |
| Other                            | 9 (13%)               |
| Clinical stage:                  |                       |
| I                                | 58 (89%)              |
| II                               | 7 (11%)               |
| Pathological stage:              |                       |
| I                                | 48 (74%)              |
| IIA                              | 16 (25%)              |
| IIIA                             | 1 (1%)                |
| No. of excised nodes:            |                       |
| Mean                             | 15                    |
| Min.                             | 11                    |
| Max.                             | 19                    |
| No. of involved nodes:           |                       |
| 0                                | 57 (88%)              |
| 1–3                              | 7 (11%)               |
| > 3                              | 1 (1%)                |
| Histopathological type of tumour:|                       |
| Carcinoma ductale                | 58 (89%)              |
| Carcinoma lobulare               | 2 (3%)                |
| Other types                      | 5 (8%)                |
| Grade of histological malignancy:|                       |
| G1                               | 12 (18%)              |
| G2                               | 36 (55%)              |
| G3                               | 7 (11%)               |
| No evaluation                    | 10 (16%)              |
| Treatment methods:               |                       |
| BCS + RTH                        | 5 (8%)                |
| BCS + RTH + CHTH                 | 14 (20%)              |
| BCS + RTH + HTH                  | 17 (26%)              |
| BCS + RTH + CHTH + HTH           | 27 (42%)              |
| BCS + HTH                        | 3 (4%)                |

BCS – breast conserving therapy, RTH – radiotherapy, CHTH – chemotherapy, HTH – hormonotherapy.

**Figure 1.** The probability of survival relative to disease-free survival of patients with breast cancer
termination of factors responsible for the recurrence in the observed group of patients probably resulted from the small number of patients (5) in whom the relapse occurred. Based on observations from medical records and questionnaires completed by the patients, late toxicity of the combined treatment was also evaluated. As many as 32 (52%) women in the study evaluated their general status and wellbeing after treatment as very good, 28 (43%) – as good, and 2 patients – as poor. In 5 patients there occurred swelling of the arm at the surgical site; in 2 of them the breast and the regional lymphatic drainage area were irradiated. In the remaining patients, the circumference of the limb on the surgical site did not differ from that of the healthy limb. Six (9%) patients reported pain complaints and limitation of shoulder joint mobility at the surgical site, whereas in the remaining patients these symptoms did not occur. The cosmetic outcome after treatment was also evaluated. The majority of patients – 58 (94%) – evaluated the cosmetic outcome after the treatment as good or very good (Table 2).

Discussion

Breast-conserving therapy is a commonly used method of treatment in patients with breast cancer [9, 10]. At present, axillary lymphadenectomy is increasingly more rarely performed due to the introduction into clinical practice, within conserving therapy, of the method of determination of the sentinel lymph node [11–14]. In the group of patients analysed, the treatment was conducted in accordance with valid Polish recommendations. In all patients, cancer was diagnosed at stage I or II of clinical advancement. The correctness of the determination of the degree of advancement of cancer and qualification for this form of treatment were confirmed after obtaining the result of histological examination of the tissue material. All patients had quadrantectomy or lumpectomy, and axillary lymphadenectomy performed, levels I and II. In the case of indications for systemic treatment, radiotherapy was postponed until the completion of chemotherapy. This decision was made based on our own observations of patients after mastectomy, simultaneously treated by means of chemotherapy and radiotherapy, in whom intensified radiation-induced reactions were noted, even in the case of application of the CMF regimen. In patients with positive steroid hormonal receptors, hormonal therapy was initiated after completion of radiotherapy [15]. Radiotherapy was applied using the conformal techniques. Dose-fractionation was performed in a classical way (50 Gy in 25 or 42.5 Gy in 17 fractions). The use of higher fractionation doses was associated with participation in a population study conducted by the Cancer Centre in Warsaw concerning the use of post-surgical radiotherapy within a shortened treatment time [16]. All patients were irradiated using the conformal technique, which allowed not only the administration of a homogeneous dose to the target area, but also assessment of the dose in healthy organs – heart and lungs. Nearly all patients (60) received an increased radiation dose to the tumour bed, which resulted in a reduction of risk of local recurrence [17, 18].

According to literature, after 10 years of observation, local failure in women treated in a combined way (surgical procedure, chemotherapy, radiotherapy) may occur in 10–15% of patients [4, 19, 20].

In the analysed group, local recurrence occurred in 2 (3%), and metastases in 3 (5%) patients. The prognostic factors in patients with breast cancer are known [21, 22]. In the analysed group the prognostic factors were not determined due to the small size of the study group and the small number of recurrences. An important element of conserving treatment is the cosmetic outcome. Literature reports show that the cosmetic outcome begins to stabilise 2–3 years after treatment, and does not change within a longer time of observation. The best cosmetic outcome is obtained after proper surgical treatment, preceded by the appropriate qualification of the patient. A small number of patients in the group analysed might be related with a cautious qualification for this management. The important factors that decide about the implementation of such a therapy are: patient decision and skills of the surgeon. Also, systemic therapy exerts an influence on the cosmetic outcome. In the reports by Johansen et al., in prospective studies, the effect of adjuvant chemotherapy and hormonal therapy on the cosmetic outcome was evaluated, as well as late complications after treatment [23, 24]. In the opinion of these researchers, chemotherapy according to the CMF regimen may exert a negative effect on the cosmetic outcome and may be related to a higher percentage of skin changes (teleangiectases). Further on, the researchers indicate that irradiation of the re-

| Feature                        | N (%) |
|-------------------------------|-------|
| **Cosmetic outcomes**         |       |
| **General condition:**        |       |
| Very good                     | 32 (52) |
| Good                          | 28 (45) |
| Bad                           | 2 (3)   |
| **Lymphoedema of the arm:**   | 5 (8)  |
| **Pain or limited mobility in the shoulder:** | 6 (10) |
| **Teleangiectases:**          | 3 (5)  |
| **Cosmetic effect:**          |       |
| Very good                     | 26 (42) |
| Good                          | 32 (52) |
| Bad                           | 4 (6)   |

Table 2. Cosmetic outcomes
gional lymph nodes may increase the percentage of patients in whom there occurred fibrosis of the breast. The percentage of patients in whom there occurred swelling of the upper limb on the surgical side in the analysed group was 8%, which is a result close to the data from the literature [23, 25, 26]. Among other factors that may decide about late outcome of therapy are mentioned: age, scope of surgical treatment, and previously mentioned irradiation of the regional lymph nodes, or a combination of these factors [24, 27].

Conclusions

Long-term results of breast-conserving treatment of patients with early-stage breast cancer carried out in the Holycross Cancer Centre are good and are comparable to the data from the literature. Proper qualification of patients is very important for late cosmetic outcome. Distant complications occurred in a small number of patients, which shows the good quality of the combined treatment applied.

Conflict of interest

The authors declare no conflict of interest.

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