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Failures of breast conserving treatment in patients with early breast cancer

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Aim. The aim of the study was to evaluate the rate and causes of failures of breast conserving treatment (BCT) in patients with early breast cancer.
Material and methods. Between the years 1985 and 2002 in the 1st Department of Radiotherapy of the Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology we have treated 571 patients with invasive breast cancer in its early stage and 28 patients with preinvasive cancer. The duration of clinical symptoms of the disease before the beginning of the treatment ranged between 0 (the tumor incidentally diagnosed by mammography or ultrasound) and 84 months. In 455 patients with invasive cancer and 23 with preinvasive cancer size of the tumor was less than 2 cm. In both groups the most frequent localization was in the external quadrants. Within 3 – 12 weeks after breast conserving surgery external beam irradiation with Co-60 or photons X 4-6 MeV to the total dose of 50 Gy in 25 fractions was performed. The irradiated area covered the whole breast with an increased dose to the tumour site, predominantly with electrons 9-15 MeV in a dose of 10-15 Gy.
Results. Treatment failure in the form of local recurrence or distant metastases was observed in 48 patients (8%). Distant metastases occurred in 37 women (6%), mainly in the lungs, the liver and the bones. Local recurrence was observed only in 9 patients (2%) with invasive cancer 12-80 months after completion of the treatment. In the group with preinvasive cancer we observed local recurrence in 2 cases. At present there are still 547 patients alive from the group of 571 patients with invasive cancer – 523 without relapse. 24 patients died during the first 5 – 115 months after the completion of treatment: 20 – due to disease progression, 4 – due to other cancers. Total 5-year survival was 97%; disease free survival was 95.4%. The only factor influencing survival was the presence of metastatic axillary lymph nodes.
Conclusions. Breast conserving treatment is safe and well tolerated by patients with early breast cancer and provides a high ratio of total and disease free survival. Failures are rare (8%) and are mostly caused by dissemination. Disseminated cancer is significantly more frequent in patients with metastases in axillary lymph nodes ($p<0.05$). Local recurrence was observed only in 2% of patients with invasive cancer, but occurred also in 2 patients with preinvasive tumors. Individually designed conformal 3-D radiotherapy can reduce regional recurrence on the borders of the irradiated area.

Niepowodzenia po leczeniu oszczędzającym u kobiet chorych na raka piersi we wczesnych stopniach zaawansowania

Cel pracy. Celem pracy jest ustalenie częstości i przyczyn występowania niepowodzeń w leczeniu oszczędzającym (BCT) chorych na wczesnego raka piersi.
Materiał i metody. W latach 1985-2002 w Zakładzie Teleradioterapii I Centrum Onkologii-Instytutu leczono 571 chorych na inwazyjnego raka piersi we wczesnych stopniach zaawansowania, oraz 28 chorych z rozpoznaniem raka przedinwazyjnego. Czas trwania objawów wahał się od 0 (guz wykryty przypadkowo w badaniu mammograficznym lub USG) do 84 miesięcy. U 455 chorych na raka inwazyjnego i u 23 chorych na raka przedinwazyjnego wielkość guza była mniejsza niż 2 cm. W obu analizowanych grupach chorych nowotwór najczęściej umiejscawiał się w kwadrantach zewnętrznych. W okresie od 3 do 12 tygodni po oszczędzającym zabiegu chirurgicznym przeprowadzono leczenie prom. Co-60 lub fotonami X 4-6 MeV w dawce całkowitej 50 Gy w 25 frakcjach na obszar całej piersi z podwyższeniem dawki w przypadkach raka inwazyjnego na lożę po guzie, przeważnie elektronami o energii 9-15 MeV w dawce 10-15 Gy.
Wyniki. Niepowodzenie leczenia w postaci nawrotu miejscowego lub przerzutów odległych obserwowano u 48 chorych, co stanowi 8% ogólnej liczby leczonych. Przerzuty odległe wystąpiły u 37 kobiet (6%), najczęściej do płuc, wątroby i kości. Wznowa miejscowa wystąpiła jedynie u 9 (2%) chorych na raka inwazyjnego w okresie od 12 do 80 miesięcy po zakończeniu

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leczenia. W grupie pacjentek leczonych z powodu raka przedinwazyjnego niepowodzenie z powodu nawrotu miejscowego stwierdzono w 2 przypadkach. W chwili obecnej spośród 571 chorych na raka inwazyjnego, żyje 547, w tym 523 bez nawrotu choroby. 24 chore zmarły w okresie od 5 do 115 miesięcy po ukończeniu leczenia. U 20 zgon był wynikiem rozsiewu procesu nowotworowego. Cztery chore zmarły z powodu innych nowotworów. Całkowite przeżycie 5-letnie w omawianej grupie wyniosło 97%, a przeżycie bezobjawowe 95,4%. Jedynym czynnikiem, który miał wpływ na rokowanie, była obecność przerzutów w węzłach chłonnych dołu pachowego.

W n i o s k i. Leczenie oszczędzające stosowane w naszym ośrodku jest bezpieczną i dobrze tolerowaną metodą postępowania u kobiet chorych na wczesnego raka piersi i pozwala osiągnąć wysoki odsetek przeżyć całkowitych i bezobjawowych. Niepowodzenia po leczeniu oszczędzającym występują rzadko (w naszym materiale u 8% chorych) i są przeważnie związane z rozsiewem choroby. Rozsiew choroby stwierdza się znamiennie częściej u chorych z zajęciem węzłów chłonnych dołu pachowego ($p<0,05$). Nawrót miejscowy był obserwowany jedynie u 2% pacjentek z rozpoznanym rakiem inwazyjnym, ale pojawił się także u 2 chorych na raka przedinwazyjnego. Indywidualnie planowana radioterapia konformalna 3-D może wpłynąć na ograniczenie nawrotów regionalnych, występujących na granicy pola napromienianego.

Key words: BCT, pattern of failures
Słowa kluczowe: leczenie oszczędzające, niepowodzenia

Introduction

Breast conserving therapy (BCT) is now the basic modality, and an alternative to mastectomy in the case of early breast cancer in women. The results of randomized studies published in the 1980's and 1990's, which were aimed at comparing the survival of patients after BCT and after mastectomy, have shown that, providing correct patient qualification, the results of BCT are identical with the results observed after mastectomy [1-9]. The results of these studies have been compared in a double meta-analysis performed by the Early Breast Cancer Trialists Collaborative Group (EBCTCG) published in 1995 and in 2000 [10, 11]. Despite the good treatment results of BCT in some 5-10% of patients local recurrence is observed during the first 5 years, and in another 5-10% of patients – over the 10 years from the completion of therapy [13, 13]. In such cases mastectomy remains the treatment of choice. In 15-20% of patients distant metastases appear – these are always an indication for systemic therapy. The aim of this study is to attempt to identify the frequency and causes of failure in patients treated for breast cancer at our institution.

Material

Between the years 1985 and 2002 571 patients were treated for invasive breast cancer in stage T1-2, N 0-1 and 28 patients were treated for *carcinoma ductale in situ* (CDIS) at the 1st Department of Teleradiotherapy of the Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology in Warsaw. The age range of the patients was 23-75 years, mean age – 50 yrs. The symptomatic history of the disease varied between 0 (tumour found accidentally in mammography or USG) to 84 months. In 366 patients from the invasive cancer group and in 24 patients with CDIS the symptomatic history did not exceed 1 month. In 455 patients from the invasive cancer group and in 23 patients with CDIS the size of the tumour was less than 2 cm. In both the groups the most common localization of the tumour was in the external quadrants of the breast (411 patients from the invasive cancer group and 20 patients from the CDIS group). Patient characteristics are presented in Table I.

Table I. Patient characteristics – women with early breast cancer treated between 1985-2002

	Invasive cancer	Preinvasive cancer
Number of patients	571	28
Age		
≤50 y.	291	12
>50 y.	280	16
Clinical staging		
T1N0	451	–
T1N1	43	–
T2N0	59	–
T2N1	17	–
TXN1	1	–
TISN0	–	28
Pathology		
ductal ca	326	–
lobular ca	91	–
others	154	–
dcis	–	28
Metastatic lymph nodes		
no	424	6
yes	128	–

Methods

All patients underwent BCT. In 534 patients from the invasive cancer group tumorectomy (excision of the tumour with a healthy tissue margin) was performed; 36 patients underwent quadrantectomy, while in the case of 1 patient the primary lesion was not found, while the excised mass turned out to be a metastatic lymph node.

27 patients from the CDIS group underwent tumorectomy, while only 1 patient had quadrantectomy. Axillary lymphadenectomy was performed in 522 patients from the invasive cancer group and in 6 patients with CDIS. 19 patients from the invasive cancer group did not undergo lymphadenectomy, because the primary lesion was less than 5 mm in diameter (T1a). The most common histopathological form of cancer was ductal carcinoma (326 patients). Lobular carcinoma was found in 91 patients. Metastases to the axillary nodes were found in 128 cases (23%). From 3 to 12 weeks after the surgical procedure the patients underwent radiotherapy of the whole breast (Co-60 or photons X 4-6 MeV) to a total dose of 50 Gy, with a boost to the

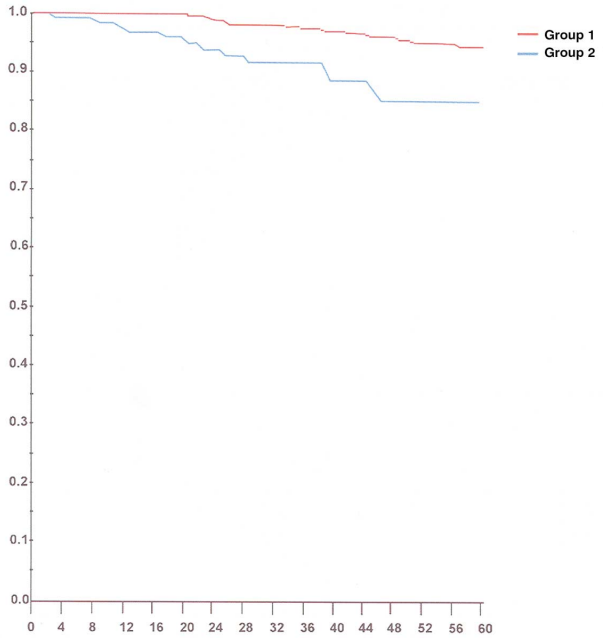

Figure 1. Survival without distant metastases in relation to the presence of metastatic axillary lymph nodes
Group 1 = pN_0 (447)
Group 2 = pN_1 (124)

tumour site in case of invasive carcinoma (usually with a 9-15 MeV electron beam). 64 patients also underwent irradiation of the local nodal fields due to the presence of nodal metastases. 150 patients were administered chemotherapy acc. to the CMF or AC protocol and 103 patients were administered hormonotherapy due to the identification of poor prognostic factors (tumour size exceeding 2 cm, high grade of histological malignancy, the presence of metastases in the axillary nodes). The treatment methods are presented in Table II.

Table II. Methods of treatment of patients with early breast cancer treated between 1985-2002

	Invasive cancer	Preinvasive cancer
Surgery		
Lumpectomy or quadrantectomy		
yes	570	28
no	1	–
Axillary lymphadenectomy		
yes	552	6
no	19	22
Radiotherapy		
Whole breast: Co^{60}, Phot X 4-6 mev, total dose 50/Gy in 25 fractions		
yes	571	28
no	–	–
Boost: electrons 9-15 mev, Co^{60}, Ir-192, total dose 10-15Gy/ 1-6 fractions		
yes	559	–
no	12	28
Chemotherapy		
yes	150	–
no	421	–
Hormonal therapy		
yes	103	–
no	468	–

In order to compare the treatment results we have used the Kaplan-Meier curve. Overall survival (OS) was defined as the time between the onset of radiotherapy and the date of the final follow-up, while disease-free survival (DFS) was defined as the time until the diagnosis of local or distant failure. The differences between the curves were analyzed with the log-rank test; the level of statistical significance was set at $p<0.05$.

Results

Treatment tolerance was good; only in 48 pts. (8%) did we have to postpone treatment for more than 7 days due to leukopenia or post-irradiative reactions. In 356 patients (94%) the cosmetic effect was estimated as very good or good. At present 547/571 women with invasive cancer are alive; of these 523 patients are disease-free. 24 patients died between 5 and 115 months after the termination of treatment – in 20 cases the cause of death was disease dissemination. Four patients died due to another malignancy – lung cancer, cancer of the oropharynx, ovarian cancer and malignant astrocytoma. Mean OS of the deceased patients was 47 months, median – 35 months. Treatment failure, both local or distant, was observed in 46 patients (8%). Distant metastases were observed in 37 women (6%) (median – 37.5 months), mainly to the lungs, the liver and bones. Local failure was observed only in 9 patients (2%) with invasive cancer – between 12 and 80 months after treatment completion (median 25 months). In 6 patients local failure was observed during the first three years, in another 3 patients – five years or more after treatment completion. In 7 patients the localization was directly in the site of the primary tumour, only in 2 cases did it appear away from the site of the primary tumour. In 6 cases salvage

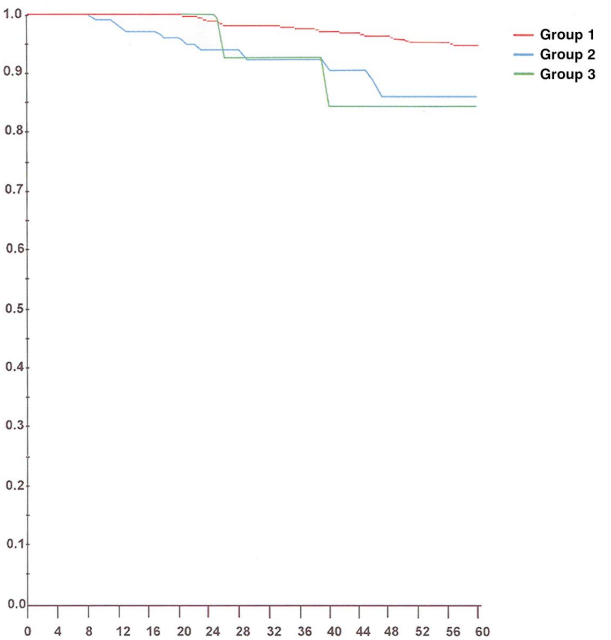

Figure 2. Survival without distant metastases in relation to the number of metastatic axillary lymph nodes
Group 1 0 lymph nodes involved (447)
Group 2 1-3 lymph nodes involved (98)
Group 3 >3 lymph nodes involved (26)

mastectomy was performed – 2 of these patients developed distant metastases and eventually died. In the CDIS group local failure was observed in 2 cases. In 1 of these patients the site was identical with the primary tumour site, in the other the local failure site was located at the verge of the irradiated filed. In both of these women these recurrence sites were invasive. They appeared 18 and 79 months after the termination of radiotherapy. During the follow-up period 8 women developed cancer of the contralateral breast – 7 of them underwent BCT and 1 – mastectomy. All of these patients are alive; only 1 of them had developed metastases to the lungs and to the brain, which were treated surgically and with radiochemotherapy and are have undergone complete regression. This patient remains in follow-up. The OS in this group was 97%, while DFS – 95.4%. The sole factor found to influence OS and DFS was the presence of metastases in the axillary nodes. Patients with metastases to the axillary nodes had a significantly poorer prognosis ($p<0.05$) as compared to patients without nodal metastases (see survival curves 1, 2, 3). Patient age, hormonal status, the size of the tumour and its histopathology did not influence survival. The treatment results have been collected and presented in Table III.

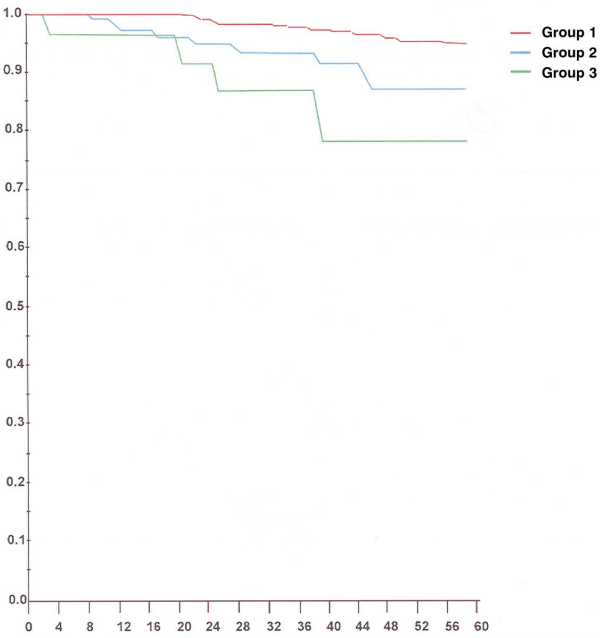

Figure 3. Survival without distant metastases in relation to the lymph node index
Group 1 lymph nodes index 0% (447)
Group 2 lymph nodes index 1-30% (105)
Group 3 lymph nodes index >30% (19)

Table III. Results of treatment of patients with early breast cancer treated between 1985- 2002

	Invasive cancer	Preinvasive cancer
Number of patients	571	28
Alive	547	28
No relapse	523	26
Local recurrence	7	2
Distant metastases	19	–
Independent cancer	11	–
Death	24	–
Local recurrence	2	–
Distant metastases	20	–
Independent cancer	4	–
Total 5-years survival	97%	–
Disease free 5-years survival	95,4%	-

Discussion

The modern approach to the treatment of women with early breast cancer should be based on the following outlines:
- highest probability of cure
- minimal risk of local and distant failure
- good cosmetic effect
- maximal amount of data concerning the type, malignancy grade and advancement of the tumour which will allow to choose the most appropriate option of adjuvant therapy

BCT supported by radiation therapy allows achieving all the listed goals. An analysis of randomized studies, which had compared BCT with mastectomy has shown, that the two treatment modalities do not differ significantly as to the risk of local recurrence which was 5.9% and 6.2%, respectively. In our material local failure was observed only in 2% of patients, which is probably the effect of a shorter follow-up period. Among the risk factors influencing local failure one should list the following: the extent of surgical excision (an important element is the histopathological analysis of the final resection margins), the presence of effuse intraductal component (EIC) adjacent to the primary tumour, emboli in the lymphatic vessels and the blood vessels around the tumour, the type and extent of irradiation, the necessity for systemic therapy and young patient age. From the point of view of surgical treatment the most important factor is the healthy tissue margin around the primary tumour. If quadrantectomy or wide tumorectomy with a margin of approx. 1.5-2 cm is performed the local recurrence risk does not exceed 2% during the first 5 years [14, 15]. Veronesi and Fisher et al. have published and compared the results of 20 years of follow-up after BCT and mastectomy in patients with early breast cancer. These results were practically identical and the local recurrence risk was 8.8% and 14.3%, respectively [16, 17]. However, if the healthy tissue margin is narrow or there is no healthy tissue margin the risk of local recurrence increases to 10-20%. The diagnosis of recurrence is problematic as the infiltration is often masked by post-irradiation fibrosis. High radiation doses limit the local recurrence risk but they also render early diagnosis of recurrence even more difficult, thus causing the danger of recognizing recurrence in a very advanced,

untreatable stage. In some 1/3 of the recurring patients the lesion may only be discerned mammographically, in another 1/3 it is discernible clinically, while in the remaining 1/3 the diagnosis may be both clinical and mammographic. Local recurrences are usually found within the primary tumour site. If the recurrence is located in a different quadrant it should not be recognized as a recurrence, but rather as another primary carcinoma of the breast. Veronesi et al. in a group of 2233 patients with breast cancer observed 119 cases of local recurrence, 50% of which were located in the direct vicinity of the primary tumour site while the remaining 50% were located in a different quadrant [18]. This data is contrary to the findings of Fowble and Kurtz, who, in their study groups, had observed a majority of local recurrences (65% and 79%, respectively) directly within the primary tumour site [19, 20]. In our material recurrence was observed in 11 cases – in 9 within the primary tumour site and in 2 in a different localization. Isolated recurrences within the breast tissue may be treated with mastectomy, after which the 5-year survival ratio reaches 50-84% [19, 21, 22]. The recent years have brought a period of interest in the biological factors and in their influence on the clinical course of breast cancer. Voogd et al. have performed a controlled trial in an attempt to verify which histological factors are connected with an increased risk of recurrence after BCT. They found that the recurrence risk increases significantly in the presence of effuse intraductal component (EIC) adjacent to the primary tumour and in the presence of intravascular emboli [23]. This opinion is supported by Veronesi, who has observed a twofold higher risk of local recurrence in patients with EIC [18]. In our institution in all the cases where EIC is found on histopathological examination we perform a radical mastectomy. Another factor potentially influencing prognosis is the grade of histological malignancy (G). Kurtz et al. have performed an analysis of 1593 patients and have observed 181 cases of local recurrence; of these patients 159 underwent mastectomy and the main prognostic factor (apart from DFS and the size of the recurrent tumour) was the grade of histological malignancy (G). Patients with a low G value (1-2) had a significantly better prognosis (72% of 5-year survivals) than patients with a high G value (40% of 5-year survivals) [20]. According to some authors younger patient age (below 40 yrs.) may also have a negative impact on survival. This is probably caused by the presence of less mature forms of the cancer and the multifocal character of the lesions [24]. In our material we found no impact of patient age upon prognosis. Radiotherapy is a very important factor in the curative process, disregarding the kind of surgical technique applied, as has been proven in a vast number of publications. The risk of local recurrence is 5-7 times lesser in irradiated patients as compared to patients treated with surgery only, although the direct influence of radiotherapy on survival has not yet been proven [25, 26, 27]. In our material all the patients underwent whole breast irradiation and only in 12 cases did we refrain from a boost to the tumour site due to the very small size of the primary lesion (i.e. below 5 mm – T1a). We applied a technique of two opposite, oblique fields in 2D system, which probably explains the appearance of two local recurrences at the border of the two irradiated fields. In order to avoid such complications since the end of the year 2003 we use individually planned conformal 3D radiotherapy in all our patients.

Among the prognostic factors directly influencing dissemination the most important one is the presence of metastases in the axillary nodes. We observed significantly shorter survivals in patients with metastases to the axillary nodes as compared to patients without axillary metastases. Similar reports have been reported in literature [7, 16-18].

Conclusions

1. At our institution BCT is a safe and well tolerated treatment modality in patients with early breast cancer. It allows achieving a high ratio of OS and DFS (97% and 95.5%, respectively).
2. Failures after BCT are rare (8%) and are usually caused by disease dissemination.
3. Generalized disease is significantly more common in patients with metastases to the axillary nodes ($p<0.05$).
4. Local failure has been observed in only 2% of patients with recognized invasive cancer but we have also noted two cases of local failure in patients with DCIS.
5. Individually planned conformal 3D radiotherapy may, in the near future, cause a further decrease in the ratio of locoregional failures.

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