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25-years experience in the breast conserving treatment of women with early invasive breast cancer

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Aim of the study. Evaluation of long term results, the identification of the causes of the treatment failure and prognostic factors in women with early invasive breast cancer after breast conserving treatment.

Material and methods. 1425 women with an early invasive breast cancer after breast conserving treatment underwent postoperative radiotherapy in the Department of Radiotherapy of The Maria Skłodowska-Curie Memorial Cancer Center in Warsaw. Duration of the symptoms before diagnosis ranged from 0 (the tumor was found incidentally by mammography or ultrasound scan) to 84 months. In 1204 patients the size of the tumor did not exceed 2 cm. Most frequent localization was in external quadrants. 3 to 24 weeks after surgery all patients underwent breast irradiation with Co-60 or photons X 4–6 MeV in the dose of 42.5–50 Gy and next, 1405 of them received additionally 10–20 Gy to the site of the removed tumor, mostly with electrons of 9–15 MeV. In 489 the treatment was combined with chemotherapy and in 592 patients with hormone therapy.

Results. The tolerance of the treatment was good. In 1357 (95%) women the cosmetic effect of the treatment was evaluated as very good and good. 15-years overall survival (OS) rate was 85% and disease free survival (DFS) rate was 79%. 15-years local recurrence rate risk was 6.9% and distant metastases occurred in 12.7%. Unfavourable prognostic factors were: size of the tumor being more than 2 cm (T2), metastatic axillary lymph nodes (N 1–2), ductal type carcinoma and beginning of the treatment before the year 2006.

Conclusions. Breast conserving treatment is a safe and well tolerated method providing a high percentage of overall and disease free survival as well as good and very good cosmetic effects. Failure of the breast conserving treatment is relatively rare and is mostly due to the generalisation of the disease. The prognosis in this group of patients depended on: the size of the primary tumor, presence of metastatic axillary lymph nodes, a ductal type of the cancer and timing of the beginning of treatment.

25 lat doświadczeń w leczeniu oszczędzającym u kobiet chorych na raka piersi we wczesnych stopniach zaawansowania

Cel pracy. Ocena odległych wyników, ustalenie przyczyn niepowodzeń i czynników rokowniczych u kobiet chorych na raka piersi we wczesnym stopniu zaawansowania.

Materiał i metody. W latach 1985–2009 w Zakładzie Teleradioterapii Centrum Onkologii — Instytutu im. Marii Skłodowskiej-Curie w Warszawie napromieniano 1425 chorych na wczesnego inwazyjnego raka piersi po leczeniu oszczędzającym. Czas trwania objawów wahał się od 0 (guz wykryty przypadkowo w badaniu mammograficznym lub USG) do 84 miesięcy. U 1204 chorych wielkość guza nie przekraczała 2 cm. Nowotwór najczęściej umiejscawiał się w kwadrantach zewnętrznych. W okresie od 3 do 24 tygodni po zakończeniu leczenia chirurgicznego wszystkie chore zostały poddane napromienianiu na pierś wiązkami Co-60 lub Fot X 4–6 MeV w dawkach 42,5–50 Gy, a następnie

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1405 z nich napromieniono dodatkowo na lożę po guzie w dawkach 10–20 Gy, przeważnie elektronami o energii 9–15 MeV. U 489 chorych leczenie skojarzono z chemioterapią, a u 592 z hormonoterapią.
Wyniki. Tolerancja leczenia była dobra. U 1357 (95%) chorych stwierdzono bardzo dobry i dobry efekt kosmetyczny. Piętnastoletnie przeżycia całkowite (OS) wyniosły 85%, a przeżycia bezobjawowe (DFS) 79%. Piętnastoletnie ryzyko nawrotu miejscowego wyniosło 6,9%, a przerzutów odległych 12,7%. Wśród czynników mających niekorzystny wpływ na rokowanie należy wymienić: wielkość guza powyżej 2 cm (T2), obecność przerzutów w węzłach chłonnych pachy (N1–2), typ histologiczny raka przewodowego oraz czas rozpoczęcia leczenia przed 2006 r.
Wnioski. Leczenie oszczędzające jest bezpieczną i dobrze tolerowaną metodą postępowania, pozwalającą osiągnąć wysoki odsetek przeżyć całkowitych i bezobjawowych, jak i bardzo dobry i dobry efekt kosmetyczny. Niepowodzenia po leczeniu oszczędzającym są stosunkowo rzadkie i przeważnie związane z rozsiewem procesu nowotworowego. Rokowanie w analizowanej grupie chorych zależało od: wielkości guza pierwotnego, obecności przerzutów w węzłach chłonnych pachy, rozpoznania raka przewodowego w badaniu mikroskopowym i czasu rozpoczęcia leczenia.

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Key words: early invasive breast cancer, breast conserving treatment, results of the treatment, prognostic factors
Słowa kluczowe: wczesny rak piersi, leczenie oszczędzające, wyniki leczenia, czynniki rokownicze

Introduction

It is now generally accepted that breast conserving surgery with subsequent irradiation (breast conserving treatment, BCT) is a standard procedure in women with early breast cancer. Many randomized controlled trials and meta-analyses published in 1990s and after 2000 showed that the results of BCT, when the patients were properly qualified, are identical with the results of the treatment of the patients who underwent mastectomy [1–6]. In all these trials a conventional method of irradiation of the whole breast in the daily dose of 1.8–2.0 Gy for five consecutive weekdays up to a total dose of 45–50.4 Gy was applied. Most patients, after whole breast irradiation, received an additional boost irradiation of the site of the removed tumor; which is a widely accepted approach in patients with a high risk of local recurrence (young age and a narrow margin of surgical excision). So far — optimal dose, the way of fractionation and the timing of additional irradiation of the site of the removed tumor are not unequivocally established. Updated results of the EORTC 22881 trial with a median follow up of 10.8 years proved a significant reduction of local recurrence in patients who received additional irradiation of the site of the resected tumor with the dose of 16 Gy in 8 fractions compared to the group which was not irradiated (6.2% vs. 10.2% , $p < 0.0001$) [7]. Similar results were published by Romestaing et al. who applied additional irradiation of postoperative site in the dose of 10 Gy in 5 fractions resulting in a reduction of local recurrence rate during 5 years follow up (3.6% vs. 4.5%, $p = 0.044$). However they observed increased number of post radiation complications such as teleangiectasiae of the 1st and 2nd degree (12.4% vs. 5.9%) [8]. Breast conserving treatment was started in our department in 1985. Our initial experience presenting early results of the treatment and causes of failure of breast conserving procedure were published in 2000 and 2005 [9, 10]. The aim of the present study is the evaluation of the the long term results of the treatment including causes of failure and risk factors based upon our own 25 years of experience.

Material and methods

Between 1985 and 2009, 1425 women with invasive early breast cancer after breast conserving surgery were treated in the Department of Radiotherapy on the Maria Skłodowska-Curie Memorial Cancer Center in Warsaw. The mean age of the analysed group was 53.3 years; range: 23–82 years. Duration of symptoms varied between 0 (the tumor was found incidentally in mammography or ultrasound scan) and 84 months. In 1204 cases the size of the tumor was 2 cm or less. Cancer was localized predominantly in external quadrants — 972 patients (68.2%). Characteristics of the analyzed group is displayed in Table I.

All 1425 women underwent breast conserving surgery — in 1325 it was tumorectomy, in 100 — quadrantectomy. In 3 patients the primary tumor was not found — the removed lesions were diagnosed as metastatic lymph nodes. Lymphadenectomy or sentinel node biopsy was performed in 1415 patients. 10 patients had no surgical procedure on their axillary lymph nodes due to being over 75 years old or because of the size of the primary tumor was less than 0.5 cm (T1a). Predominant microscopic finding was ductal carcinoma (771 patients). Lobular carcinoma was found in 196 patients. Metastatic axillary lymph nodes were found in 304 patients (21.3%). 3 to 24 weeks after surgery all patients underwent radiotherapy of the whole breast. Initially we used the technique of two tangential 2D fields with use of Co-60 or photons X 4–6 MeV in the daily dose of 2 Gy up to the total dose of 50 Gy in 25 fractions. Since 2004, in order to reduce the risk of relapse, especially on

Table I. Descriptive statistics of variables defined for analysis

Name of the variable	Category	N = 1.425	%
Breast side	left	720	50.4
	right	705	49.6
Age (years)	< 47	342	24.0
	47–51	351	24.6
	52–65	360	25.3
	> 65	372	26.1
Start-of Therapy (year)	< 2000	311	21.8
	2000–2002	352	24.7
	2003–2005	382	26.8
	≥ 2006	380	26.7
Symptoms duration (month)	< 1	836	58.7
	(1, 2)	244	17.1
	(2, 4)	180	12.6
	≥ 4	165	11.6
Location	outer quadrants	972	68.2
	inner quadrants	162	11.5
	central portion	129	9.8
	borderline	157	11.1
	between quadrants		
	no data	5	
T-stage	T1	1,204	84.5
	T2	215	15.5
	no data	6	
N-stage	N-	1,111	88.7
	N+	304	21.3
	no data	10	
Histological malignancy G	G1	268	18.8
	G2	541	37.9
	G3	225	15.8
	no data	391	27.5
Histology type	ca ductale	771	54.1
	ca lobulare	196	13.8
	mixed + other	6 + 452	32.1
Menopausal status	premenopause	515	36.2
	postmenopause	907	63.8
	no data	3	
ER receptors	ER positive	638	44.8
	ER negative	157	11.0
	unknown	630	44.2
PGR receptors	PGR positive	571	40.0
	PGR negative	221	15.6
	unknown	633	44.4
HER2 receptors	HER2 positive	20	1.4
	HER2 negative	50	3.5
	unknown	1.355	95.1

the border of irradiated fields, we have used conformal 3D radiotherapy in the same doses. In 2006, in order to reduce the duration of the treatment we have increased the fraction dose to 2.5 Gy and reduced the total dose to 42.5 Gy (17 fractions). 1405 patients received additionally boost of 10–20 Gy to the site of the removed tumor, mostly with electrons at 9–15 MeV. 114 women were additionally irradiated because of metastatic axillary lymph nodes. If the patient was qualified for chemotherapy, especially with anthracyclines, radiotherapy was performed after completion of chemotherapy. In 489 patients radiotherapy was combined with chemotherapy — CMF or anthracyclines — due to unfavourable prognostic factors and in 592 patients with hormonal treatment due to positive estrogen and/or progesterone receptors. Most often chemotherapy or hormonal treatment was used in patients treated since 2005. Chemotherapy was applied in 167 and hormonal treatment in 182 patients out of 380 treated between 2006–2009. Only 31 women did not receive any form of systemic therapy. Methods of the treatment are displayed in Table II.

Statistical methods

Efficacy of the treatment was evaluated by overall survival (OS) from surgery until death — irrespective of the cause and by disease free survival (DFS) — from surgery till relapse: locoregional, distant metastasis or cancer unrelated death. The Kaplan-Meier method was used for evaluation of survival [11]. Cox proportional hazard models were used to evaluate the influence of selected factors on the risk of death and risk of failure [12]. Following variables were included in the model : localization of the tumor (right or the left side), age of the patient, year of treatment, size of tumor, presence or absence of metastatic lymph nodes, histological type of the tumor, histological malignancy G, duration of symptoms and hormonal status. Definition of included variables is displayed in Table I. Final models have been obtained by a backward selection procedure for inclusion and exclusion conditions: $p = 0.05$ and $p = 0.1$ respectively. Proportional hazards assumption was verified by graphical method. As a measure of local efficacy the cumulative incidence function (CIF) for the loco-regional recurrences has been applied. For the CIF estimation, competing risks methodology was used with local recurrence as the event and distant metastasis or cancer unrelated death as the competing risks [13]. The 0.05 value was adopted as the general statistical significance level. To evaluate the cosmetic effect we used 10-point and 4-point scale developed and introduced in 1979 by Harris [14].

Results

In 85 (6%) of patients we had to suspend the treatment for more than 7 days because of an irradiation reaction of the 2nd degree according to RTOG or leucopenia, especially in

Table II. Treatment methods

Metods	Category		No. of patients	%
Surgery	lumpectomy		1,325	93.0
	quadrantectomy		100	7.0
	regional lymphadenectomy		1,362	95.6
	sentinel node biopsy (SNB)		53	3.7
	without lymph node assessment		10	0.7
Radiotherapy	the whole breast:	yes	1,425	100.0
	Co^{60}, photons X 4–6 MeV	no	0	0.0
		local lymph nodes	114	8.0
	boost: *e 9–15 MeV,*	yes	1,405	98.6
	Co^{60}, photons X 4–6 MeV, Ir^{192}	no	20	1.4
Chemotherapy	yes		489	34.3
	no		936	65.7
	CMF		454	31.9
	anthracyclines (AC, FAC, FEC)		35	2.5
	herceptin		3	0.2
Hormonotherapy	yes		592	41.5
	no		833	58.5

A — doxorubicin, C — cyclophosphamine, E — epirubicin, F — fluorouracil, M — methotrexate

Table III. Overall and disease free survival probability and cumulative incidence function for failures with 95%-confidence intervals for 5, 10 and 15 years of follow-up

	5 years	10 years	15 years
Overall survival (OS)	0.96 (0.95; 0.97)	0.91 (0.89; 0.93)	0.85 (0.81; 0.89)
Disease free survival (DFS)	0.93 (0.92; 0.94)	0.84 (0.82; 0.87)	0.79 (0.75; 0.82)
Cumulative incidence function (CIF)			
loco-regional recurrence	.0114 (.0057; .0172)	.0406 (.0262; .0551)	.0685 (.0431; .0939)
distant metastasis	.0537 (.0415; .0658)	.0950 (.0767; .1134)	.1271 (.0976; .1566)
cancer unrelated death	.0037 (.0005; .0069)	.0146 (.0062; .0230)	.0191 (.0070; .0312)

cases with combined chemotherapy. In 1357 (95%) patients cosmetic effect was estimated as very good or good.

Fifteen-years overall survival (OS) was 85% and disease free survival (DFS) was 79% (Table III). OS and DFS curves for the whole group are shown in Fig. 1 and Fig. 2. Cumulated incidence function is displayed in Fig. 3. Estimated values of respective functions with 95% confidence interval for 5, 10 and 15 years follow-up are displayed in Table III. Fifteen-years risk of loco-regional recurrence was 6.9%, of distant metastasis — 12.7% and of death unrelated to cancer — 1.9%. Parameters of Cox models are displayed in Table IV. Statistically significant influence on the death risk was stated for the year of beginning the therapy, size of the tumor — T and lymph nodes status — N. The death risk for women who started the treatment in 2006 or later constitutes 31% of the

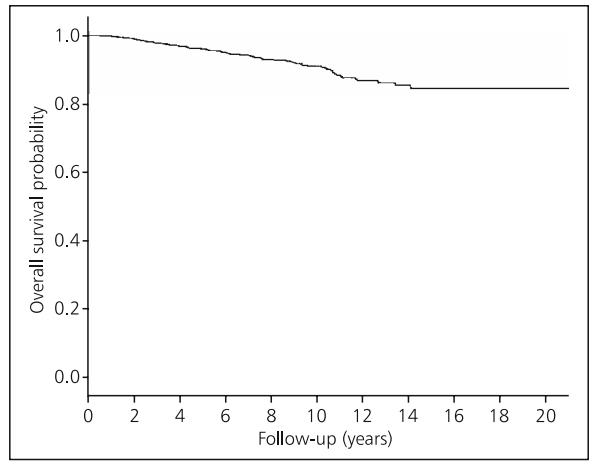

Figure 1. Overall survival (OS) for the whole group

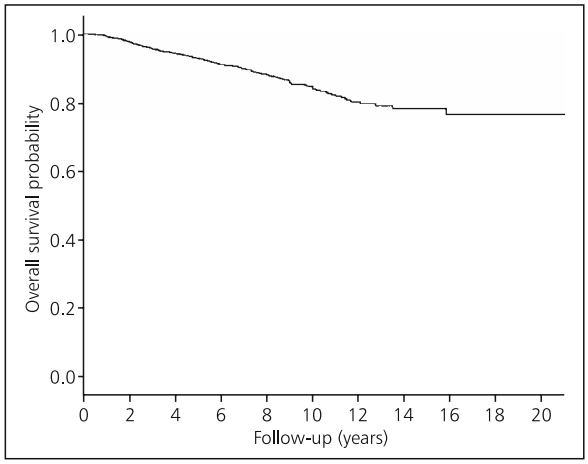

Figure 2. Disease free survival (DFS) for the whole group

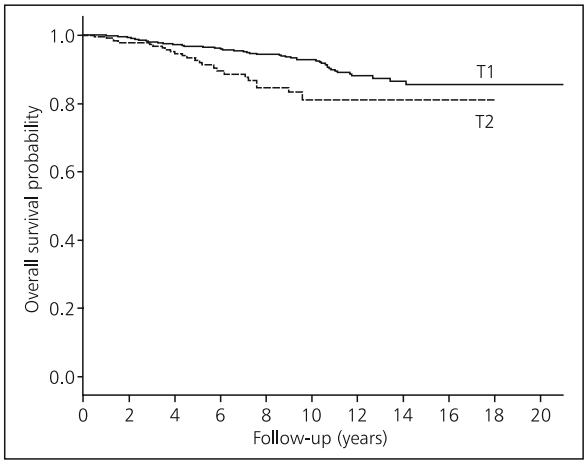

Figure 4. Overall survival for T-stage groups

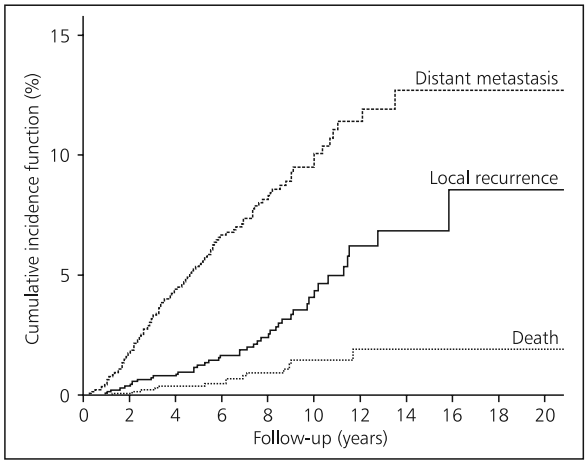

Figure 3. Cumulative incidence function (CIF) for the whole group

death risk of the patients treated earlier (p = 0.012). Death risk for women with T2 tumors was 2 times higher than for women with T1 tumors (p = 0.002). Similarly, the death risk for patients with metastatic lymph nodes — N1–2 is twice as high for women without metastases — N0 (p = 0.004). Also these parameters, as well as the histological type of tumor, have a statistically significant impact on the risk of failure. Patients who started the treatment in 2006 or later have 42% of the recurrence or death risk of those patients treated earlier (p = 0.005). Recurrence or death risk for women with T2 tumors is 2 times higher compared to those women with T1 tumors. Similarly, risk of failure is more than twice as high for women with N1–2 tumors compared to women with N0 tumors (p < 0.001). The failure risk is 1,5 times higher for women with ductal carcinoma than for women with other types of cancer (p = 0.018). Kaplan-Meier's curves dependant on prognostic factors are displayed in Figs. 4–10. We found no statistically significant influence on prognosis by age, hormonal status, duration of symptoms and degree of histological malignancy G.

Discussion

The present approach to breast conserving treatment in women with early invasive breast cancer should achieve following goals:

— to give a maximal chance for a curative result,
— to minimalize the risk of local recurrence and distant metastases,

Table IV. Parameters of final Cox's models

	B	BS	p	Relative Risk	95%-confidence interval	
The Cox's model for function of risk of death						
Therapy year (≥ 2006/< 2006)	–1.184	.472	.012	.306	.121	.771
T-stage (T2/T1)	.722	.235	.002	2.058	1.298	3.263
N-stage (N1/N0)	.709	.243	.004	2.033	1.262	3.273
The Cox's model for function of risk of failure						
Therapy year (≥ 2006/< 2006)	–.879	.311	.005	.415	.226	.764
T-stage (T2/T1)	.758	.183	< .001	2.135	1.492	3.054
N-stage (N1/N0)	.708	.190	< .001	2.030	1.400	2.943
Histology type (ca ductale/other)	.385	.163	.018	1.469	1.068	2.022

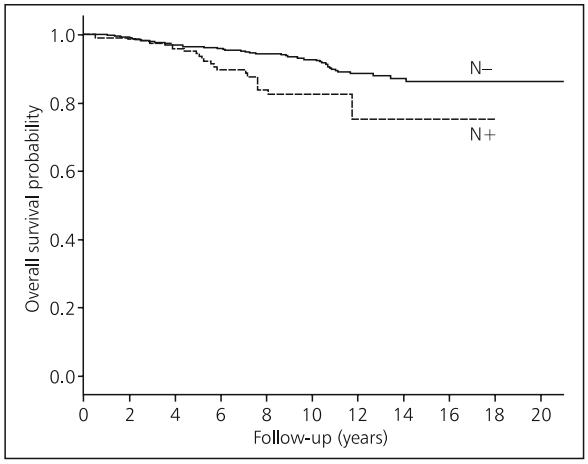

Figure 5. Overall survival for N-stage groups

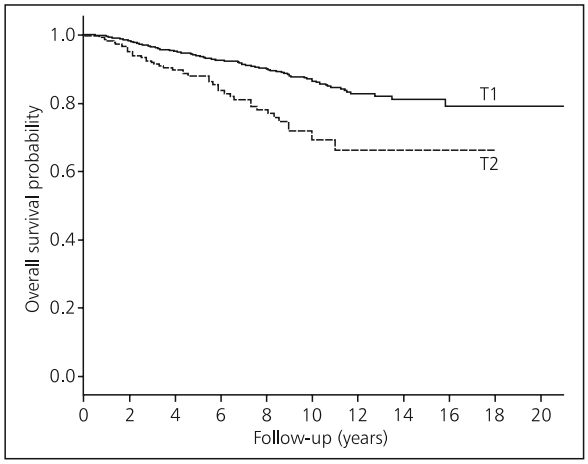

Figure 8. Disease free survival for T-stage groups

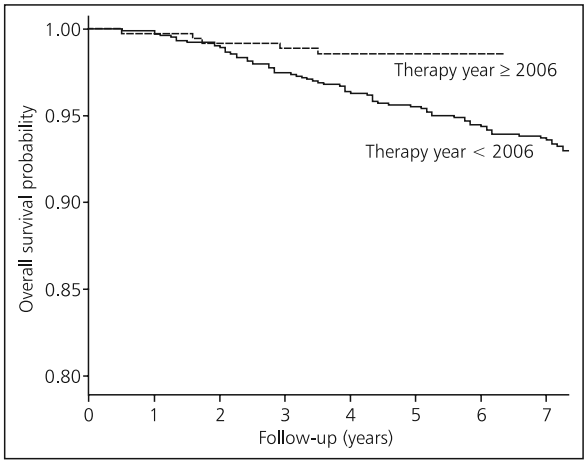

Figure 6. Overall survival for patients treated before and in or after 2006 year

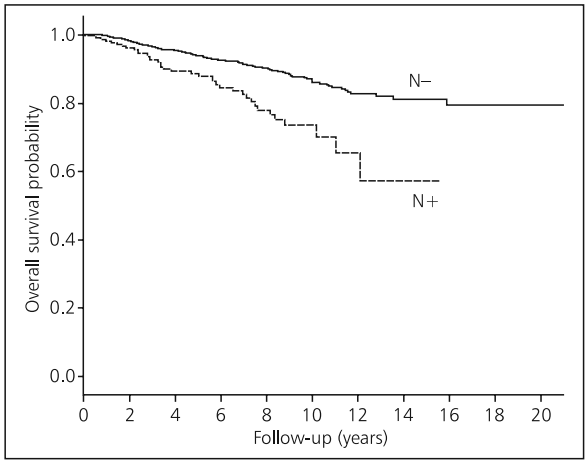

Figure 9. Disease free survival for N-stage groups

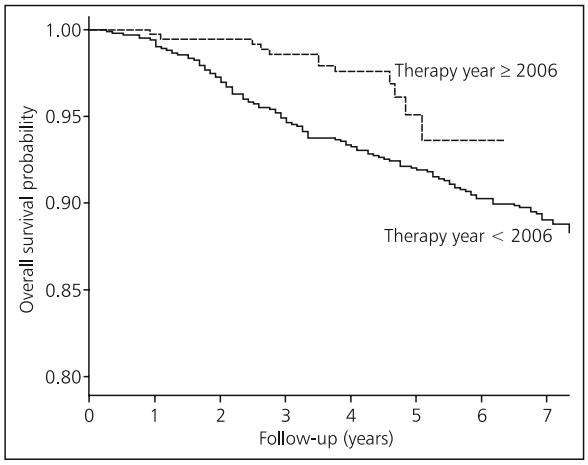

Figure 7. Disease free survival for patients treated before and in or after 2006 year

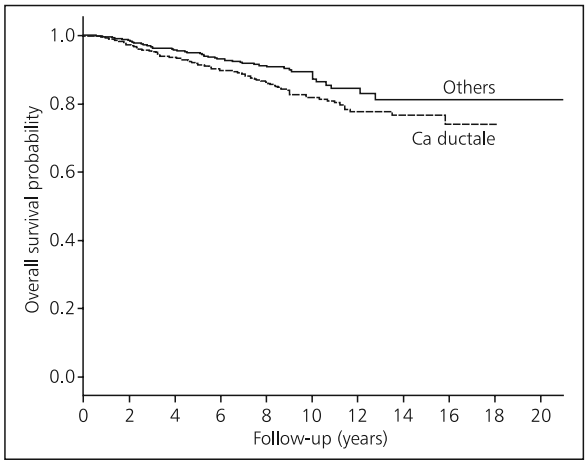

Figure 10. Disease free survival for ca ductale group versus different histopathological diagnosis

— to achieve a good cosmetic effect,
— to obtain optimal data about type, malignancy and staging of the tumor in order to choose proper adjuvant treatment. Breast conserving surgery with subsequent radiotherapy meets all these requirements.

It is now generally accepted that breast conserving treatment can be recommended for more than 50% of women with early invasive breast cancer. Analysis of randomized studies comparing breast conserving therapy with mastectomy proved that both approaches are equal with respect to overall survival, however local recurrence occurs more frequently in women after breast conserving treatment — it appears in 10–20% of patients within 10 years after completion of their therapy [15]. The risk of local recurrence is highest during the first 5 years and ranges from 5 to 10% [16]. The highest percentage of recurrences — 23.3% within 25 years was stated in the NCI trial published in 2012 [17]. There are the following risk factors of local recurrence: the extent of the surgical excision (it is an important factor when evaluating the margins in a pathological examination), the presence of extensive intraductal component (EIC) adjacent to the primary tumor, emboli in the blood and lymphatic vessels surrounding the tumor, the mode and area of the irradiation, the necessity of introducing systemic therapy and the young age of the patients. The most important prognostic factor from a surgical point of view is the extent of excised normal tissue surrounding the primary lesion. If either the quadrantectomy or tumorectomy with a margin of healthy tissue of 1.5–2 cm are performed, the risk of local recurrence does not exceed 2% within the first 5 years [18, 19]. Veronesi and Fisher compared and published results of a 20-year follow-up of patients with early invasive breast cancer after breast conserving treatment and mastectomy. Results from both authors were in fact the same and the risk of local recurrence was 8.8% and 14.3% respectively [3, 4]. In Arriagada's trial, local recurrence was observed in 9% of the patients within a 15 year follow-up [1]. However, if the margin of healthy tissue is narrow or not present at all, the risk of local recurrence is 10–20%. Diagnosis of local recurrence can be difficult as the neoplasmatic infiltration is often masked by fibrous post-radiation lesions. High doses applied during radiotherapy reduces the risk of local recurrence but simultaneously makes early diagnosis more difficult and can cause fatal delays resulting in unresectability of the reoccurrent tumor. In 1/3 of the patients local recurrence is diagnosed by mammography, in a 1/3 by clinical examination and in a 1/3 by both clinical examination and mammography. Local recurrence is usually localized in the same place or near the primary tumor. If it is localized in a different quadrant of the breast than the primary tumor, it should not be classified as recurrence but rather as another primary cancer [20]. Veronesi et al. found local recurrence in 119 cases out of 2233 women with early invasive breast cancer. In 50% it was localized at the site of the removed primary tumor or adjacent to it; in the other 50% it was localized in a different quadrant of the breast [21]. Fowble and Kurtz published different data — they found local recurrence mainly at the site of the removed primary tumor — in 65% and 79% respectively [20, 22].

In our material the risk of recurrence was 6.9% and in most cases it was localized at the site of the removed primary tumor (80%). Isolated local recurrent tumors can be effectively managed by radical mastectomy. In such cases survival for 5-years is between 50% and 84% [20, 23]. Recently, there is a growing interest in biological factors and their influence on clinical course of breast cancer. Voogd et al. have presented results of a controlled trial evaluating the influence of histological factors on increased risk of recurrence after breast conserving treatment. They found a significantly increased risk of recurrence in cases with extensive intraductal component (EIC) or with emboli in blood and lymphatic vessels surrounding the tumor [24]. Similar results were obtained by Veronesi who stated that there was a double increase in the risk of local recurrence in cases with extensive intraductal component (EIC) [21]. In our institution all the patients in whom we found EIC on pathologic examination underwent radical mastectomy. The role of the emboli in blood and lymphatic vessels in prognosis of the outcome was not evaluated in our study due to insufficient information in our data base. Another factor with a potential influence on prognosis is the degree of histological malignancy (G). The patients with low G value (1-2) had significantly better prognosis (72% of 5-year survival) than the patients with high G value (40% of 5-year survival) [22]. In our material, however, this factor had no prognostic value. According to some authors the young age of the patient (less than 40 years) can have unfavourable prognostic value. Presumably this can be caused by the presence of less mature forms of the cancer and its multifocal character [25, 26]. In our study the age of the patients did not influence the prognosis.

The size of the tumor in our study played an important role as a prognostic factor. The patients with T2 tumor had a 2 times higher death risk and even higher risk of loco-regional recurrence. Our data are similar to those published by Aristei et al. who analysed a group of 575 patients and found an increased risk of distant metastases in patients with T2 tumors [27]. One of most important prognostic factors with a direct influence on survival was the presence of metastatic lymph nodes. In our material we observed a 2 times higher risk of recurrence and death in patients with metastatic lymph nodes — N1–2 compared to the patients without metastases — N0. This data corresponds with data from other authors [4, 27, 28]. The ductal type of breast carcinoma also appeared to be an unfavourable prognostic factor and was probably caused by a high percentage

of the special form of breast cancer which generally have a better prognosis. Better prognosis for patients treated after the year 2006 can be explained by an increased use of systemic treatment despite potentially better prognostic factors. Radiotherapy is an important element of the treatment irrespective of the kind of surgical procedure. Many randomized trials published during last 15 years proved that patients who received radiotherapy have a 2–5 times lower risk of local recurrence than patients who were treated by surgery only, although direct influence of radiotherapy on overall survival has not been unequivocally proven [29–32]. However, meta-analysis of 17 randomized trials published in 2011 by the Early Breast Cancer Trialists Collaborative Group (EBCTCG) proved that reduction of local reoccurrences due to postoperative irradiation also resulted in improvement of overall survival [33]. In our material all patients received irradiation of the whole breast — only 20 patients did not receive radiotherapy of the site of the removed tumor because of their age or the size of the primary tumor being less than 5 mm (T1a).

Conclusions

1. Breast conserving treatment in patients with early invasive cancer is a safe and well tolerated procedure and enables achievement of a high percentage of overall and disease free survival (87% and 79% during 15-years follow-up, respectively).
2. Failures after breast conserving treatment are rare. Fifteen-years risk of local recurrence was 6.9% and of distant metastases — 12.7%.
3. The treatment should be carefully considered in patients with unfavourable prognostic factors like size of the tumor being more than 2 cm (T2), metastatic lymph nodes (N1–2), ductal type of carcinoma and the treatment being performed before 2006.

Conflict of interest: none declared

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References

1. Arriagada R, Le MG, Rochard F et al. Conservative treatment versus mastectomy in early breast cancer: patterns of failure with 15 years of follow-up data. Instytut Gustave-Roussy Breast Cancer Group. *J Clin Oncol* 1996; 14: 1558–1564.
2. van Dongen JA, Voogd AC, Fentiman IS et al. Long-term results of a randomized trial comparing breast — conserving therapy with mastectomy: European Organisation for Research and Treatment of Cancer 10801 trial. *J Natl Cancer Inst* 2000; 92: 1143–1150.
3. Fisher B, Anderson S, Bryant J et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med* 2002; 347: 1233–1241.
4. Veronesi U, Cascinelli N, Mariani L et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *N Engl J Med* 2002; 347: 1227–1232.
5. Pogoi MM, Danforth DN, Sciuto LC et al. Eighteen-year results in the treatment of early breast carcinoma with mastectomy versus breast conserving therapy: The National Cancer Institute Rondomized Trial. *Cancer* 2003; 98: 697–702.
6. Blichert-Toft M, Nielsen M, During M et al. Long-term results of breast conserving surgery vs. mastectomy for early stage invasive breast cancer: 20-year follow-up of the Danish randomized DBCG-82TM protocol. *Acta Oncol* 2008; 47: 672–681.
7. Bartelink H, Horiot JC, Poortmans PM et al. Impact of a higher radiation dose on local control and survival in breast-conserving therapy of early breast cancer: 10-year results of the randomized boost versus no boost EORTC 22881-10882 trial. *J Clin Oncol* 2007; 25: 3259–3265.
8. Romestaing P, Lehingue Y, Carrie C et al. Role of a 10-Gy boost in the conservative treatment of early breast cancer: results of a randomized clinical trial in Lyon, France. *J Clin Oncol* 1997; 15: 963–968.
9. Jodkiewicz Z, Malinowski Z, Skowrońska-Gardas A. Early results of treatment and cosmetic effect in patients after breast conserving surgery. *Nowotwory* 2000; 50: 141–147.
10. Jodkiewicz Z, Skowrońska-Gardas A. Failures of breast conserving treatment in patients with early breast cancer. *Nowotwory J Oncol* 2005; 55: 294–299.
11. Kaplan FL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958; 52: 457–481.
12. Cox DR. Regression models and life tables. *J R Stat Soc B* 1972 34: 187–220.
13. Arriagada R, Rutquist LE, Johansson H. Competing risks determining event.-free survival in early breast cancer. *Br J Cancer* 1992; 66: 951–957.
14. Harris JR, Levene MB, Svensson G i wsp. Analysis of cosmetic results following primary radiation therapy for stage I and II In carcinoma of the breast. *Int J Radiat Oncol Biol Phys* 1979 5: 257–261.
15. Kini VR, Vicini FA, Frazier R et al. Mammographic, pathologic and treatment-related factors associated with local recurrence in patients with early-stage breast cancer treated with breast conserving therapy. *Int J Radiat Oncol Biol Phys* 1999; 43: 341–346.
16. Recht A, Silen W, Schnitt SJ et al. Time-course of local recurrence following conservative surgery and radiotherapy for early-stage breast cancer. *Int J Radiat Oncol Biol Phys* 1988; 15: 255–261.
17. Silone NL, Dan T, Shih J et al. Twenty-five year results of the National Cancer Institute randomized breast conserving trial. *Breast Cancer Res Treat* 2012; 132: 197–203.
18. Veronesi U, Salvatori B et al. Breast conserving trials from the Milan National Cancer Institute. In Harris IR, Liman ME, Morrow M, Hellman S. *Diseases of the breast*. Philadelphia-New York: Lippincott Pavey; 1996: 579–584.
19. Peterson ME, Schultz DJ, Reynolds C et al. Outcomes in breast cancer patients relative to margin status after treatment with breast conserving surgery and radiation therapy; The University of Pennsylvania experience. *Int J Radiat Oncol Biol Phys* 1999; 43: 1029–1035.
20. Fowable B, Solin LJ, Schultz DJ et al. Breast recurrence following conservative surgery and radiation: patterns of failure , prognosis, and pathologic findings from mastectomy specimens with implications for treatment. *Int J Radiat Oncol Biol Phys* 1990; 19: 833–842.
21. Veronesi U, Marubini E, Del Vecchio W et al. Local recurrences and distant metastases after conservative breast cancer treatments: partly independent events. *J Natl Cancer Inst* 1995; 87: 19–27.
22. Kurtz JM, Amalric R, Brandone H et al. Local recurrence after breast-conserving surgery and radiotherapy. Frequency, time course and prognosis. *Cancer* 1989; 63: 1912–1917.
23. Arriagada R, Le MG, Guinebretiere JM et al. Late local recurrences in a randomized trial comparing conservative treatment with total mastectomy in early breast cancer patients. *Ann Oncol* 2003; 14: 1617–22.
24. Voogd AC, Petrese JL, Crommelin MA et al. Histological determinants for different types of local recurrence after breast-conserving therapy of invasive breast cancer. *Eur J Cancer* 1999; 35: 1828–1837.
25. Borgers J, Kemperman HJ, Hart H et al. Risk factors in breast conserving therapy. *J Clin Oncol* 1994; 12: 653–1660.
26. de Bock GH, van der Hage JA, Putter H et al. Isolated loco-regional recurrence of breast cancer is more common in young patients and following breast conserving therapy: long -term results of European Organisation for Research and Treatment of Cancer studies. *Eur J Cancer* 2006; 42: 351–356.

27. Aristei C, Leonardi C, Stracci F et al. Risk factors for relapse after conservative treatment in T1-T2 breast cancer with one to three positive axillary nodes: results of an observational study. *Ann Oncol* 2011; 22: 842–847.
28. Neri A, Marelli D, Rossi S et al. Breast cancer local recurrence: risk factors and prognostic relevance of early time to recurrence. *Word J Surg* 2007; 31: 36–45.
29. Liljegren G, Holmberg L, Bergh J et al. 10-Year results after sector resection with or without postoperative radiotherapy for stage I breast cancer: a randomized trial. *J Clin Oncol* 1999; 17: 2326–2333.
30. Malstrom P, Holmberg L, Andersen H et al. Breast conserving surgery, with and without radiotherapy, in women with lymph node-negative breast cancer: a randomised clinical trial in population with access to public mammography screening. *Eur J Cancer* 2003; 39: 1690––1697.
31. Ford HT, Coombes RC, Gazet JC et al. Long-term follow-up of a randomised trial designed to determine the need for irradiation following conservative surgery for the treatment of invasive breast cancer. *Ann Oncol* 2006; 17: 401–408.
32. Holli K, Hietanen P, Saaristo R et al. Radiotherapy after segmental resection of breast cancer with favorable prognostic features: 12-year follow-up results of a randomized trial. *J Clin Oncol* 2009; 27: 927–932.
33. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patent data for 10801 women in 17 randomised trials. *Lancet* 2011; 378: 1707–1716.