Locoregional recurrence of breast cancer: a retrospective comparison of treatment methods

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The study was made to evaluate the clinical and pathological features of breast cancer patients with locally recurrent breast cancer and to assess the impact of the treatment method on their prognosis.

Fifty-four patients with local recurrence after breast cancer were treated in Greatpoland Cancer Center between 1983 and 1995. It constituted 6.2% (54/878) of all patients with breast cancer treated in this period. Median length of interval between primary lesion and recurrence was 26.6 months, in 12/54 cases (22.2%) was longer then 5 years. Patients in time of recognizing primary breast cancer had tumor in clinical stage T2 (n=25) and T3 or T4 (n=29), in stage N0 (n=16) and N1 (n=36). Patients with recurrent breast cancer were treated using different methods. In 26 cases recurrent tumor was excited and then, in 15 cases irradiated, in 11 cases irradiated and additionally treated by chemotherapy or by hormonotherapy. In 28 cases patients were disqualified for excision due to local advance of disease. They were all irradiated and then treated by chemotherapy (n=17) or hormonotherapy (n=11). 5-year survival rates were compared with the chosen clinical factors (age, clinical stage, histopathology), length of interval between primary tumor and recurrence and with different methods of treatment including excision or not.

5-year overall survival rate was 33.3%. In locally advanced tumors (stage T3) the effect was worse then in stage T2 tumors. Five-year survival rates after recurrence were 20.8% and 52.0%, respectively (p=0.001). No statistically important correlations between lymph node involvement, age, histology and survival rate were found.

Differences between 5-year survival rate were observed according to length of interval between recognizing the primary lesion and recurrence. Patients with interval shorter then 24 months had survival rate 14.3%, between 24 and 60 months – survival rate 64.3% and with interval longer then 60 months – 41.7%. Statistically important differences were noted between first and second group (p=0.01) and first and third group (p=0.03).

Patients treated with local excision followed by radiotherapy and/or systemic therapy had greater 5-year survival rate (53.9%) then patients disqualified for incision (14.3%) (p=0.0001).

Key words: Breast cancer, local recurrence, radiotherapy.

Recurrence of a disease many years after successful treatment or removal of the primary tumor is a frequent clinical observation. Local recurrence of breast cancer means first occurrence of tumor after disease-free period.

Local recurrence following mastectomy is usually presented as one or more asymptomatic nodules in or under the skin of the chest wall typically located in or near the mastectomy scar. It can occur as a tumor in the chest wall, surrounding skin, residual breast tissue and in ipsilateral axillary and supraclavicular lymph nodes [17].

A few patients present with diffuse chest wall involvement, more commonly seen in patients with locally advanced tumors originally. Carcinoma *en cuirasse* is a distinct form of diffuse infiltration of the skin or subcutaneous tissues of the chest wall with woody induration and spread of tumor well beyond the limits of standard surgical or RT boundaries.

Local recurrence following mastectomy differs from recurrence after tumorectomy in the clinical follow-up, method of treatment and prognosis.

Risk of local recurrence depends on tumor size (T), presence and number of axillary lymph node metastasis (N), method of surgical treatment and complementary treatment [8, 12, 15, 17].

Approximately 80% of local recurrences appear by 5 years after mastectomy and nearly all occur by 10 years [14]. However, local recurrences occurring 15 to 50 years after initial surgery have been reported [9, 11, 14].

We have analyzed the outcome of recurrent breast cancer patients compared with chosen clinical factors, length of interval between primary and recurrence and with different method of treatment including excision or not.

Material and methods

Fifty-four patients with recurrent breast cancer were treated in Greatpoland Cancer Center between January 1983 and December 1995. It represented 6.2% (54/878) of all patients with breast cancer treated in this period.

Median age of patients with primary breast cancer was 46.2 years, median age of patients with recurrent breast cancer was 53.2 years (age ranged from 29 to 76). Median length of interval between primary lesion and recurrence was 26.6 months, in 12/54 cases (22.2%) was longer then 5 years. Patients in time of recognizing primary breast cancer had tumor in clinical stage T2 (n=25) and T3 or T4 (n=29) and stage N0 (n=16) and N1 (n=36). The histopathology of the lesions consisted of: ductal invasive cancer (n=23), tubular cancer (n=11), lobular invasive cancer (n=9), solid cancer (n=7), non-classified cancer (n=4).

Patients with recurrent breast cancer were treated using different methods. In 26 cases recurrent tumor was excised and then: irradiated (n=15), irradiated and additionally treated by chemotherapy (n=10) or hormonotherapy (n=1). In 28 cases patient were disqualified for excision due to local advance of disease. They were all irradiated and then treated by chemotherapy (n=17) or hormonotherapy (n=11). Patients were treated by radiotherapy up to median total dose 4600 cGy, dose fraction 200 to 400 cGy. In 45 cases Co-60 beams were used, in 9 cases orthovoltage energy was used. Irradiated field encompassed tumors with adjacent tissue determined individually in each case.

Chemotherapy was used in 27 cases, usually CMF scheme (n=15) or FAC scheme (n=12). In 12 cases hormonotherapy with tamoxifen was used (20 mg daily) in course of disease.

5-year survival rate was compared with chosen clinical data (age, clinical stage, histopathology), methods of treatment (to groups divided according to presence of excision) and length of interval between primary tumor and recurrence.

Median follow-up was 76 months, ranged from 6 to 108 months.

Presented material was analyzed based on retrospective observation of the course of disease, statistical analysis was performed using F. Cox test. Survival rates were analyzed using Kaplan-Meier method.

Results

Five years survived 33.3% (18/54) of all patients treated for local breast cancer recurrence, most of them in age between 41 and 50 (55.6%). Median age at the time of recurrent breast cancer diagnosis was compared with the length of survival. No statistically important correlations were found. Histology did not influence survival rate, either.

Prognosis according to TNM staging of the primary lesion was analyzed (Tab. 1). Longer 5-year survival rate after recognition of recurrence was observed in patients with lower clinical stage of the primary lesion (F Cox test, p=0.001). In a group of patients with T2 tumor 13/25 patients (52%) survived 5 years, with T3 tumor 5 years survived 5/24 patients (20.8%), with T4 none of 5 patients survived longer then 5 years.

In group of 16 patients without nodal involvement (N0) 5 years survived 37.5% of patients (6/16), in group with nodal involvement (N1, N2) 5 years survived 31.6% (12/38) of patients. Statistically important difference depending on N feature was not observed.

Differences between 5-year survival rate were observed according to the length of interval between recognizing the primary lesion and recurrence (Tab. 2, Fig. 1). Patients were divided into three groups – with interval shorter then 24 months (survival rate – 14.3%), between 24 and 60 months (survival rate – 64.3%) and longer then 60 months (41.7%). Statistically important differences were noted between first and second group (p=0.01) and first and third group (p=0.03).

Correlations between 5-year survival rate after the end of recurrence treatment and methods of treatment were analyzed (Tab. 3, Fig. 2). Patients were divided into two groups. First group contained 26 patients treated surgically (excision of recurrent tumor) and additionally irradiated and treated with chemotherapy or hormonotherapy – 5-year survival rate in this group was 53.9% (14/26). Second group contained 28 patients disqualified for surgery, irradiated and then treated with chemotherapy or hormonotherapy – 5-year survival rate was in this group 14.3% (4/28).

Differences between all analyzed groups were statistically important (p=0.0001).

Discussion

Prognosis for patients with local recurrence of breast cancer is relatively bad. 20 to 30% of patients survive disease – free 5 years, median survival time range from 2 to 3 years [1, 17, 31]. Favorable prognostic factors are: long interval between occurring of primary lesion and recurrence, low clinical stage (T1–2 and N0–1) and presence of estrogens receptors [17]. The interval between mastectomy and

Table 1. 5-year survival rate in correlation with clinical stage of primary breast tumor (according to TNM)

TNM	n	Survival <5 years			Survival >5 years	
		n	%	Median survival (months)	n	%
T2N0	6	2	33.3	34.0	4	66.7
T2N1	19	10	52.6	34.6	9	47.4
T3N0	10	8	80.0	32.6	2	20.0
T3N1	14	11	78.6	21.0	3	21.4
T4N1	3	3	100.0	27.0	–	–
T4N2	2	2	100.0	4.0	–	–
	54	36	66.7		18	33.3

Table 2. 5-year survival rate in correlation with interval length between primary tumor and recurrence

Interval length (in months)	n	5-year survival rate	
		n	%
<24	28	4	14.3
24–60	14	9	64.3
>60	12	5	41.7
Total	54	18	33.3

Table 3. Correlation between methods of treatment and 5-year survival rate

Method of treatment	N	<5 years		>5 years	
		n	%	n	%
1. excision and radiotherapy	15	6		9	
2. excision, radiotherapy and chemotherapy	10	5		5	
3. excision, radiotherapy and hormonotherapy	1	1		0	
With excision	26	12	46.2	14	53.9
4. radiotherapy and chemotherapy	17	14	82.4	3	17.6
5. radiotherapy and hormonotherapy	11	10	90.9	1	9.1
Without excision	28	24	85.7	4	14.3
Total	54	36	66.7	18	33.3

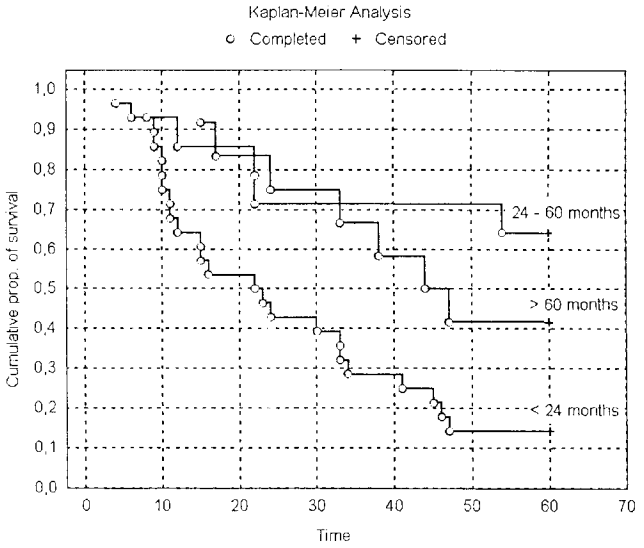

Figure 1. Cumulative proportion of survival (Kaplan-Meier) for group of patients with different interval length between primary lesion and recurrence. F Cox test (p=0.01 for groups 24 and 24–60 months, p=0.03 for groups <24 and >60 months).

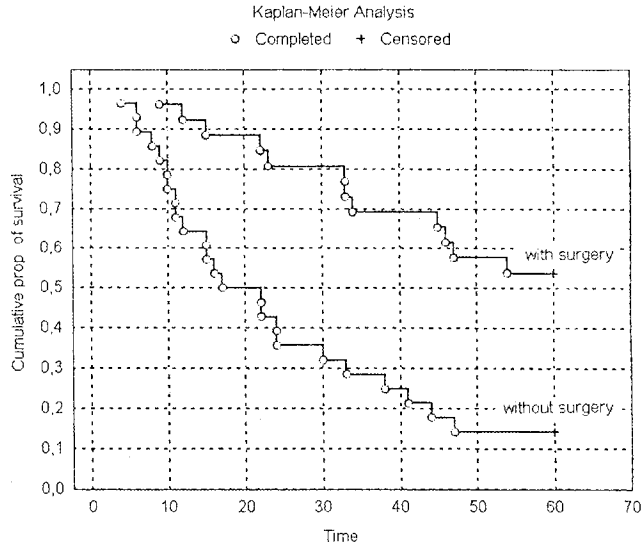

Figure 2. Cumulative proportion of survival (Kaplan-Meier) for patients treated with surgery and treated without surgery. F Cox test (p=0.0001).

local recurrence is the most reliable indicator of the time to subsequent distant failure and overall survival. This likely reflects the intrinsic growth rate of the tumor [16, 33].

For example, the relapse-free survival at 3 years was 20% for patients treated with aggressive RT who had isolated local recurrence less than 24 months after initial surgery, compared with 36% in patients who had isolated local recurrence at 24 months or longer after surgery. The respective 10-year survival rates were 7% versus 36% [1]. Similar results have been found in nearly all RT series [3, 7, 9, 16, 27, 33]. Lymph node status at the time of mastectomy [16, 22, 33] and the number of sites of recurrence [7, 9, 11, 16, 27, 33, 35] also appear to influence prognosis.

In 12 to 27% of women with involved axilla lymph nodes we can expect recurrence during 5 years of observation in comparison with 10% without involved lymph nodes [12].

Despite aggressive local treatment, almost all patients with an isolated local recurrence following mastectomy eventually manifest distant metastases. In a series of patients with local or regional recurrence or both, the 5- and

10-year actuarial rates of freedom from distant metastases were 30% and 7%, respectively [17]. The corresponding rates of overall survival were 50% and 26% [10, 21, 36]. However, patients surviving without disease 15 or more years after treatment with RT have been described [24].

Patients with local recurrence after mastectomy should have a complete restaging to rule out distant metastases. In particular, a CT scan of the chest is recommended because many patients have additional sites of involvement discovered only in this manner [25, 32]. Limited local excision has been used in some patients with further local failure occurring in over half of patients treated in this way [3, 30, 37]. For selected patients, local control rates in excess of 75% have been reported with very wide local excision of skin and subcutaneous tissue or partial or full-thickness chest wall resection, [26, 38] with some patients surviving 5 years or more.

RT has been the standard form of local treatment for patients with local recurrence after mastectomy. Radiotherapy allows to achieve local remission ranged from 63 to 97% [1, 3, 4, 6, 13].

The volume of disease remaining at the time of RT is a critical determinant of the likelihood of achieving long-term local control and gross excision is recommended if feasible [13, 28]. Patients with a recurrence in one portion of the chest wall or draining lymph node areas should receive RT to the entire chest wall [22]. Similarly, patients with chest wall recurrence may subsequently recur in the supraclavicular region (and the axillary region if not previously dissected) if only the chest wall is irradiated [33]. In general, the higher the dose of RT delivered, the less likely is an in-field failure, and doses in the range of 60 Gy to the site of recurrence are recommended, even following gross excision [7, 29]. However, even with technically optimal RT, further local recurrence is seen in some patients. Attempts to improve this have included the addition of hyperthermia [20] or the use of photodynamic therapy [23, 34]; however, such approaches have not yet been established.

It is not clear whether using "adjuvant" systemic therapy in conjunction with local treatment can prolong disease-free or overall survival time. Although a number of retrospective studies have suggested a benefit to "adjuvant" systemic therapy, (16,18,19,33) the only randomized trial addressing this issue is from Switzerland and has only a limited number of patients -167 (5). Entry in this trial was restricted to patients with a positive or undetermined estrogen receptor assay, disease-free interval greater than 1 year, and only having 3 or fewer nodules, each 3 cm or smaller in diameter, without fixation. Randomized patients underwent complete gross tumor resection and RT and were randomly allocated either to receive tamoxifen until relapse or to observation.

With a median follow-up of 6.3 years, the 5-year relapse-free survival rates were 59% and 36% in the tamoxifen and observation arms, respectively (P = NS). However, this difference had nearly disappeared by 8 to 9 years and the overall survival rates were the same in both groups. Other retrospective series have, however, suggested a benefit to "adjuvant" systemic therapy [3, 16, 18, 19, 33].

At present, the available information does not clearly identify which patients benefit from different available treatments or at what point in the course of the disease treatment should be instituted. Local treatment of patients with no evidence of distant metastases will reduce morbidity for many and may increase survival time for a few and is, therefore, generally recommended. In patients with an ER-positive cancer, hormonal therapy is often considered in addition to local treatment given the suggestion of benefit in some studies and the limited toxicities associated with such treatment.

In the described group of patients treated in Greatpoland Cancer Center 5-year survival rate after recurrence was 33.3%. More patients with lower clinical stage survived 5 years than patients with advanced tumors. Differences between 5-year survival rate were observed according to length of interval between both breast cancers. Longer intervals between two primaries were correlated with longer survival – with interval shorter then 24 months survival rate was 14.3%, with interval between 24 and 60 months survival rate was 64.3% and with interval longer then 60 months – 41.7%. Our results were similar to those achieved by others authors.

We observed influence of the treatment methods on survival. Prognosis for patients cured with combined treatment – firstly, with excision and secondly irradiated, was significantly better than for patients without excision.

In first group with 26 patients treated surgically and additionally irradiated and treated with chemotherapy or hormonotherapy, 5-year survival rate was 53.9%.

In second group with 28 patients disqualified for surgery, irradiated and then treated with chemotherapy or hormonotherapy, 5-year survival rate was 14.3% (4/28).

Conclusions

1. Higher clinical stage of primary lesion was correlated with worse prognosis.
2. Length of interval between primary lesion and recurrence influenced survival rate.
3. Greater survival rate was achieved in cases with combined treatment consisting of surgical excision and followed by radiotherapy than in cases without excision of recurrence.

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