



Postoperative radiotherapy after conservative surgery for early breast cancer: 5-year results

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BACKGROUND: Breast conserving surgery followed by postoperative radiotherapy, as alternative to radical mastectomy, has been accepted as an optimal method for loco-regional treatment of the majority of women with early stage of breast carcinoma. The aim of the study was to evaluate the results of postoperative radiotherapy after breast conserving surgery in the Institute for oncology and radiology of Serbia.

METHODS: During the 3-year period, 109 breast cancer patients with stage I and II were treated with postoperative radiotherapy after breast conserving surgery. Ninety-four patients underwent quadrantectomy with axillary node dissection, and 15 patients underwent only tumorectomy. After surgery all patients received postoperative radiotherapy to the whole breast with tumor dose 50 Gy in 15 fractions every second day. In 52 patients radiotherapy was given to the regional lymphatics with tumor dose 45 Gy in 15 fractions every second day. Twenty-eight patients received a booster dose (10 Gy) to the tumor bed. Adjuvant systemic therapy was administered depending on the nodal involvement and steroid receptors content: 17 patients received adjuvant chemotherapy (CMF or FAC), 18 received adjuvant hormonal therapy (tamoxifen or ovarian ablation), and 6 patients received both chemo- and hormonotherapy.

RESULTS: After median follow-up period of 62 months, there was no evidence of loco-regional recurrence in any of the patients. Distant metastases occurred in 7 patients (6.4%) with median disease free interval of 27.6 months. At last follow-up 91 patients (83.4%) were alive, 4 patients (3.7%) were dead of disease, and the same number was dead of other causes. The 5-year overall survival rate was 92.9% and disease-free survival rate was 92.7%.

CONCLUSION: According to our results the combined surgery and radiotherapy approach provides good local control of early breast cancer patients. Postoperative radiotherapy after breast conserving surgery with or without adjuvant systemic therapy has important role in adjuvant treatment of early breast cancer.

KEY WORDS: Breast Neoplasms; Mastectomy, Segmental; Radiotherapy, Adjuvant

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INTRODUCTION

Breast conserving surgery (BCS) followed by postoperative radiotherapy (RT), as alternative to total radical mastectomy, has been accepted as an optimal method for locoregional treatment of the majority of women with early stage of breast carcinoma (1). A numerous randomized trials have shown that over-

all survival in patients with small tumors were the same whether they were treated with limited surgery plus irradiation or total mastectomy (2-4). There is a general agreement that postoperative RT as an addition to surgery prevents locoregional recurrence and improve the disease-free interval (DFI), but makes little differences to overall survival (5-7). In order to reduce the risk of local recurrences, conservative procedures require a postoperative RT, which is applied to the whole breast with a dosage varying from 50 Gy to 60 Gy with or without a booster dose on the tumor bed. Early Breast Cancer Trialist's Collaborative Group, in their analysis of 10-year results from 40 randomized trials, showed a reduction of about two-thirds in local recurrence after postoperative RT, irrespective of whether breast surgery involved mastectomy or conservation (8).

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The aim of the study was to evaluate the results of postoperative RT after BCS in the Institute for Oncology and Radiology of Serbia.

PATIENTS AND METHODS

Between January 1994 and December 1996, 109 patients with early stage breast cancer (stage I and II) were treated with BCS followed by postoperative RT with or without systemic adjuvant therapy. Patients' characteristics are presented in Table 1.

Table 1. The patients characteristics

Number of patients	109
Age	
Mean	51.45
Range	23 - 72
Menopausal status	
Premenopausal	61
Postmenopausal	47
Perimenopausal	1
Stage	
I	56
IIA	28
IIB	25
Type of operation	
Quadrantectomy + axillary dissection	94
Tumorectomy	15
Pathology	
Ca ductale in situ	15
Ca ductale invasivum	51
Ca lobulare invasivum	29
Other	14
Nodal status	
Negative	64
Positive	30
Adjuvant therapy	
Radiotherapy alone	68
Radiotherapy + chemotherapy	17
Radiotherapy + hormonal therapy	18
Radiotherapy + chemotherapy + hormonal therapy	6

Half of the patients were in clinical stage I of disease (56 patients) and 53 patients in stage II. Sixty-five patients had clinical T1 tumors, 38 had T2 tumors, and 6 were classified as TX. Ninety-four patients underwent quadrantectomy or segmentectomy with axillary node dissection, while 15 patients underwent only tumorectomy without axillary dissection. Patients who had only tumorectomy were clinically with no palpable axillary lymph nodes and with histopathologically confirmed carcinoma in situ. Most frequent histological finding was ductal invasive carcinoma (51 patients), lobular invasive carcinoma was found in 29 patients, while 15 patients had ductal carcinoma in situ. In 94 patients who had quadrantectomy with axillary node dissection the mean number of removed nodes were 12.4 with range from 2 to 28. Sixty-four patients had histologically negative axillary nodes and 30 patients had positive axillary nodes. Among of them 22 patients had 1 to 3 positive nodes and 8 patients had 4 or more positive nodes.

After surgery, all patients received postoperative RT to the whole

breast with parallel opposing medial and lateral tangential fields. Tumor dose (TD) for breast was 50 Gy in 15 fractions every second day. In 52 patients radiotherapy was given also to the regional lymph nodes (supraclavicular, infraclavicular, axillary, and internal mammary nodes), with the tumor dose of 45 Gy in 15 fractions every second day. The internal mammary nodes were treated by a direct field, which covered ipsilateral nodes in the first three intercostal spaces. Dose was specified at 2 cm depth. Axillary and supraclavicular nodes were irradiated by another direct anterior field with calculated doses at the 1/3 from antero-posterior diameter. All fields were treated on tele cobalt therapy unit over a six weeks period. Twenty-eight patients received a boost dose to the tumor bed with TD 10 Gy in 5 fractions.

Adjuvant systemic therapy was administered depending on the nodal involvement and steroid receptors content. Seventeen patients received adjuvant chemotherapy (CMF or FAC), 18 received adjuvant hormonal therapy (tamoxifen or ovarian ablation), and 6 patients received both, chemo- and hormonotherapy. Survival rates were calculated by the Kaplan-Meier method.

RESULTS

After the median follow-up period of 62 months (range: 3-86 months) there was no evidence of locoregional recurrence in any of the patients. Distant metastases occurred in 7 patients (6.4%) with median disease-free interval of 27.6 months (range: 6-53 months) (Table 2).

Table 2. Relapse rates

	No. of patients	%
Locoregional relapse	0	0%
Distant metastases	7	6.4
Bones metastases	1	
Liver metastases	2	
Bones + pleura	1	
Bones + brain metastases	1	
Bones + pleura + liver	1	
Retroperitoneal lgl	1	

Four patients with distant metastases died due to primary disease. First one had liver metastases, second had multiple metastases in liver, lungs and bones, third had retroperitoneal metastases with ascites, and fourth had brain and bone metastases.

Two patients with distant metastases are alive, both have bone metastases, and one patient with solitary liver metastases had metastasectomy and now is in NED stadium of disease.

All patients who developed distant metastases were in stage II of disease and had positive axillary lymph nodes.

After the end of follow-up 81.6% patients is alive without evidence of disease, while 1.8% is alive with disease.

Eight patients died - four because of tumor progression and four because of other causes (Table 3).

Table 3. Status at the end of follow-up

	No. of patients	%
Alive, disease-free	89	81.6
Alive with disease	2	1.8
Died with disease	4	3.7
Died, concomitant cause	4	3.7
Lost to follow-up	10	9.2

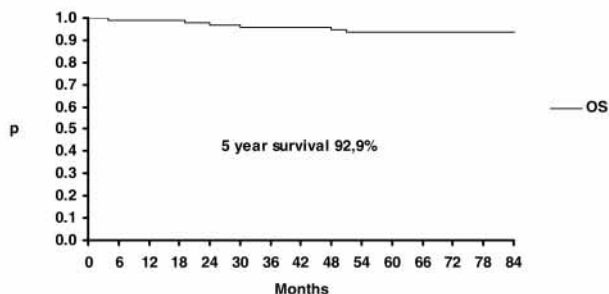


Figure 1. Overall survival for all patients, OS - overall survival, p - percent surviving

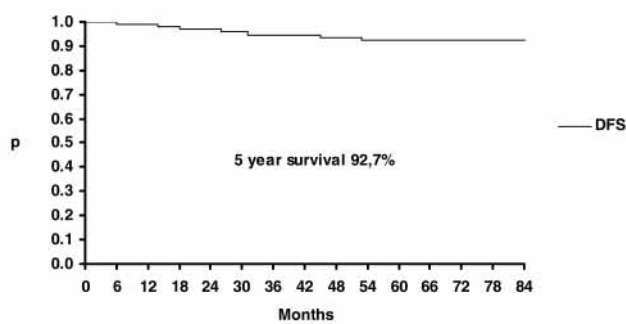


Figure 2. Disease free survival for all patients, DFS - disease free survival, p - percent surviving

The 5-year overall survival rate was 92.9% (Figure 1) and disease-free survival rate was 92.7% (Figure 2).

The most common complication following treatment was moderate to severe arm edema, which occurred in 5 patients (4.6%).

DISCUSSION

BCS traditionally implies the postoperative RT of the mammary gland. Whether the importance of radiotherapy lies only in reducing the risk of local recurrences or also in reducing mortality is still the opening question. Local control is an important factor in treatment of breast cancer and especially in breast conserving therapy.

A wide range of local recurrence rates have been reported in the literature (0%-46%) in T1 and T2 lesions, because of the wide range of surgical and radiation therapy techniques and doses used in the preliminary investigations but in randomized trials, the rates have ranged from 6% to 10% (1). Early Breast Cancer Trialists's Collaborative Group, comparing BCS plus axillary dissection with the same surgery plus RT, showed the reduction of two-thirds in local recurrence after postoperative RT in 10 years

(8.8% vs. 27.2% in control group) (8). They also showed that large reduction in local recurrence corresponded to the substantial reduction in the incidence of any recurrence (45.2% vs. 58.3% in control group). Veronesi et al. reported 5.4% local recurrences after BCS and postoperative RT vs. 21.6% in control group of patients treated with surgery alone (7).

Local recurrence is a highly significant predictor of distant metastasis, but it is only a marker of risk. There are important differences between local recurrences occurring after mastectomy and after BCS. Relapses after mastectomy are accompanied or immediately followed by distant metastases in more than half of cases (9). Local recurrences after BCS appear much slower and can be rescued by second-line mastectomy. The relative risk of distant metastasis is greatest for recurrences occurring within one year (75% < 1 year vs. 44% > 1 year). For recurrences occurring after 5 years the incidence of distant metastases is 18% (10).

From the available data, it becomes apparent that local control is dependent on the extent of surgery and on the given radiation dose. Very high radiation doses with good local control also results in high incidence of cosmetically inadequate results. With very low radiation doses of 35 Gy, a local failure rate is about 40%. With increasing radiation doses (50-60 Gy), this rapidly rises to a local control of 90%, and for significantly higher doses (above 70 Gy) local control approaches a 100% (9). Doses up to 50 Gy are generally accepted to reduce local recurrences at 5 years from 30% to 50% down to 10% to 15%. Booster dose given to the tumor bed after whole breast irradiation has been confirmed as an essential part of the treatment despite its negative effect on cosmesis (11). Both interstitial brachytherapy of the tumor bed and external electron beam irradiation have been proved to be equally effective as boost measures (12).

In our study there was no evidence of local recurrence. We cannot offer a clear explanation of this finding, but some reasons in excellent local control might be in wide local excision of tumor with clear margins and adequate tumor dose of irradiation. All patients received TD 50 Gy to the whole breast, but in 15 fractions every second day. This dose is similar to dose of 60Gy in 30 fractions comparing the values of TDF factors of both fractionated schedules. Twenty-eight patients received also a booster dose to the tumor bed with 10 Gy in 5 fractions. The booster dose was delivered to the patients with high histology grade and positive axillary lymph nodes.

It was showed that the interval between surgery and the beginning of radiotherapy was correlated with the breast recurrence rate (13). In a series of patients from the Institute Gustave Roussy was reported significant increase in local recurrence rate with increase in interval between surgery and radiotherapy. The local recurrence rate was 5% for patients who started RT within 7

weeks, compared with 14% for patients who did not start RT until 7 weeks or more after surgery (14). Adjuvant chemotherapy was not used in that series. For our patients, mean period for the beginning of radiotherapy was 7.5 weeks after surgery (range: 2-15 weeks) irrespective of whether chemotherapy was given or not. As the interval between surgery and the start of radiotherapy may affect mainly at the risk of locoregional recurrences, in such a way a delay in beginning chemotherapy may increase the risk of distant failures. Anelli et al. presented a retrospective evaluation of the timing of irradiation and adjuvant chemotherapy in early stage disease and impact on systemic and local recurrence (15). In patients who received postoperative radiotherapy before chemotherapy there was a significantly higher rate of systemic failure (33%), compared with those who received chemotherapy first (26%), but there was no difference in local failure rate (11% vs. 7%). However, the appropriate sequencing of radiotherapy and chemotherapy is still unclear. Randomized trials are required to define the optimal treatment sequence, especially in patients with multiple positive lymph nodes, who are at great risk for distant metastasis and might benefit from early initial adjuvant chemotherapy (13). Radiotherapy also carries some long-term side effects, such as lung fibrosis, some risks of cardiac failure and increased risk of soft tissue sarcoma (7,16).

But the use of megavoltage beams, precise treatment planning, and modern radiotherapy techniques have been shown to reduce the irradiation dose to the heart and this decrease in cardiac dose reduces morbidity for patients with early breast cancer (17).

The follow-up included routine clinical examination, blood tests every four months, and chest radiography and ultrasonography of the liver every year, and bone scanning if there were any symptoms. On the basis of these data we did not observe any cases of interstitial pneumonitis or rib fractures. Also, there was no clinical evidence of cardiac failure.

Results that we had require discussing the plan of treatment patients with early breast carcinoma in such a way to carry out radiotherapy treatment every day instead of every second day. That should in one hand reduce the total dose from about 60 Gy to 45-50 Gy, and on the other will give probably better cosmetic results. Also, the new technical condition that our Institute plans to have in near future shall make possible more precise treatment planning which will be in this case mostly directed on improvement cosmetic effects.

CONCLUSION

Locoregional tumor control has significant impact on survival in early breast cancer and there is clear evidence that inadequate locoregional treatment can lead to subsequent dissemination.

Therefore, postoperative RT after BCS with or without adjuvant

systemic therapy has important role in adjuvant treatment of early breast cancer. The optimal timing of surgery, RT and chemotherapy, particularly in patients with high risk for relapse, has to be evaluated in goal to obtain maximal effect from therapy and to avoid unfavourable effects.

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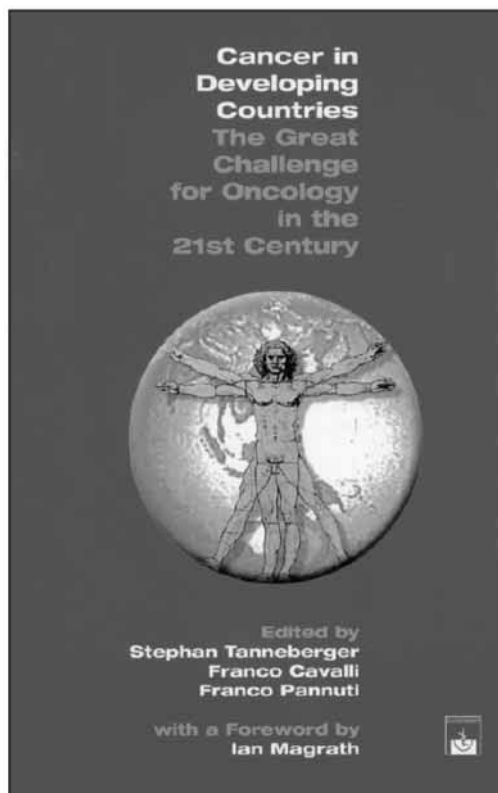
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