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The role of postoperative radiotherapy after radical mastectomy in treatment of early breast cancer

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BACKGROUND: *Radical or modified radical mastectomy was considered for many years the standard therapy for operable patients. Following radical mastectomy, postoperative irradiation of the chest wall and peripheral lymphatics is indicated in selected high-risk patients. Some studies on breast cancer patients who underwent radical mastectomy and received adjuvant chemotherapy tried to find out whether the addition of irradiation treatment to the chest wall and regional lymph nodes increases survival. The hypothesis in favor of irradiation is that chemotherapy can eliminate distant micrometastases, but is less effective against local and regional diseases, which are better controlled by radiotherapy.*

METHODS: *In one-year period, 110 patients with early stage of breast cancer were treated with radical mastectomy, and postoperative radiotherapy. Forty-one patients had only postoperative radiotherapy, 27 received also adjuvant chemotherapy, 40 received adjuvant hormonal therapy and 2 patients received both adjuvant chemo- and hormonotherapy. Postoperative irradiation was given on the regional lymph nodes (supra- and infraclavicular, axillary and internal mammary nodes) with the tumor dose 48 Gy in 22 fractions over a period of four and a half weeks. All fields were treated with Cobalt-60.*

RESULTS: *After the median follow-up of 67 months, 33 patients (30 %) had some kind of failure in form of local recurrence, distant metastases or both. Locoregional relapse alone or associated with distant metastases occurred in 10 patients (9.1 %). Only 1.8 % of patients had local recurrence as the first failure. Distant metastases occurred in 32 patients (29.1%). After the end of follow-up, 60 % patients are alive without evidence of disease, while 16.4 % patients are alive with disease. The 5-year overall survival rate was 78.19% and 5-year disease-free survival rate was 67.44%.*

CONCLUSION: *Postoperative radiotherapy after radical mastectomy has important role in adjuvant treatment of early breast cancer in combination with adjuvant chemotherapy and hormonotherapy.*

KEY WORDS: *Breast Neoplasms; Mastectomy, Radical; Radiotherapy; Postoperative Period*

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INTRODUCTION

Treatment of early breast cancer (stage I and II) consists of mastectomy or breast conserving surgery with axillary dissection, followed by adjuvant chemotherapy or hormonal therapy, or postoperative radiotherapy, in case of patients with increased risk for relapse. A radical or modified radical mastectomy was considered for many years the standard therapy for operable patients (1). After radical mastectomy, postoperative irradiation of the chest wall and peripheral lymphatics is indicated in selected high-risk patients (2).

Like surgery, radiotherapy is a locoregional treatment method. The purpose of postoperative radiotherapy is to achieve local control of the disease and to improve disease-free survival, but it

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makes little difference to overall survival.

Some studies on breast cancer patients who underwent radical mastectomy and received adjuvant chemotherapy, tried to find out whether the addition of irradiation treatment to the chest wall and regional lymph nodes increases survival (3). The hypothesis in favor of irradiation is that chemotherapy can eliminate distant micrometastases, but is less effective against local and regional disease, which are better controlled by radiotherapy (4,5). Early Breast Cancer Trialists Collaborative Group showed a reduction of about two-thirds in local recurrence after postoperative radiotherapy, irrespective of whether breast surgery involved mastectomy or conservation (6).

The purpose of this study was to evaluate the results of postoperative radiotherapy after radical mastectomy, and to estimate the effects of timing of postoperative radiotherapy and adjuvant chemo- or hormonotherapy on local control of the disease and overall survival.

PATIENTS AND METHODS

Between January 1 and December 31, 1994, 110 patients with early-stage breast cancer (stage I and II) were treated with radical mastectomy and postoperative radiotherapy. Forty-one patients had only postoperative radiotherapy, 27 patients received also adjuvant chemotherapy (6 cycles of CMF), 40 received adjuvant hormonal therapy (Ro castration or tamoxifen) and 2 patients received both adjuvant chemo and hormonotherapy.

Postoperative irradiation was given on the regional lymph nodes (supra- and infraclavicular, axillary and internal mammary nodes) with the tumor dose 48 Gy in 22 fractions over a period of four and a half weeks. All fields were treated with Cobalt-60.

The internal mammary nodes were treated by a direct field, which covered ipsilateral nodes in the first three intercostal spaces. Doses were specified at 2 cm depth. Another direct anterior field irradiated axillary and supraclavicular nodes with calculated doses at the 1/3 from anterio-posterior diameter.

Patients' characteristics are given in Table 1. The median age was 60 years, with a range of 44 to 72 years. There were 100 postmenopausal and 8 premenopausal women. All of the patients were with early, operable breast cancer (stage I - 13 patients and stage II - 97 patients). Twenty-three patients had clinical T1 tumors, 83 had clinical T2 tumors and 4 patients had T3 tumors. Most frequent histology was ductal invasive carcinoma (47.3%), then lobular invasive carcinoma (40.9%), whereas the other types of carcinomas were rare.

All patients underwent axillary node dissection. The median number of nodes removed was 12 (range 1 to 31). Forty patients had histologically negative axillary nodes and 68 patients had positive axillary nodes; in 2 patients nodal status was unknown.

The patients were followed with clinical examination at regular intervals for up to 5 years. Median follow-up was 67 months (min. 2, max. 87). Survival rates were calculated by the Kaplan-Meier method.

Table 1. Patients characteristics

Number of patients	**110**
Age	
Median	60
Range	44-72
Menopausal status	
Premenopausal	8
Postemenopausal	100
Perimenopausal	2
Stage	
I	13
IIa	35
IIb	62
Pathology	
Ca ductale	52
Ca lobulare	45
Others	13
Grade	
I	5
II	93
III	9
Unknown	3
Nodal status	
Negative	40
Positive	68
Unknown	2
Adjuvant therapy	
RT	41
RT+HT	27
RT + hormonoth.	40
RT + HT + hormonoth.	2

RESULTS

After mean follow-up of 53 months, 33 patients (30 %) had failures in form of local recurrence, distant metastases or both. Mean disease-free interval was 29.8 months (range 5-70 months) (Table 2).

Table 2. Relapse rates

	No of patients	%
Locoregional recurrence alone	1	0.9
Locoregional with distant metastases	9	8.2
Distant metastases alone	23	20.9
Without relapse	73	66.4
Lost to follow-up	4	3.6

Locoregional relapse alone or associated with simultaneous distant metastases occurred in 10 patients (9.1%). Only 2 patients (1.8 %) had local recurrence as the first failure. Among 10 patients with locoregional recurrence 7 had chest wall recurrence and 3 had clinical evidence of supraclavicular node involvement. Distant metastases occurred in 32 patients (29.1%). The mean disease-free interval (DFI) for locoregional relapse was 28.9 months (range 13 - 52) and for distant metastases DFI was 30.4 months (5-70).

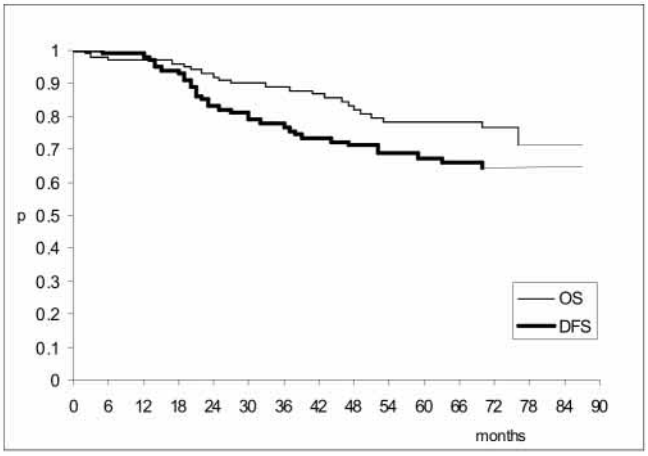
After the end of follow-up, 60 % of patients are alive without evidence of disease, and 16.4 % are alive with disease (Table 3).

Table 3. Status at the end of follow-up

	No of patients	%
Alive, disease-free	66	60.0
Alive with disease	18	16.4
Died with disease	13	11.8
Died concomitant cause	9	8.2
Lost to follow-up	4	3.6

Thirteen patients died of tumor progression, and 9 patients died from other causes. The 5-year overall survival rate was 78.19% and 5-year disease-free survival rate was 67.44% (Figure 1).

Figure 1. Overall survival and disease-free survival for all patients



The analysis of the influence of time from surgery to the beginning of radiotherapy showed no statistically significant difference in overall ($p>0.05$) or disease-free survival ($p>0.05$) between patients who started with postoperative radiotherapy in 6 weeks after surgery compared with more than 6 weeks (Figures 2a, 2b).

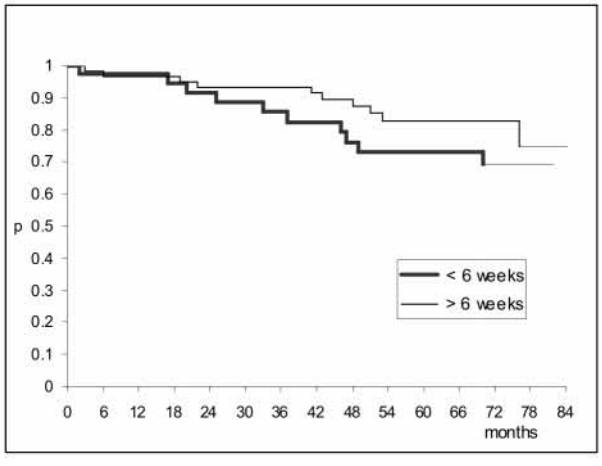


Figure 2a. Overall survival according to time from surgery to the beginning of radiotherapy

There is no statistically significant difference in overall survival ($p>0.05$) between three subgroups of patients (RT, RT+ HT and RT + hormonotherapy) (Figure 3a), but there is significant difference in disease-free survival ($p<0.05$) between patients with postoperative radiotherapy only and group with combined RT and chemotherapy (in favor of RT group) (Figure 3b).

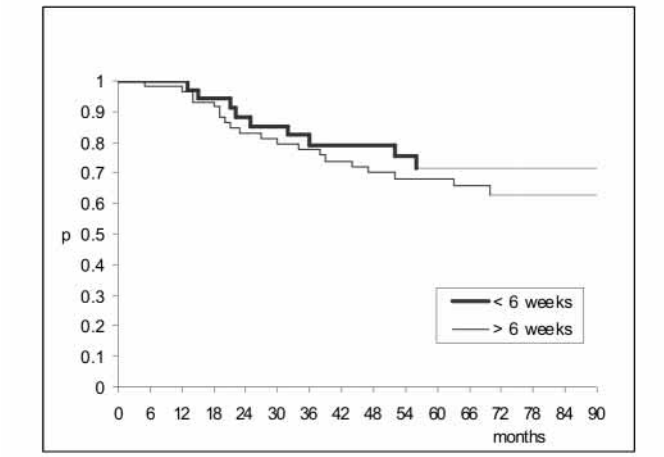


Figure 2b. Disease-free survival according to time from surgery to the beginning of radiotherapy

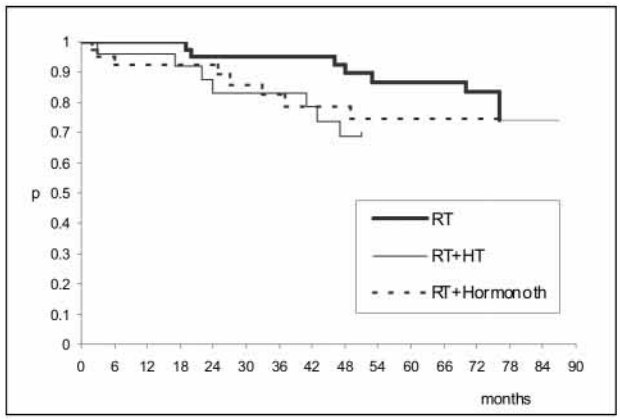


Figure 3a. Overall survival in three subgroups of patients

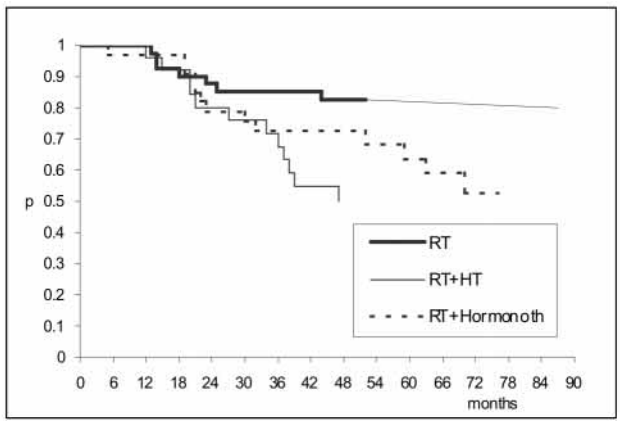


Figure 3b. Disease-free survival in three subgroups of patients

In combined RT/HT group there is no statistically significant difference in overall ($p>0.05$) and disease-free survival ($p>0.05$) regarding the number of received cycles of chemotherapy before starting postoperative radiotherapy (Figures 4a, 4b).

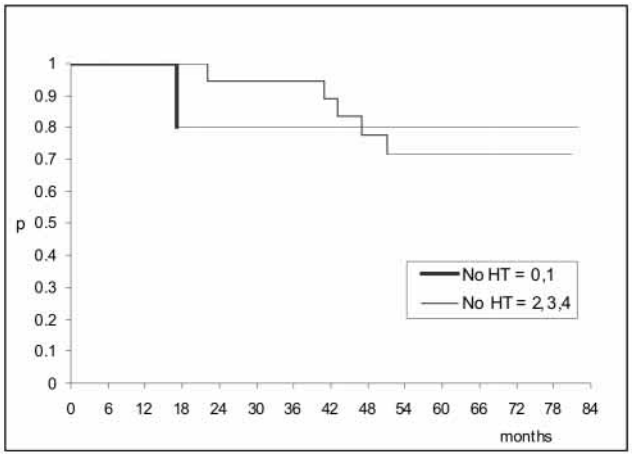


Figure 4a. Overall survival according to number of received cycles of HT before starting radiotherapy

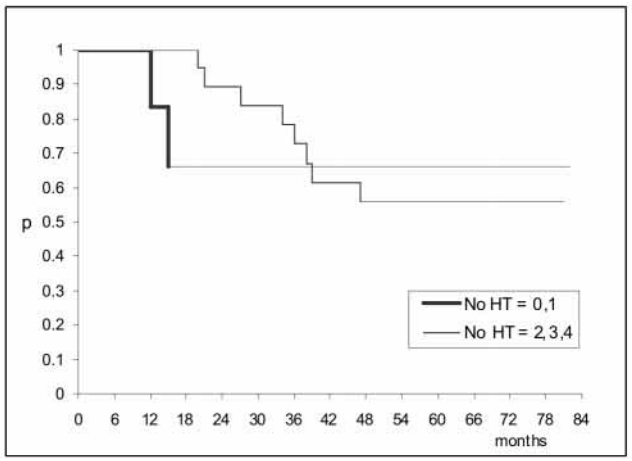


Figure 4b. Disease-free survival according to number of received cycles of HT before starting radiotherapy

DISCUSSION

Numerous clinical trials have shown that overall survival of patients with small tumors is the same disregarding whether they are treated with limited surgery plus irradiation or total mastectomy. However, total mastectomy is still the treatment of choice for many patients (7,8). The role of radiotherapy after mastectomy has been evaluated in many studies; a significant reduction in locoregional recurrences with postoperative irradiation, but no improvement in long-term survival has been shown (9,10). The question whether to irradiate regional lymphatics in patients with positive axillary lymph nodes is an extremely controversial issue, especially because these patients are receiving chemotherapy.

According to the protocol valid in our Institute at that time, the patients with positive axillary nodes had postoperative radiotherapy of all lymphatics. Patients with negative axillary nodes and medial and central localization of tumor had postoperative radiotherapy of internal mammary and supraclavicular lymph nodes.

The Danish trial of postoperative radiotherapy regional lymphatics and chest wall after radical mastectomy reported 9% of locoregional recurrence, while Canadian trial reported 10% of local relapse (5,11). Early Breast Cancer Trialists Collaborative Group, which analyzed 10-year results from 40 randomized trials, showed reduction of two-thirds in local recurrence after postoperative radiotherapy (8.8 % vs. 27.2 % in control group). They also showed that large reduction in local recurrence coincided with substantial reductions in the incidence of any recurrence (45.2% in radiotherapy vs. 53.8 % in control group) (6).

In our study, locoregional recurrence alone or with distant metastasis was observed in 10 patients (9.1%). Among them 7 patients had chest wall recurrence, but it should be mentioned that we did not irradiate the chest wall. Of patients who developed chest wall recurrence, 42.8 % had vascular invasion. Only 3 patients had clinical evidence of supraclavicular node involvement; axillary recurrence was not observed. Local recurrence was the first failure in 1.8 % of patients.

Ogawa et al. reported13.6% with chest wall recurrence in patients treated with postoperative radiotherapy of regional lymph nodes after mastectomy (12). They showed that 40% of cases with vascular invasion had chest wall recurrence, indicating that status of vascular invasion had a significant impact on chest wall control and should be treated with chest wall irradiation.

One argument against the use of prophylactic radiation therapy is that locoregional recurrences can be treated when they occur, thus allowing patients cured by surgery alone to be spared of inconvenience and potential long-term hazards of adjuvant radiation therapy. However, several studies have shown that it is very difficult to achieve long-term control of clinically manifested locoregional disease (13). For example, some retrospective studies have shown only 35-60% locoregional control rates use radiotherapy at time of chest wall failure, thus reinforcing the importance of chest wall prophylactic radiotherapy in high-risk patients (14).

In analysis of axillary lymph node involvement in subsequent chest wall failure, Haagensen reported that patients with <4 positive nodes had less than 5% local failure as first failure, which increased to 8-12% in patients with 4-7 positive nodes, and 20-42% in patients with >8 positive nodes (15). In our study, 5 % node negative and 11.7 % node positive patients had local relapse.

It is agreed that there are important differences between local recurrences occurring after radical mastectomy or after breast conserving surgery. Local relapses after mastectomy are accompanied or immediately followed by distant metastases in more than half of the cases (16). Local failures are also the expression of biologically aggressive behavior of the tumor that has already permeated tissues outside the mastectomy specimen. The relative risk for distant metastases is the greatest for recurrences

occurring within one year (17).

The analysis of time influence from surgery to the beginning of radiotherapy showed no significant difference in overall and disease-free survival between patients who started with postoperative radiotherapy in 6 weeks after surgery and those with more than 6 weeks. Buchholz et al. also showed that mastectomy patients treated with radiotherapy in 6 months after surgery and more than 6 months after surgery, did not have significant differences in local control or survival, although a trend for improved control was suggested for treatment within 6 months (18).

Since the adjuvant HT is unavoidable in adjuvant treatment of early breast cancer, the appropriate sequencing of radiotherapy and chemotherapy is still unclear.

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 (19). 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%).

Our results showed no significant difference in overall and disease-free survival with regard to the number of received cycles of chemotherapy before starting radiotherapy.

The analysis of the results between three subgroups of patients (RT alone, RT+HT and RT+ hormonotherapy), showed no significant difference in overall survival, but there was significant difference in disease-free survival between RT group and RT+HT group in favor of the former group. This can be explained by the fact that majority of node positive patients with higher risk for relapse, received adjuvant HT.

Another argument against prophylactic radiation therapy, particularly treatment that includes the regional nodes, is the risk of radiation pneumonitis, rib fractures, brachial plexus neuropathy, arm edema and decreased shoulder mobility (20). These effects are related to type of surgery, as well as the biological dose of radiation and the irradiated volume. Treatment techniques that include large fraction sizes (>2.0 Gy) should probably be avoided, since they have been demonstrated to increase the risk of late side effects (21).

The follow-up included routine clinical examination and 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, rib fractures or brachial plexopathy. Also, there was no evidence of heart failure, but our follow-up was too short to express cardiac toxicity.

CONCLUSION

In conclusion, postoperative radiotherapy after radical mastectomy, has important role in adjuvant treatment of early breast cancer. The indications for both postoperative radiotherapy and adjuvant chemotherapy should be based on realistic estimations of the risk of local recurrences and distant metastases. The aggressiveness of the therapy and the acceptable risk of complications, which could influence the cosmetic outcome, must therefore be balanced against the risk of recurrence.

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