Journal of BUON **12:** 215-220, 2007

ORIGINAL ARTICLE

Postmastectomy radiotherapy in intermediate risk stage I-II breast cancer patients

J. Mladenovic[1], S. Susnjar[2], D. Gavrilovic[3], N. Borojevic[1]

[1]Department of Radiotherapy, [2]Department of Medical Oncology, [3]Data Center, Institute for Oncology and Radiology of Serbia, Belgrade, Serbia

Summary

Purpose: *To evaluate the correlation of postmastectomy radiotherapy (PMRT) with local relapse rate, disease-free survival (DFS) and overall survival (OS) in a group of breast cancer (BC) patients at intermediate risk for locoregional relapse (stage I-II with either 1-3 positive axillary nodes, or node-negative grade III BC) treated with radical mastectomy.*

Patients and methods: *We evaluated 482 stage I-II BC patients, with either node-negative grade 3 tumors or with 1-3 positive nodes irrespective of tumor grade, treated with radical mastectomy at our Institute from 1986 to 1994. After mastectomy they received either adjuvant CMF (cyclophosphamide, methotrexate, 5-fluorouracil) chemotherapy (N=172), or adjuvant endocrine therapy (N=310). Postoperative radiotherapy (RT group) to the regional lymph nodes with tumor dose (TD) 48 Gy in 22 fractions was delivered to 199 patients.*

Results: *After a median follow-up of 79.5 months, no difference in relapse rate between the two groups was seen (30.6% in the RT group vs. 36.7% in the no RT group; x^2, p=0.1). Local recurrence rate occurring alone or with distant metastases was 4.52% in the RT group vs. 7.77% in the no RT group (x^2, p=0.1). However, local recurrence rate alone was significantly higher in the RT group compared to the no RT group (2.01 vs. 6.01%, x^2, p=0.041). In premenopausal patients local relapses occurred in 3.2% of patients with postoperative RT and in 8.2% in patients without RT (Fisher's exact test, p=0.48). Non significant difference was registered in postmenopausal patients with (4.76%) or without RT (6.58%). Ten-year DFS and OS were 53.5% and 68.7% in the RT group vs. 52.9% and 75.2% in the no RT group (non significant difference).*

Conclusion: *Our results did not show that PMRT significantly influences the incidence of disease relapse, DFS and OS in stage I-II BC patients with intermediate risk for disease relapse. However, it seems that PMRT might influence the occurrence of locoregional recurrence in these patients.*

Key words: early breast cancer, postoperative radiotherapy

Introduction

It has been documented earlier that postoperative RT has an important role not only in achieving locoregional disease control, but also in reducing the risk for systemic disease relapse [1,2]. One of the most controversial areas in postoperative RT in BC is the role of postmastectomy chest wall and nodal irradiation, especially in the intermediate risk group (node negative grade 3 tumors or 1-3 positive nodes irrespective of grade) [3,4]. Postmastectomy irradiation aims at preventing recurrent disease in the chest wall and regional lymph nodes [5,6]. The meta-analysis updated by the Early Breast Cancer Trialist's Collaborative Group (EBCTCG) showed that postoperative RT reduces the local recurrence rate by two-thirds [7]. Although PMRT was an established treatment for BC patients with 4 or more positive axillary lymph nodes, it is still unclear whether PMRT should be recommended to women at intermediate risk for locoregional recurrence, such as patients with 1-3 positive nodes [8-10].

The purpose of this retrospective analysis was to evaluate the disease outcome in relation to postopera-

Received 12-02-2007; Accepted 07-03-2007

Author and address for correspondence:

Dr. Jasmina Mladenovic
Department of Radiotherapy
Institute for Oncology and Radiology of Serbia
Pasterova 14
Belgrade
Serbia
Tel: +381 11 2067187
Fax: +381 11 2685300
E-mail: mladenovicj@ncrc.ac.yu

tive regional-nodal irradiation in node-negative grade 3 tumors or 1-3 node positive BC patients irrespective of tumor grade who had undergone radical mastectomy.

Patients and methods

A group of 482 stage I-II BC patients who were treated with radical mastectomy at the Institute of Oncology and Radiology of Serbia from 1986 to 1994 was analyzed. They were either node-negative with grade 3 breast tumors or had 1-3 positive axillary nodes irrespective of tumor grade. After surgery, they were treated with either adjuvant CMF chemotherapy, or adjuvant endocrine therapy (premenopausal women with ovarian ablation by irradiation and postmenopausal women with tamoxifen). Adjuvant endocrine therapy was given to patients with progesterone receptors (PgR)-positive tumors regardless of estrogen receptor (ER) status. In patients with PgR-negative BC adjuvant CMF chemotherapy was given.

Postoperative RT was given to the regional lymph nodes (axillary, supraclavicular and infraclavicular or internal mammary regions) with TD 48 Gy in 22 fractions, 2.18 Gy per fraction, over 4.5 weeks. All fields were treated with Cobalt-60 according to the localization of the primary tumor and the axillary status. Patients with negative axillary nodes and medial localization of primary tumors were irradiated to the supraclavicular and internal mammary regions, while patients with 1-3 positive nodes and lateral localization had irradiation of the axillary region also. The internal mammary nodes were treated with direct field, which covered the ipsilateral nodes in the first 3 intercostal spaces. Doses were specified at a depth of 2-3 cm. Supraclavicular and axillary nodes were irradiated by another anterior direct field with calculated doses at the 1/3 of the antero-posterior diameter.

The endpoints of this study were locoregional relapse rate (LRR), DFS and OS. Locoregional relapse was defined as recurrence on the ipsilateral chest wall and/or ipsilateral axillary and/or supraclavicular region. DFS was defined as the interval from breast cancer operation until local recurrence or distant metastases or death without relapse, whichever occurred first. OS was defined as the interval from the operation until death from any reason.

Statistics

Comparison of the patterns of failure in the groups were examined with the Pearson's x^2 test and Fisher's exact test. Survival curves were calculated by the Kaplan-Meier method, while log-rank was used for comparison between the treatment groups. All p-values were two-tailed and a $p \leq 0.05$ was considered significant.

Results

Of 482 patients, 199 (168 post- and 31 premenopausal) received postoperative RT (RT group), while 283 women did not receive postoperative RT (no RT group). Patient characteristics are given in Table 1 and adjuvant systemic treatments are presented in Table 2.

Table 1. Patient characteristics

Characteristic	*RT n (%)*	*no RT n (%)*
Menopausal status		
Premenopausal	31 (15.5)	207 (73.14)
Postmenopausal	168 (84.42)	76 (26.86)
Tumor size (cm)		
< 2	89 (44.72)	104 (36.75)
2-5	108 (54.27)	170 (60.07)
> 5	2 (1.01)	9 (3.18)
Involved axillary nodes		
0	34 (17.09)	75 (26.5)
1-3	165 (82.91)	208 (73.5)
Tumor histology		
CDI	126 (63.32)	172 (60.78)
CLI	62 (31.16)	85 (30.04)
Other	11 (5.53)	22 (7.77)
Unknown	–	4 (1.41)
Tumor grade		
1	10 (5.03)	15 (5.3)
2	141 (70.85)	181 (63.96)
3	48 (24.12)	87 (30.74)
ER		
Positive	137 (68.84)	161 (56.89)
Negative	35 (17.59)	78 (27.56)
Unknown	27 (13.57)	44 (15.55)
PgR		
Positive	101 (50.75)	157 (55.48)
Negative	71 (35.68)	82 (28.98)
Unknown	27 (13.57)	44 (15.55)
Total	199 (100)	283 (100)

RT: radiotherapy, ER: estrogen receptor, PgR: progesterone receptor, CDI: invasive ductal Ca, CLI: invasive lobular Ca

Table 2. Adjuvant systemic treatment modalities

Treatment	*RT group (n=199) n (%)*	*no RT group (n=283) n (%)*
Ovarian ablation by irradiation	20 (10.05)	119 (42.05)
Tamoxifen	128 (64.32)	43 (15.19)
CMF	51 (25.63)	121 (42.76)

The groups were homogeneous with regard to tumor size, tumor histology and grade but they differed in menopausal status, axillary nodal status and ER status.

After a median follow up of 79.5 months (range 2-232) there was a similar relapse rate in both groups: 30.6% in the RT group vs. 36.7% in the no RT group (x^2, p=0.1). The results of the disease outcome are given in Table 3. The frequency of local recurrence, occurring alone or together with distant metastases, was 4.52% in the RT group vs. 7.77% in the no RT group (x^2, p=0.1). However, there was a significant difference in the occurrence of local recurrence between RT and no RT group (2.01 vs. 6.01%, x^2, p=0.041). In premenopausal patients local relapse occurred in 3.2% in the RT group and in 8.2% in the no RT group (Fisher's exact test, p=0.48). Also, in postmenopausal patients there were more local relapses in the no RT group than in the RT group: 6.58% and 4.76%, respectively (x^2, p=0.55). There was no significant difference in local recurrence rates between premenopausal patients with 1-3 positive nodes treated with RT vs. no RT: 4.3% vs. 8.2% (Fisher's exact test, p=1), as well as in postmenopausal patients with 1-3 positive nodes treated with RT vs. no RT: 4.2% vs. 5.1% (Fisher's exact test, p=0.68).

At the time of analysis, more than half of the patients in both groups were alive without evidence of disease. BC-specific survival was similar in both groups, while more than twice as many patients in the RT group died due to concomitant diseases compared to the no RT group (Table 4). Ten-year DFS for the RT group was 53.5% and for the no RT group it was 52.9% (log-rank test, p=0.98) (Figure 1). Ten-year OS for the RT and no RT groups was 68.7% and 75.2%, respectively (log-rank test, p=0.35) (Figure 2). Median DFS in the RT group was 143 months and in the no RT group 127 months (log rank, p=0.98). Median OS in both groups has not been reached.

Table 3. Recurrences in the RT and no RT groups

Recurrence	*No RT n (%)*	*RT n (%)*	*p-value*
Without recurrence	170 (60.07)	137 (68.84)	0.48
Locoregional recurrence only	17 (6.01)	4 (2.01)	0.041
Locoregional plus distant metastases	5 (1.77)	5 (2.51)	0.57
Distant metastases only	82 (28.98)	52 (26.13)	0.49
Unknown status	9 (3.18)	1 (0.5)	0.052
Total	283 (100)	199 (100)	

Table 4. Survival status at the time of analysis

Survival status	*No RT n (%)*	*RT n (%)*	*p-value*
Alive, disease-free	160 (56.54)	119 (59.80)	0.47
Alive with disease	58 (20.49)	33 (16.58)	0.27
Dead due to primary disease	46 (16.25)	28 (14.07)	0.51
Dead due to concurrent disease	10 (3.53)	18 (9.04)	0.011
Unknown status	9 (3.18)	1 (0.5)	0.052
Total	283 (100)	199 (100)	

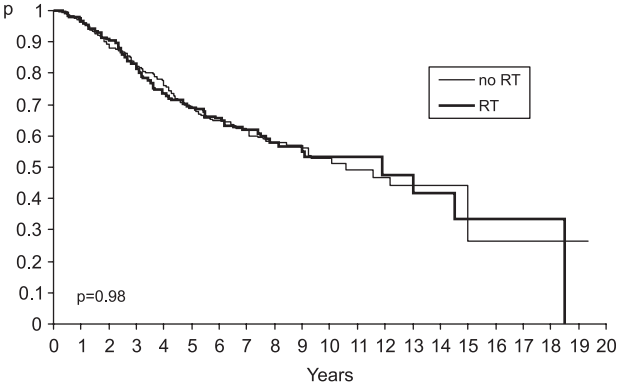

Figure 1. Disease - free survival in both groups.

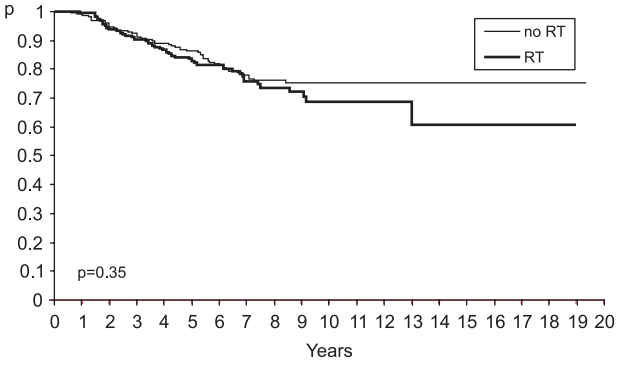

Figure 2. Overall survival in both groups.

Discussion

LRR rate in BC patients after radical mastectomy ranges from 5 to 40% [11], and depends on tumor size and the number of the regional axillary lymph nodes involved. Recht et al. analyzed data from 4 randomized trials conducted by the Eastern Cooperative Oncology Group (ECOG) on 2016 node-positive patients who had undergone radical mastectomy and adjuvant chemotherapy or endocrine therapy without postop-

erative RT [12]. The 10-year LRR rate was 13% for patients with 1-3 positive nodes and 29% for those with 4 or more positive nodes. Similar results of LRR rates were obtained in the analysis of 5758 mastectomized patients with node-positive BC from 5 NSABP randomized trials [13]. On the contrary, the Danish [14] and British Columbia [15] trials reported unexpectedly high 10- and 15-year LRR in operated early node-positive BC patients who did not have postoperative RT: in the 1-3 positive node group 30% and 33%, respectively, and in the ≥4 positive node group 42% and 46%, respectively. The main objection for these results was the low median number of the excised regional axillary lymph nodes [16]. In our analysis, patients with 1-3 positive nodes and with node-negative grade 3 tumors that were not treated with RT had LRR rate 7.77%. The lower LRR in our patients might be explained by the shorter median follow-up period compared with the majority of reported studies (the median follow-up in our study was 79.5 months compared with 114 months in the Danish and 150 months in the British Columbia trials) [14,15].

It is well known that the use of PMRT results in a reduction of the LRR by approximately two thirds [7]. The commonly used indications for PMRT are ≥ 4 positive nodes and tumors greater than 5 cm, where the 10-year risk for LRR is 20-40%. PMRT in these patients reduces the risk of local recurrence from 25-40% to 6-8% [17]. The 10-year risk for local recurrence in BC patients with 1-3 positive nodes ranges from 4-19% [16] and PMRT reduces the risk of local recurrence from 13% to 3-4% [17]. However, the value of PMRT in reducing the LRR in patients with intermediate risk of local recurrence (1-3 positive nodes, and node-negative with grade 3, T1-2 BC) has to be investigated. In our patients with intermediate risk for local recurrence PMRT reduced the LRR from 7.77% to 4.53%. Although irradiation of the chest wall was not performed in our patients, the LRR rate was low.

Two issues that deserve further investigation in patients with intermediate risk for local recurrence are primary tumor size and tumor penetration through the nodal capsule [extracapsular extension (ECE)].

Both, the Danish and the British Columbia trials found that patients with ECE benefit more from RT than those without ECE [18]. In the MD Anderson analysis, Katz et al. identified a subgroup of patients with 1-3 positive nodes at higher risk of LRR [19]: patients with larger tumor size, ECE > 2 mm and inadequate lymph node dissection. Without PMRT patients with tumors larger than 4 cm had LRR of 26%, and in those with ECE >2 mm LRR was 33%. In the International Breast Cancer Study Group (IBCSG) study, the authors identified patients with 1-3 positive nodes with grade 3 tumors greater than 2 cm and vascular invasion as a high-risk group for local recurrence [20].

The next issue was to demonstrate if a significant benefit of PMRT on locoregional control translates into significant benefit for OS. Recently reported trials demonstrated that PMRT not only reduces locoregional failure, but also improves 10-year OS up to 10% [14,15]. Perhaps the most surprising finding of the Danish [14] and the British Columbia [15] trials was the distinct survival benefit in women with 1-3 positive nodes. In the Danish trial the 10-year OS in patients with 1-3 positive nodes treated with PMRT was 62% and in the similar group of patients not treated with PMRT it was 54%. Similar results were observed in the British Columbia trial, where the 17-year OS in the PMRT group was 64% and in the group without PMRT 53% [15].

In our study the 10-year OS was 68.7% in the RT group and 75.2% in no RT group. These differences in OS are not statistically significant, but the better survival in the no RT group is a result of more non-BC induced deaths in the RT group, probably due to PMRT-induced concurrent diseases: non-cancer deaths were 9.04% in the RT group vs. 3.53% in the no RT group (p=0.011). These differences between RT and no RT groups are probably due to RT-induced cardiovascular diseases, supported also by the fact that the RT group consisted mostly of postmenopausal women who had already preexisting cardiac disease. Moreover, the planning of PMRT was not sophisticated at that time as it is nowadays. However, BC-specific mortality rates were similar in both groups: 16.25% in the no RT vs. 14.07% in the RT group.

The speculation that patients with 1-3 positive nodes benefited more from PMRT than patients with ≥ 4 positive nodes is based on the hypothesis that the former may have smaller burden of micrometastatic disease which can thus be effectively eradicated by the addition of locoregional and systemic therapy, while in the latter (patients with 4 or more positive nodes) systemic spread of tumor cells is much more extensive and locoregional therapy will not have a significant impact on survival [5]. It is possible therefore that while locoregional RT may confer most benefit in locoregional control in larger tumors, a greater survival benefit might be achieved in smaller tumors and fewer number of involved nodes.

Despite this finding, the use of PMRT in patients with 1-3 positive nodes has not been widely accepted. A recent survey among European radiation oncologists over the use of PMRT in women with 1-3 positive nodes showed wide variations among those advocat-

ing PMRT (from 19% in Italy to 74% in Spain and Portugal) [21]. A similar survey was conducted in the United States where only 58% of radiation oncologists would use PMRT in this group of BC patients. In the NSABP trials (B-30 and B-31) only 39-44% of patients with 1-3 positive nodes were treated with PMRT [13]. On the other hand, there is also evidence that the use of regional nodal irradiation has been increasing since 1997 after the publication of new data from the Danish and the British Columbia trials [22]. Nevertheless, further research is required to define the role of PMRT in intermediate risk BC patients. One of the clinical trials of PMRT in this subgroup of patients is the SUPREMO trial, the objective of which is to assess the impact of postoperative RT to the chest wall on locoregional control, OS and cardiac morbidity.

Conclusion

Although our results did not show significant differences between RT and no RT groups concerning disease relapse rate, DFS and OS in intermediate risk BC patients, they imply that PMRT might influence the occurrence of locoregional recurrence in these patients. There is no consensus about the use of adjuvant PMRT in such patients to improve local control rates. Further investigations to evaluate the balance between risks and benefits of PMRT are strongly recommended, since RT-induced morbidity may significantly deteriorate the quality of life in patients without BC relapse.

Acknowledgement

The authors wish to thank Tina Kocan from the Data Center of the Institute for Oncology and Radiology of Serbia for her help in preparing the manuscript.

References

1. Nielsen HM, Overgaard M, Gran C, Jensen AR, Overgaard J. Study of Failure Pattern Among High-Risk Breast Cancer Patients With or Without Postmastectomy Radiotherapy in Addition to Adjuvant Systemic Therapy: Long-Term Results From the Danish Breast Cancer Cooperative Group DBCG 82 b and c Randomized Studies. J Clin Oncol 2006; 24: 2268-2275.
2. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005; 366: 2087-2106.
3. Buchholz TA, Strom EA, Perkins GH, McNeese MD. Controversies regarding the use of radiation after mastectomy in breast cancer. Oncologist 2002; 7: 539-546.
4. Pierce LJ. Postmastectomy radiotherapy: future directions. Semin Radiat Oncol 1999; 9: 300-304.
5. Van der Hage JA, Putter H, Bonnema J et al. Impact of locoregional treatment on the early-stage breast cancer patients: a retrospective analysis. Eur J Cancer 2003; 39: 2192-2199.
6. Kurtz J. The curative role of radiotherapy in the treatment of operable breast cancer. Eur J Cancer 2002; 38: 1961-1974.
7. Early Breast Cancer Trialists' Collaborative Group. Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer:An overview of the randomised trials. Lancet 2000; 355: 1757-1770.
8. Pierce LJ. Treatment guidelines and techniques in delivery of postmastectomy radiotherapy in the management of operable breast cancer. J Natl Cancer Inst Monogr 2001; 30: 117-124.
9. Recht A, Edge SB, Solin LJ et al. Postmastectomy radiotherapy: Clinical practice guidelines of the American Society of Clinical Oncology. J Clin Oncol 2001; 19: 1539-1569.
10. Harris JR, Halpin-Murphy P, McNeese M, Mendenhall NP, Morrow M, Robert NJ. Consensus statement on postmastectomy radiation therapy. Int J Radiat Oncol Biol Phys 1999; 44: 989-990.
11. Cheng JC, Chen C, Liu M et al. Locoregional failure of postmastectomy patients with 1-3 positive axillary lymph nodes without adjuvant radiotherapy. Int J Radiat Oncol Biol Phys 2002; 52: 980-988.
12. Recht A, Gray R, Davidson NE et al. Locoregional failure 10 years after mastectomy and adjuvant chemotherapy with or without tamoxifen without irradiation:experience of the Eastern Cooperative Oncology Group. J Clin Oncol 1999; 17: 1689-1700.
13. Taghian A, Jeong JH, Mamounas E et al. Patterns of locoregional failure in patients with cancer treated by mastectomy and adjuvant chemotherapy with or without tamoxifen and without radiotherapy: Results from five National Surgical Adjuvant Breast and Bowel Project Randomized Clinical Trials. J Clin Oncol 2004; 22: 4247-4254.
14. Overgaard M, Hansen PS, Overgaard J et al. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. N Engl J Med 1997; 337: 949-955.
15. Ragaz J, Jackson SM, Le N et al. Adjuvant radiotherapy and chemotherapy in node-positive premenopausal women with breast cancer. N Engl J Med 1997; 337: 956-962.
16. Fowble B. Postmastectomy radiation in patients with one to three positive axillary nodes receiving adjuvant chemotherapy: An unresolved issue. Semin Radiat Oncol 1999; 9: 230-240.
17. Olivotto IA, Troung PT, Chua B. Postmastectomy radiation therapy: Who needs it? J Clin Oncol 2004; 22: 4237-4239.
18. Kuske RR. Adjuvant irradiation after mastectomy in women with one to three positive axillary nodes: Then no; Now yes. Semin Radiat Oncol 1999; 9: 254-258.
19. Katz A, Strom EA, Buchholz TA et al. Locoregional recurrence patterns after mastectomy and doxorubicin-based chemotherapy: implications for postoperative irradiation. J Clin Oncol 2000; 18: 2817-2827.
20. Wallgren A, Bonetti M, Gelber RD et al. Risk factors for locoregional recurrence among breast cancer patients: Results from the International Breast Cancer Study Group Trials I

through VII. J Clin Oncol 2003; 21: 1205-1213.
21. Ceilley E, Jagsi R, Goldberg S et al. Radiotherapy for invasive breast cancer in North America and Europe: Results of a survey. Int J Radiat Oncol Biol Phys 2005; 61: 365-373.
22. Chua B, Olivotto IA, Weir L, Kwan W, Truong P, Ragaz J. Increased use of adjuvant regional radiotherapy for node-positive breast cancer patients in British Columbia. The Breast 2004; 10: 38-44.