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Postmastectomy radiotherapy and locoregional recurrence rate in high-risk breast cancer patients

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BACKGROUND: *Postmastectomy radiotherapy has been the topic for many debates over several years about its role on locoregional control as well as overall survival in premenopausal and postmenopausal breast cancer patients.*

METHODS: *From 1994 till 1999, 233 patients underwent modified radical mastectomy for breast cancer. Among them there was 92 premenopausal patients (median age was 44 years) and 141 postmenopausal patients (median age was 60 years). Traditional prognostic factors were used to assess risk of locoregional recurrence: 84 patients were node-negative, 71 patients had 1 to 3 lymph nodes positive, and 71 patients had 4 and more positive lymph nodes; 103 patients had tumor less than 3 cm diameter and 130 patients had tumors grater than 3 cm. According to this, postmastectomy radiotherapy was applied in 125 patients of whom 117 patients (94%) had also adjuvant systemic therapy (chemotherapy and/or hormonal therapy).*

RESULTS: *The locoregional recurrence was observed in 42 patients while 191 patients were free of (median follow-up time was 49 months). Locoregional recurrence developed in 10 patients who had postmastectomy radiotherapy and in 32 patients who did not had postmastectomy radiotherapy (p=0.0001). In the group of patients with locoregional recurrence event 5-year overall survival was 28% while 70% in the group of patients free of (p=0.00001). There was statistically significant advantage for postmastectomy radiotherapy in the group of patients with 1 to 3 positive lymph nodes as well as for 4 and more positive lymph nodes group (p=0.0008). In addition there was statistically significant difference among postmastectomy radiotherapy group and no postmastectomy radiotherapy group for disease free survival (74% vs. 50%, 5-year disease free survival, p=0.0001) and overall survival (71% vs. 53%, 5-year overall survival, p=0.0422).*

CONCLUSION: *Postmastectomy radiotherapy reduces locoregional recurrence rate and improves overall survival in premenopausal and postmenopausal breast cancer patients with tumors grater than 3cm diameter and positive axillary lymph nodes.*

KEY WORDS: *Breast Neoplasms; Mastectomy; Radiotherapy, Adjuvant; Neoplasm Recurrence, Local; Survival Rate*

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INTRODUCTION

Despite years of clinical study, there are still many unanswered questions regarding postmastectomy radiation (PMRT). It is accepted that PMRT is not required for most women with noninvasive disease or stage I disease. Randomized clinical trials studying radiation treatments for women with stage II or III breast cancers have shown that the addition of radiation after mastectomy can reduce locoregional recurrence (LR) rates, which then improves survival. However, other data have indicated that the risk of LR after mastectomy and chemotherapy is low for patients with small tumors and one to three positive lymph nodes (LN), leading some to question whether PMRT is useful for this group (1).

The overall importance of local tumor control in the management of breast cancer, specifically the influence of local control on survival, remains one of the fundamental questions for oncologists (2). PMRT is often recommended for patients at high risk for LR

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after mastectomy. However, long-term outcomes after radiation therapy are not well described (3-5). Randomized clinical trials have established that adjuvant chemotherapy or hormonal treatment prolongs the survival of breast cancer patients. As a result of these studies, large numbers of women with breast cancer now receive one or both of these treatments postoperatively. A number of randomized trials have also shown that overall survival (OS) in patients with small tumors was the same whether they were treated with limited surgery plus irradiation or total mastectomy. For this reason, many patients are now treated locally with conservative measures, such as lumpectomy plus axillary dissection and irradiation to residual breast tissue; some also receive adjuvant systemic therapy. Total mastectomy, however is still the treatment of choice for many patients. The role of radiotherapy (RT) after mastectomy has been evaluated in several randomized trials. Overall, these studies have shown a significant reduction in LR with PMRT but no improvement in long-term survival, irrespective of nodal status. Radiotherapy has been evaluated mainly in trials in which chemotherapy was not given. The widespread use of adjuvant chemotherapy calls for a reassessment of RT, because the efficacy of systemic therapy in preventing local or regional recurrence after mastectomy is only moderate and it is not clear whether local or regional control is required for prolonged survival in patients who also receive adjuvant chemotherapy (6-15).

The trial by Ragaz et al. from British Columbia, Canada, reports a 5-year LR rate of 21% among women who did not undergo RT and 10% among those who received radiation; 10-year rates were 25% and 13%, respectively. Similarly, the Danish trial by Overgaard et al. reports a 114-month rate of LR alone of 26% for women given chemotherapy without RT and 5% for those given both chemotherapy and RT. Rates of LR are considerably lower in the United States. Fisher et al. reported a 6.2% rate of LR among women treated without RT at 8 years; Lichter et al. reported 7.8% at 68 months; and Jacobson et al. reported 8.6% at 10.1 years. Notably, Fisher et al. find the same rate of LR in stage I and II disease, which probably reflects a positive effect of adjuvant chemotherapy. Parenthetically, the actuarial eight year rate of LR at other European centers was 9% in pts treated with mastectomy, as reported by van Dongen et al. Thus, the incidence of LR after mastectomy reported by Ragaz et al. and Overgaard et al. is extremely high (16-24).

A more comprehensive meta-analysis concerning postmastectomy radiation was recently updated by the Early Breast Cancer Trialists' Collaborative Group. This group analyzed the actual data from over 15 000 patients treated in clinical trials investigating the use of PMRT. The data from this analysis showed that PMRT reduced isolated LR rates (1).

Aim of our study was to assess to role of PMRT on LR rate and OS in high risk premenopausal and postmenopausal breast cancer pts. We defined high-risk status for pts with tumors grater than 3 cm diameter and positive axillary ln.

PATIENTS AND METHODS

From 1994 till 1999, 233 patients underwent modified radical mastectomy for breast cancer at Clinical Centre of Montenegro. Among them there was 92 premenopausal (median age was 44 years) and 141 postmenopausal women (median age was 60 years). Traditional prognostic factors were used to assess risk of LR: 84 patients were node-negative, 71 had 1 to3 LN positive, and 71 patients had 4 and more positive ln; 103 patients had tumor less than 3 cm diameter and 130 had tumors grater than 3 cm (Table 1).

Table 1. Patients' characteristics

All patients (pts) = 233
Age:
< 50 yr.-premenopausal pts = 92 (median = 44 yr.; min = 28; max = 50)
> 50 yr.-postmenopausal pts = 141(median = 60 yr.; min = 51; max = 77)
Ln status:
0 = 84 pts
1 – 3 = 71 pts
> 4 = 71 pts
Size of tumor:
< 3 cm = 103 pts (38 pts premenopausal, 65 pts postmenopausal)
> 3cm = 130 pts (54 pts premenopausal, 76 pts postmenopausal)
Menopausal status:
Premenopausal = 92 pts
Postmenopausal = 141 pts
PMRT:
Yes = 125 pts
No = 108 pts
Therapy
Adjuvant Systemic Therapy:
Yes = 194 pts
No = 39 pts
Chemotherapy / Hormonotherapy: 84 pts
Chemotherapy: 43 pts
CMF = 100 pts
FAC = 27 pts
Hormonotherapy: 67 pts
Ovarian ablation + / - Tamoxifen = 24 pts
Tamoxifen = 43 pts
Locoregional recurrence:
Yes = 42 pts
(PMRT = 10 pts (12%))
(NoPMRT = 32 pts (33%))
No = 191 pts
Follow up:
49 months (min = 11; max = 102)

To be eligible for the study a woman had to have no evidence of metastatic disease as determined by physical examination, biochemical tests, chest radiography, bone radiography and no other previous or concomitant malignant disease.

According to this, PMRT was applied in 125 patients. RT was delivered to the chest wall, including the surgical scar and regional LN (i.e., supraclavicular, infraclavicular and axillary nodes as well as internal mammary nodes) depending on the primary site

of the tumor. Each patient had received PMRT on the surgical scar (125 patients), patients with positive axillary LN on the supra- and infraclavicular ln, on the axilla after incomplete dissection, and patients with inner tumor localization - on the internal mammary nodes. The intended dose was a median absorbed dose in the target volume of either 50 Gy, given in 25 fractions over a period of 5 weeks, or 48 Gy given in 22 fractions over a period of 4.5 weeks, according to report 50 of the ICRU (International Commission on Radiation Units and Measurements). The recommended field arrangement involved the use of an anterior photon field against the supraclavicular, infraclavicular, axillary regions, the internal mammary nodes and tangential fields against the chest wall. The patients were treated on the linear accelerator, 6 MeV energy, Clinac 600 C, Varian.

Also, 194 patients had systemic therapy (chemotherapy and/or hormonal therapy). A combination of cyclophosphamide (600 mg per square meter of body surface area), methotrexate (40 mg per square meter of body surface area) and fluorouracil (600 mg per square meter of body surface area) was given 1 and 8 day, IV every four weeks, up to six cycles, with the first cycle beginning three to four weeks after surgery. Patients who were assigned to RT plus CMF started RT concomitantly with chemotherapy. Among them there were pts with FAC chemotherapy (fluorouracil 500 mg per square meter of body surface area; Adriamycin 50 mg per square meter; cyclophosphamide 500 mg per square meter, IV, 1 day, every 3 weeks, up to 6 cycles) preceding RT. Hormonal therapy was given as tamoxifen for postmenopausal women and ovarian ablation +/- tamoxifen for premenopausal women according prognostic factors. Same dose and schedule of chemotherapy was given in the group of patients without RT.

The patients were followed with clinical examination at regular intervals for up to 5 years and further tested only if they had symptoms or evidence of recurrent disease.

LR was defined as the appearance of the disease on the chest wall and axillary ln. The lengths of time until treatment failure were measured from the date of mastectomy. Disease free survival (DFS) was defined as the duration of survival without LR or distant metastases, cancer in the opposite breast, or other malignant disease. OS was calculated as the length of time until death, irrespective of cause. The values were compared by chi square test. We used the life table method to estimate the probability of treatment failure for the end points of DFS and OS (16). The median potential follow-up was 49 months.

RESULTS

By the time of the analysis (median follow-up, 49 months) the LR was observed in 42 patients while 191 patients were free of. The probability of DFS was significantly higher in the group that received RT plus chemotherapy than in the group treated only with chemotherapy. Among those with PMRT, 10 patients (12%) had LR while 32 patients (33%) with no PMRT (p=0.0001). In the group of patients with LR event 5-year OS was 28% while 70% in the group of patients free of (p=0.00001) (Figure 1). There was statistically significant advantage for PMRT in the group of patients with 1 to 3 positive LN as well as for 4 and more positive LN group (p=0.0008). In addition there was statistically significant difference between PMRT group and no PMRT group for DFS (74% vs. 50%, 5-year DFS, p=0.0001) and OS (71% v. 53%, 5-year OS, p=0.0422) (Figure 2, 3).

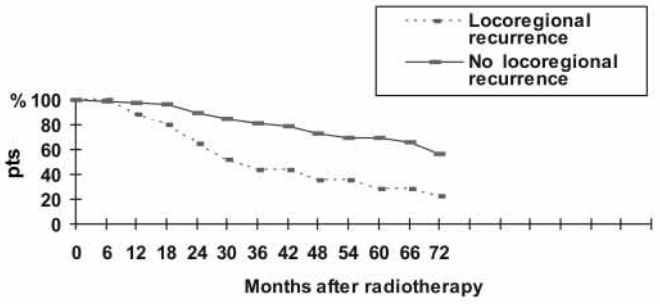

Figure 1. Locoregional recurrence/No locoregional recurrence - In the group of 42 patients with LR event 5-year OS was 28% while 70% in the group of patients free of (191 patients) (p= 0.00001)

Figure 2. Postmastectomy radiotherapy/No postmastectomy radiotherapy - There was statistically significant difference between PMRT group and no PMRT group for DFS (74 % vs. 50 %, 5-year DFS, p=0.0001) (233 patients)

Figure 3. Postmastectomy radiotherapy/No postmastectomy radiotherapy - There was statistically significant difference between PMRT group and no PMRT group for OS (71 % vs. 53 %, 5-year OS, p=0.0422) (233 patients)

DISCUSSION

Trials of postoperative radiotherapy for breast cancer conducted during the 1960s and 1970s showed significant reductions in rates of LR but no improvement in OS. Failure of PMRT to improve OS was explained with micrometastatic nature of breast cancer even in an early stage of the disease. Additional concern was raised by data suggesting that irradiated patients have reduced survival rates due to either immunosuppression or cardiac complications. In the late 1970s, adjuvant chemotherapy became a standard treatment for high-risk premenopausal patients with breast cancer. The use of adjuvant RT subsequently declined, because it did not appear to prolong survival. Nevertheless, there are reasons to reconsider RT including the limited value of adjuvant chemotherapy for bulky disease, a synergistic effect of chemotherapy plus radiation on residual locoregional tumor, and the possibility that eliminating bulky disease with radiation may improve the effect of chemotherapy, because chemotherapy may be more effective when the overall disease burden is low (17,18). Also, in the recent years it has become recognized that DFS and not only the OS represents very important treatment objective being defined as time with good quality of life (18).

Surgical technique is known to affect the incidence of local recurrence. The data thus seem more relevant to the role of RT after total mastectomy rather than modified radical mastectomy. The value of axillary irradiation in the former case is established; the rate of recurrence in untreated, clinically negative axillae is about 20 percent as opposed to 1 to 2 percent after axillary node dissection or irradiation. The National Surgical Adjuvant Breast and Bowel Project (in Protocol B-04) detected no difference in the OS of patients who underwent primary or delayed axillary dissection or RT.

Our results indicate that the addition of RT to adjuvant chemotherapy after modified radical mastectomy reduces LR and improves survival (PMRT group vs. no PMRT group for DFS [74% vs. 50%, 5-year DFS, p=0.0001) and OS [71% vs. 53%, 5-year OS, p=0.0422]).

Previous studies of RT showed improvement in the control of locoregional tumors and suggested improvement in survival. During the surgical procedure some of the cancer cells are implanted within the scar region and could be spread by lymphatics to surrounding cutaneous tissue. The postoperative RT reduces this long-term risk to 10-12% (2-5).

There might have been important variations in the extent of the surgery. Our surgeons found relatively few LN in the axilla, but the number also relies on the pathologist who counted the LN in the specimen. More than half of the recurrences were on the chest wall. Recurrences on the chest wall and in the axilla (without concomitant distant metastases) were treated with curative intent. Most patients who did not receive RT were treated with resection of the recurrent tumor followed by RT, whereas pts who had received RT were treated with surgery alone.

The significant difference in OS between the group treated with RT plus chemotherapy and the group given chemotherapy alone indicates that second line treatment cannot compensate for inadequate primary therapy.

Our study indicates that optimal results of the treatment of breast cancer pts can be achieved only by controlling both locoregional and systemic tumors. With current surgical methods of treatment, RT as treatment modality should be applied in purpose to achieve good locoregional control, especially in high-risk breast cancer patients and also in combination with adjuvant chemotherapy to achieve better OS.

CONCLUSION

PMRT reduces LR rate and improves OS in premenopausal and postmenopausal breast cancer patients with tumors grater than 3cm diameter and positive axillary ln.

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