



Postmastectomy Radiotherapy Decision for Patients without Lymph Node Metastases: Turkish Radiation Oncology Society Breast Cancer Working Group

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OBJECTIVE

Recent meta-analysis have not revealed any positive effects of postmastectomy radiotherapy (PMRT) on locoregional recurrence (LRR) or overall survival in axilla-negative patients. However, risk of LRR increases to 15% in the presence of two or more adverse factors for the same patient group. In this study, PMRT indications and volume selections of radiation oncologists in Turkey for axilla-negative breast cancer was investigated.

METHODS

Questionnaires were distributed to members of the breast cancer study group. Data of patients with axillary negative or isolated/micrometastasis and PMRT over 10 years (2006–2016) were collected from 10 participating centers. Clinical and tumor histopathological features and treatment details of 185 patients were analyzed.

RESULTS

The median age of patients was 48 years. Ratio of early-stage patients was 60% (T1-15%, T2-45%). There were 147 (79%) negative cases, 32 (17%) with micrometastasis, and 6 (3%) with isolated tumor cells. Half of the patients had only their chest walls (CW) irradiated. Peripheral lymphatics were also included in the rest. In Nmic cases, ratio of irradiation of supraclavicular and axillary lymph nodes with CW were statistically significant compared to CW irradiation (72% and 28%, respectively; p=0.015).

CONCLUSION

Considering the low number of patients treated over 10 years in 10 different centers in Turkey, it can be said that PMRT is often done in node-negative breast cancer. It is difficult to reach a definite conclusion for patients with Nmic, due to lack of data from patients with PMRT. However, the general tendency is to irradiate peripheral lymphatics in Nmic cases if PMRT is to be performed.

Keywords: Axillary node negative; mastectomy; radiotherapy.

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Introduction

Postmastectomy radiotherapy (PMRT) for patients without axillary lymph node metastases is debatable. Retrospective studies and meta-analysis have shown that if there are combined risk factors, the local recurrence risk is up to 20%. [1-4] On the other hand, Early Breast Cancer Trialists' Collaborative Group's meta-analysis indicates that after complete axillary dissection, PMRT does not have any impact either on local control (LC) or on overall survival (OS) rates. However, patients without lymph node metastases still benefit from PMRT in terms of LC if the axillary approach was just sampling instead of a full dissection. [5-6]

Recently, considering the cosmetic outcome, skin-sparing mastectomy (SSM) and nipple areola sparing mastectomies (NSM) have replaced more aggressive surgeries. Although this approach is generally accepted as a safe procedure, some risk factors, such as flap thickness and surgical margin positivity, triple-negative biology, or young age, are considered as adverse factors on LC. [7] Therefore, the decision to treat patients without axillary lymph node metastases with PMRT depends on multiple factors with a tailored treatment approach. If a consensus is difficult to obtain, a questionnaire among practitioners or retrospective evaluation of the characteristics of treated patients might be useful. [8]

Therefore, Turkish Radiation Oncology Society Breast Cancer Working Group designed a study to assess indications of radiation oncologists for PMRT and selection of radiotherapy volumes by retrospectively analyzing the patients without axillary metastases that were treated in Turkey.

Materials and Methods

Patients who have undergone mastectomy for invasive breast carcinoma and were pathologically diagnosed negative for axillary lymph node metastases and who received radiotherapy between the years 2006 and 2016 were retrospectively evaluated. Additionally, patients with minimal axillary tumor burden such as isolated tumors or micrometastasis in the axillary lymph nodes, determined pathologically, were included in the analysis. A spreadsheet consisting of all patient and tumor characteristics such as age, tumor type, stage, hormone receptor status, histologic grade, lymphovascular invasion (LVI), Ki-67 proliferation index, surgical margin, mastectomy, and

axillary surgery type, RT volumes (chest wall, supraclavicular, axillary level 1, 2, 3 and internal mammary lymph nodes), and the total dose and fractionation was prepared. Mastectomy technique is classified into four groups: simple mastectomy, modified radical mastectomy (MRM), SSM and NSM. The surgical assessment of the axilla is divided into two: sentinel lymph node biopsy (SLNB) and axillary dissection.

The approval of ethical committee was obtained. Following the approval and support of the society, the spreadsheet was distributed via email to the members of breast cancer working group of Turkish Society of Radiation Oncology.

We received responses of 13 attendees from 10 different radiation oncology centers. Information on 185 patients was qualified for further analysis. The data on 185 patients were transferred to the SPSS 23 software program (IBM SPSS Statistics for Windows, Version 23.0, Released 2015, IBM Corp. Armonk, NY). Statistical analysis using chi-square, Student t test, and Mann-Whitney U test were carried out. A p value <0.05 was accepted as significant.

Results

The median age of patients was 48 years (range 22–82 years). Out of 185 patients, 118 (64%) were premenopausal. In 140 patients (76%), the tumor histology was invasive ductal carcinoma. The most frequently used surgical technique was MRM (57%). Dissection was performed to assess the axilla in 108 patients (58%); and the median number of dissected lymph nodes was 16 (min. 1, max. 40). (The number of patients with less than 10 dissected lymph nodes was 19 (10%).) The number of sampled lymph nodes with SLNB was 3 (min. 1, max. 7) in 77 patients (42%). Among all patients, 147 (80%) were node negative.

In 60% of patients who had undergone PMRT, the tumor stage was detected as T1 (15%) and T2 (45%). The ratio of patients with histological grade 2 and grade 3 were 41% and 47%, respectively. Presence of LVI was found as 50%. The number of patients with triple-negative cancer was 33 (18%). C-erb2 status was positive in 67 patients (36%). Surgical margins were reported as negative in 125 patients (68%). Patient and tumor characteristics are summarized in Table 1.

A total of 50% of the patients had chest wall (CW) RT, and 50% had lymphatic volume irradiation in addition to CW RT. There were 32 patients with micrometastases to axillary lymph nodes; 14 of them underwent axillary dissection (AD) after SLNB (44%),

Table 1 Patients and tumor characteristics

Characteristic	n (%)
Age	Median 48.5 (22 min-83 max)
Menopausal status	
Premenopausal	120 (65%)
Postmenopausal	65 (35%)
Tumor stage	
T1	28 (15%)
T2	84 (45 %)
T3	66 (36%)
T4	7 (4%)
Histology	
Invasive ductal	140 (76%)
Invasive lobular	15 (8%)
Other	30 (16%)
Lymphovascular space involvement	
Present	92 (50%)
Absent	70 (38%)
Unknown	23 (12%)
Grade (G)	
G1	9 (5%)
G2	76 (41%)
G3	87 (47%)
Unknown	13 (7%)
Ki 67	median 30%
<20%	48 (26%)
≥20%	61 (33%)
Unknown	76 (41%)
Estrogen receptor status	
Negative	72 (39%)
Positive	109 (59%)
Unknown	4 (2%)
HER2 status	
Negative	111 (60%)
Positive	67 (36%)
Not tested	7 (4%)
Triple negative	33 (18%)
Surgery	
Simple mastectomy	59 (32%)
MRM	106 (57%)
Skin sparing	11 (6%)
NAC sparing	9 (5%)
Nodal Status	
Negative	147 (79%)
Isolated	6 (3%)
Micrometastasis	32 (17%)
Surgical Margin	
Positive (ink+)	30 (16%)
<1 mm	24 (13%)
<2 mm	6 (3%)
>2 mm	125 (68%)

and only 3 patients without AD (8%) had CW RT without lymphatic RT. In Nmic patients, the rate of irradiation of level 1, 2, 3 axillary supraclavicular lymph nodes along with CW was considerably higher than the patients only with CW irradiation (72% and 28% respectively; $p=0.015$).

Six of seven patients (14%) with tumor stage of T4 received lymphatic irradiation in addition to CW ($p=0.07$). The small number of patients in this group limited further evaluation.

The patients who had undergone NSM significantly received CW RT than lymph volume RT in addition to CW only ($p=0.013$).

Discussion

There is still no consensus regarding the indication and the volume to be irradiated for PMRT of node-negative breast cancer patients. This study aimed to determine the everyday practices of radiation oncologists in Turkey. It was observed that the total number of cases reported from the centers was quite low, and most of the cases had more than one of the adverse factors such as premenopausal status, T2 and T3 stages, grade 3 for PMRT.

In certain guidelines, the existence of the tumor size >5 cm was given as the sole indication of PMRT. [9] However, it must be emphasized that tumors reaching these dimensions without lymph node involvement might have unusual biological properties. It has been shown that when these patients do not receive systemic and hormonal therapy after mastectomy, the risk of LR for them is approximately 15%. In the case of chemotherapy and/or hormonal therapy, this risk reduces to 7%–8%. Thus, CW irradiation is not recommended when the only indication is the tumor size being greater than 5 cm and other adverse factors are absent.[10] However, a recent meta-analysis of PMRT for T3N0 patients presented at American Society of Radiation Oncology 2017 shows that LR decreases with PMRT.[11] In this study, the ratio of T3 patients is 36%. Of these patients, 47% had grade 3 tumors. The remaining 53%, who had grade 1 and 2 histopathology, definitely had one or more accompanying adverse factors. T3 stages does not seem to be a sole indicator for PMRT among the practitioners in Turkey.

LVI is also associated with reduced locoregional control and survival in women with node-negative breast cancer treated with mastectomy and systemic therapy.[12] In this study, it was observed that half

of the patients had a positive LVI status that might have impact on the decision for PMRT. Ki-67 expression also has been shown as an independent factor for DFS and OS in patients with breast cancer.[13] In this study, patients with unknown Ki-67 consisted 41% of the population. In the remaining, percentage of patients with an increased proliferation index ($\geq 20\%$) was higher than the percentage of patients with ki-67 < 20% (33% vs. 26%, respectively). The percentage of patients with unknown ki-67 and LVI were quite high that might impacted statistical result (41% and 12%, respectively).

Triple-negative breast cancer accounts 15%–20% of all breast cancers.[14] Patients with T1-T2N0 TNBC treated with MRM without RT have worse outcome with significant increased risk of LRR.[15] In our study, the number of TN case was 33 (18%). This ratio is in agreement with other published ratios. This would suggest that tumor biology does not influence PMRT indications of axillary negative cancers.

Furthermore, PMRT indications are not clear for conserving mastectomies, such as SSM and NAC, which might leave residual breast tissue due to cosmetic concerns. Marta et al. conducted a survey study with 292 radiation oncologists. The participants prioritized post SSM and NAC RT criteria as involvement of lymph node, positive of surgical margin, large diameter of tumor, histologic grade 3, LVI, patient age (<40 years), multicentric tumor, and triple-negative receptor status. Additionally, PMRT is suggested for NAC cases where flap thicknesses exceeds 5 mm in the mentioned study as a clinical expert opinion⁸. In this study, the ratios of SSM and NAC were relatively low. The surgical margin was close to 1 mm or positive in 60% of these patients.

Randomized studies have shown that dissection does not have a positive impact in cases with isolated tumor cells or axillary micrometastasis after breast conserving surgery.[16,17] It has been suggested that the low regional recurrence rates in these trials might be due to the partially incidental irradiation of the axilla during whole breast radiotherapy. In the IBCSG 23-01 trial, 9% of the patients underwent mastectomy, and 19% had only intraoperative radiotherapy giving 28% who did not receive incidental axillary irradiation.[18] A prospective randomized study BOOG 2013-07 has evaluated the role of further treatment of axillary in patients with micrometastasis after mastectomy.[19] In the AMAROS trial, the percentage of the patients with micrometastasis or isolated tumor cell was 41%, and all of them received further axillary

treatment (either dissection or axillary radiotherapy).[20] Furthermore, in the AMAROS trial, patients received axillary radiotherapy including the contents of all three levels of the axilla and the medial part of the supraclavicular fossa. On the other hand, in a recent study, patients with early-stage tumors (T1-T2) who underwent mastectomy where Nmic involvement is present, CW recurrence rate was found as 2%–3%. [21] PMRT does not seem to be effective with so low recurrence rates.

The majority of the local recurrences after mastectomy are on the chest wall.[22] Therefore, CW is accepted as the essential volume for PMRT. Lymphatic volume selection is debatable, and there is no consensus for pN0 patients. Current study indicates that only tumor stage T4 and Nmic are significant factors for the selection of lymphatic volumes among radiation oncologists, and there is no consensus regarding the selection of lymph nodes as well.

This study is designed just for the indication of PMRT; therefore, locoregional control, disease-free survival, and OS rates were not obtained. The major shortcoming of the current analysis is the lack of information regarding the total number and the features of the N0 or Nmic cases pursuant mastectomy.

Conclusion

Considering the small number of cases reported for a 10-year period from the major breast centers of Turkey, it has been found that the number of patients with N0 or Nmic who underwent PMRT was not high. The indications depended on the presence of one or more adverse factors (such as premenopausal status, high tumor stage, grade, proliferation index, LVI and biology of the tumor) did not have a significant impact. Regarding PMRT indications of the patients with Nmic, it is difficult to reach a certain conclusion due to the lack of information for those who did not receive radiotherapy. On the other hand, it was observed that comprehensive lymphatic irradiation was preferred after SLNB in the presence of micrometastasis.

Implementation of effective systemic treatments and considerations of the results of recent meta-analysis showing that PMRT does not have any effect on LC and survival rates reduces the number of patients chosen for PMRT.

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