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Prognostic Impact of Adjuvant Radiotherapy in Breast Cancer Patients with One to Three Positive Axillary Lymph Nodes

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Abstract

Background: Radiotherapy, as an adjuvant treatment, plays a well-known role in prevention of locoregional recurrence in breast cancer patients. This study aims to investigate the impact of radiotherapy in patients with N1 disease.

Methods: In this retrospective study, we reviewed the characteristics and treatment outcomes of 316 patients with a biopsy proven diagnosis of breast carcinoma and 1-3 positive axillary lymph nodes. The patients received treatment between 1995 and 2014. The patients had a median follow-up of 60 (range: 6-182) months.

Results: This study was conducted on 316 patients with a median age of 48 (range: 26-86) years. Among patients, 215 underwent modified radical mastectomy and 101 had breast-conserving surgery before adjuvant treatment. Indeed, 259 patients received radiotherapy (radiation group) and 57 did not (control group). There was locoregional recurrence in one control group patient and two patients in the radiation group. Multivariate analysis results indicated hormone receptor status as an independent prognostic factor for the 5-year disease-free survival rate. Estrogen and progesterone receptor negativity (HR = 1.80, 95% CI: 1.02-3.19, P=0.043) also had a negative influence on the 5-year disease-free survival rate. However, radiotherapy had no significant effect on disease-free survival (P=0.446) and overall survival (P=0.058) rates.

Conclusion: The results showed that adjuvant radiotherapy had no prognostic impacts on locoregional and distant disease control in breast cancer patients with N1 disease.

Keywords: Breast cancer, Axillary, Positive lymph node, Adjuvant radiation, Treatment, Prognosis

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Introduction

Breast cancer is one of the most frequent and leading causes of cancer deaths worldwide.[1] Distant failure accounts for the vast majority of

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mortality causes in these patients. Therefore, adjuvant systemic therapy has become a mainstay of breast cancer treatment even in early stage one cancer. Despite substantial improvements in outcome of breast cancer using chemotherapy, locoregional control remains a major concern in these patients.[2] Locoregional recurrence is associated with increasing morbidity, mortality, and treatment cost in breast cancer patients.[3, 4]

The number of positive axillary lymph nodes is the main indicator of locoregional recurrence risk in these patients. Many clinical trials have revealed the role of adjuvant radiation in decreasing locoregional recurrences, especially in patients with poor risk factors, such as extra-nodal extension of the disease and the presence of four or more positive lymph nodes.[5, 6] Axillary lymph node dissection is the standard treatment of the axilla and may be substituted by axillary radiation with comparable regional control.[7] Although the role of radiation in patients with one to three positive lymph nodes is controversial, some investigators have recommended post-mastectomy radiotherapy in patients with intermediate and high lymph node ratios (the ratio of positive nodes to total dissected nodes).[8]

In the present retrospective study, we aimed to analyze and present our institute's data regarding the effectiveness of radiotherapy in breast cancer patients with one to three positive axillary lymph nodes.

Patients and Methods

This retrospective study aimed to review and analyze the characteristics, treatment outcomes, and survival of women with newly histologically proven stage T1-2 N1 invasive breast adenocarcinoma who underwent treatment and follow-up between 1995 and 2014. We excluded patients with other epithelial pathologies (squamous cell carcinoma) and non-epithelial tumors (lymphomas and sarcomas) from the analysis. The patients with inadequate axillary lymph node dissection and those who received neoadjuvant treatment were excluded.

We used the seventh edition of the American Joint Committee on Cancer TNM (AJCC) staging system for tumor staging. The preliminary evaluation included a comprehensive history and physical examination, bilateral mammography, chest radiography, echocardiography, complete blood cell (CBC) count, and liver and renal function studies. Selected symptomatic cases underwent further investigations that included whole body bone scintigraphy, CT scan of the chest, abdomen, and pelvis, and brain MRI to rule out metastatic disease. All patients underwent initial surgery as modified radical mastectomy (MRM; n=215) or breast conserving surgery (BCS; n=101). Adjuvant radiotherapy consisted of conventional external beam radiation with 6 MV megavoltage linear accelerator photons. The radiation portals consisted of the whole breast or chest wall (n=245), supraclavicular (n=209), and posterior axillary (n=170) fields. The patients received a total dose of 45-50.4 Gy with a daily fraction of 1.8-2 Gy, 5 fractions per week. Adjuvant chemotherapy consisted of a median of 8 (range: 6–8) cycles of one of the following regimens: 1. six cycles of docetaxel, doxorubicin, and cyclophosphamide (TAC regimen); 2. four cycles of doxorubicin and cyclophosphamide followed by four cycles of paclitaxel or docetaxel (AC → P regimen) every three weeks; 3. six cycles of 5-fluorouracil (5-FU), doxorubicin, and cyclophosphamide (FAC regimen); 4. six cycles of 5-FU, epirubicin, and cyclophosphamide (CEF regimen); or 5. six cycles of 5-FU, methotrexate, and cyclophosphamide (CMF regimen). Patients with estrogen receptor (ER) and/or progesterone receptor (PR) positive breast cancer received hormone therapy with tamoxifen or aromatase inhibitors, such as letrozole or exemestane, for 5 years.

Statistical analysis

Clinical and pathological variables were analyzed using the IBM SPSS statistical software, version 22. Categorical variables of tumor characteristics (tumor stage and hormone receptor status) and treatment modalities (type of surgery, radiotherapy, and chemotherapy) were compared using the chi-square test. The student's t-test was used for continuous variables, such as patients' age.

Local control rate was defined as the proportion of patients free of locoregional recurrent disease at 5 years. Disease-free survival (DFS) rate was defined

Table 1. Clinical and pathological characteristics of 316 patients with T1-2N1 breast cancer.

Variable	Adjuvant radiation		*P*-value
	Received	Not received	
Total	259	57	
Age, years (mean±SD)	47.3±9.9	57.4±11.8	<0.001
Type of surgery			<0.001
MRM	158	57	
BCS	101	0	
Tumor stage			0.008
T1	72	26	
T2	187	31	
Involved nodes			0.706
One	128	32	
Two	86	17	
Three	45	8	
Surgical margins			0.590
Free	254	57	
Involved	5	0	
ER or PR receptor			0.983
Positive	197	43	
Negative	60	13	
Unknown	2	1	
Her2 status			0.037
Positive	71	8	
Negative	186	48	
Unknown	2	1	
Chemotherapy regimens			<0.001
Taxane-based†	178	24	
Anthracyclin-based‡	69	27	
Other	12	6	

SD: Standard deviation; MRM: Modified radical mastectomy; BCS: Breast conserving surgery; ER: Estrogen receptor; PR: Progesterone receptor; †: Four cycles of doxorubicin + cyclophosphamide followed by 4 cycles of paclitaxel or docetaxel (AC → T regimen) or 6 cycles of docetaxel + doxorubicin + cyclophosphamide (TAC regimen); ‡: Six cycles of 5-Fluorouracil (5-FU) + doxorubicin + cyclophosphamide (FAC regimen) or six cycles of 5-FU, epirubicin and cyclophosphamide (CEF regimen).

as the percentage of patients who were free of breast cancer at 5 years. In addition, the overall survival rate was defined as the percentage of patients who were alive at 5 years. Survival durations were measured from the date of initial treatment until locoregional recurrence (locoregional control), any type of treatment relapse (DFS), death for any reason (overall survival), or the last follow-up. The significance of differences in survival rates was evaluated using the log-rank test. Kaplan-Meier was also used to estimate survival experience of different groups of prognostic factors. Multiple-covariate analysis was performed using the stepwise regression hazards regression model. Hazard ratio (HR) for death with 95% confidence interval (CI) was calculated for the variable groups. We used the log-rank test to compare treatment results in each variable group. All *P*-values were 2-tailed. Those less than 0.05 were considered to be statistically significant.

Results

Patients and tumor characteristics

We conducted this study on 316 patients, from which 259 (radiation group) received postoperative adjuvant radiation and 57 (control group) did not receive adjuvant radiation. The patients' median age was 48 (range: 26-86) years. Patients in the radiation group were significantly younger compared to the control group (median age: 46 vs. 57 years, *P*<0.001). T2 lesions were more frequent in the radiation group (72%) compared to the control

Table 2. Univariate analysis of prognostic factors for 5-year disease-free survival rate in 316 patients with T1-2N1 breast cancer.

Variable	5-year DFS rate (%)	*P*-value	HR	95% CI
Age (years)			1.07	0.62-1.83
<50	83.3			
≥50	82.5	0.798		
Tumor stage			1.21	0.67-2.20
T1	84.5			
T2	82.2	0.519		
Involved nodes			1.21	0.67-2.16
One	83.6			
Two	81.0			
Three	84.9	0.773		
Surgical margins			20.6	0.00-2087
Free	82.6			
Involved	100.0	0.332		
ER or PR receptor			1.85	1.04-3.27
Positive	86.5			
Negative	73.4	0.031		
Her2			1.43	0.79-2.58
Positive	78.9			
Negative	84.8	0.229		
ChT regimens			1.79	0.24-13.19
Taxane-based†	84.5			
Anthracyclin-based‡	76.5			
Other	75.0	0.221		
Adjuvant RT			1.33	0.63-2.83
Received	85.2			
Not received	81.7	0.446		

DFS: Disease-free survival; HR: Hazard ratio; CI: Confidence interval; ER: Estrogen receptor; PR: Progesterone receptor; RT: Radiation therapy; ChT: Chemotherapy; †: Four cycles of doxorubicin + cyclophosphamide followed by 4 cycles of paclitaxel or docetaxel (AC → T regimen), or 6 cycles of docetaxel + doxorubicin + cyclophosphamide (TAC regimen); ‡: Six cycles of 5-Fluorouracil (5-FU) + doxorubicin + cyclophosphamide (FAC regimen) or six cycles of 5-FU, epirubicin and cyclophosphamide (CEF regimen)

group (54%, *P*=0.008). The radiation group had a higher rate of Her-2 over-expression and use of more aggressive chemotherapy compared to the control group (Table 1).

Oncological outcomes

After a median follow-up of 60 (range: 6-182) months for the surviving patients, 270 patients were alive and free from the disease, 20 were alive with the disease, and 26 died due to the disease. Only three patients (two in the radiation and one in the control group) developed locoregional recurrence. Patients had a 5-year local control rate of 99.3%, DFS of 82.9%, and overall survival rate of 91.1%. The 10-year local control for patients was 98.3%, with a DFS of 77.6%, and overall survival rate of 87.5%.

Univariate analysis indicated that only hormone receptor status (log-rank test, *P*=0.003) was found to be a prognostic factor for the 5-year DFS. Table 2 shows the results of univariate analysis of prognostic factors for the 5-year DFS rate in 316 patients with T1-2 N1 breast cancer. Accordingly, adjuvant radiation had no prognostic impact on local control survival or DFS rates in these patients. Multivariate analysis showed that only hormone receptor status was an independent prognostic factor for the 5-year DFS rate. ER and PR negativity (HR = 1.80, 95% CI: 1.02-3.19, *P*=0.043) also had a negative effect on the 5-year DFS rate.

Patients had a 5-year overall survival rate of 91.4 and 10-year overall survival rate of 87.5. The results of univariate and multivariate analyses revealed no prognostic factors for the 5-year survival rate (Table 3). Consequently, adjuvant radiation had no prognostic impacts on oncological outcomes

Table 3. Univariate analysis of prognostic factors for 5-year overall survival rate in 316 patients with T1-2N1 breast cancer.

Variable	5-year overall survival rate (%)	*P*-value	HR	95% CI
Age (years)			1.62	0.71-3.70
<50	89.1			
≥50	90.5	0.242		
Tumor stage			1.98	0.74-5.25
T1	94.7			
T2	89.8	0.162		
Involved nodes			1.36	0.38-4.77
One	91.3			
Two	83.4			
Three	94.0	0.745		
ER or PR receptor			2.03	0.89-4.61
Positive	92.6			
Negative	83.2	0.081		
Her2			1.81	0.80-4.15
Positive	87.5			
Negative	93.1	0.146		
ChT regimens			1.1	0.53-2.62
Taxane-based†	91.6			
Anthracyclin-based‡	88.9			
Other	100.0	0.557		
Adjuvant RT			4.60	0.85-24.78
Received	90.1			
Not received	96.4	0.058		

HR: Hazard ratio; ER: Estrogen receptor; PR: Progesterone receptor; RT: Radiation therapy; ChT: Chemotherapyے †: Four cycles of doxorubicin + cyclophosphamide followed by 4 cycles of paclitaxel or docetaxel (AC → T regimen) or 6 cycles of docetaxel + doxorubicin + cyclophosphamide (TAC regimen); ‡: Six cycles of 5-fluorouracil (5-FU) + doxorubicin + cyclophosphamide (FAC regimen); or six cycles of 5-FU, epirubicin and cyclophosphamide (CEF regimen)

in patients with T1-2 N1 breast cancer.

Discussion

Breast cancer recurrence results in substantial increase in treatment costs[9] and negatively affects cancer-specific domains of quality of life.[10] During recent decades, many efforts have been made to identify the risk factors for developing recurrence and locate appropriate preventive treatments. Previous studies disclosed that high-risk breast cancer patients for locoregional recurrence included those with involved resected margins, more than three positive axillary nodes, and negative ER and PR receptors should receive adjuvant locoregional radiation therapy.[11] Numerous researchers have investigated the role of post-mastectomy adjuvant radiotherapy in patients with one to three involved axillary lymph nodes. A study on 207 post-mastectomy women with T1-2 N1 disease revealed that radiotherapy decreased locoregional recurrence and increased overall survival only in patients with lymphovascular invasion.[12] In another retrospective study on 767 breast cancer patients with N1 disease, the number of positive axillary nodes, negative hormone receptor, extracapsular extension, higher nuclear grade, and lymphovascular invasion had prognostic impacts on supraclavicular fossa recurrence.[13]

According to a number of recent studies, lymph node ratio might be a more predictive factor compared to absolute positive nodes in breast cancer patients.[14-19] Duraker et al. conducted a retrospective study on 575 patients and revealed that post-mastectomy radiotherapy reduced locoregional recurrence in T1N1 patients with a lymph node ratio more than 0.25 and in T2N1 patients with a lymph node ratio more than 0.08.[20]

Wen et al. evaluated the value of molecular subtyping of tumors in patients with N1 breast cancer for prediction of locoregional relapse. The results of multivariate analysis indicated that enriched and basal-like subtypes of HER-2, age ≤35 years, pathological T2 tumors, and medial

tumors were prognostic factors for locoregional relapse. Thus, they concluded that patients with three or more risk factors needed post-mastectomy adjuvant radiotherapy.[21]

Several precise meta-analyses by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) attempted to end the debate regarding the role of post-mastectomy adjuvant radiotherapy in this subgroup of patients. The results of these meta-analyses showed the benefit of post-mastectomy adjuvant radiotherapy in reduction of locoregional recurrence and mortality rates in all patients with positive axillary nodes, regardless of the type of axillary management, use of adjuvant systemic therapy, and numbers of positive lymph nodes.[22-24]

Due to some concerns regarding late toxicity of radiotherapy on cardiopulmonary systems in older trials, a number of authors suggested sparing patients considered at low risk for recurrence.[25,26] However, recent trials reported that the use of modern radiotherapy techniques, such as 3-dimensional conformal radiotherapy (3DCRT) and intensity modulated radiotherapy (IMRT), had an association with a significant reduction in cardiopulmonary adverse effects.[27,28]

The findings of the present study showed that adjuvant radiation had no prognostic impacts on oncological outcomes in patients with T1-2 N1 breast cancer. In addition, the results of multivariate analysis only revealed hormone receptor status as an independent prognostic factor for the 5-year DFS rate.

Our study had some limitations that included differences between the radiation and control groups regarding age, number of T2 lesions, and HER-2 status. Regardless of the differences that might have a prognostic impact on tumor control, both groups had similar oncological outcomes.

Conclusion

The results of the current study indicated that adjuvant radiotherapy had no significant prognostic impacts on breast cancer patients with one to three involved lymph nodes. This might be due to differences between the radiation and control groups regarding baseline characteristics. This study also showed that low-risk patients (older women with smaller tumors, particularly, those with positive hormone receptors and negative Her2) could be spared from post-mastectomy adjuvant radiotherapy and have an identical oncological outcome compared to high-risk patients.

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Conflict of Interest

No conflict of interest is declared.

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