Lack of Prognostic Impact of Adjuvant Radiation on Oncologic Outcomes in Elderly Women with Breast Cancer

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Abstract

Background: Radiotherapy plays an important role as adjuvant treatment in locally advanced breast cancer and in those patients who have undergone breast-conserving surgery. This study aimed to investigate the prognostic impact of adjuvant radiation on oncologic outcomes in elderly women with breast cancer. Materials and Methods: In this retrospective study, we reviewed and analyzed the characteristics, treatment outcome and survival of elderly women (aged ≥ 60 years) with breast cancer who were treated and followed-up between 1993 and 2014. The median follow up for the surviving patients was 38 (range 3-207) months. Results: One hundred and seventy-eight patients with a median age of 74 (range 60-95) years were enrolled in the study. Of the total, 60 patients received postoperative adjuvant radiation (radiation group) and the remaining 118 did not (control group). Patients in the radiation group were significantly younger than those in the control group (P value=0.004). In addition, patients in radiation group had higher node stage (P value<0.001) and disease stage (P=0.003) and tended to have higher tumor grade (P=0.031) and received more frequent (P value <0.001) adjuvant and neoadjuvant chemotherapy compared to those in the control group. There was no statistically significant difference between two groups regarding the local control, disease-free survival and overall survival rates. Conclusions: In this study, we did not find a prognostic impact for adjuvant radiation on oncologic outcomes in elderly women with breast cancer.

Keywords: Elderly women - breast cancer - adjuvant radiation - prognosis - survival

Introduction

Radiotherapy has a well established role as adjuvant treatment in locally advanced breast cancer and in those patients who have undergone breast conserving surgery (Guire et al., 2007; Tinterri et al., 2009; Phua et al., 2010; Yavas et al., 2013). However, this is a time consuming treatment, has a high cost and can be associated with painful side effects in the majority of patients. Additionally, Breast radiotherapy can expose heart to ionizing radiation which increases the rate of coronary heart diseases (Darby et al., 2013; Guan et al., 2015).

Breast cancer in elderly postmenopausal women tend to be less biologically aggressive and to have favorable outcome compared to younger patients. Patients younger than 40 years have higher rates of local recurrence than older patients (Zhou and Recht, 2004; Oran et al., 2014). Because of other associated diseases, older patients with breast cancer are less likely to receive standard treatments and radiotherapy may be omitted in this age group and even results in a better quality of life (Yancik et al., 2001; Tinterri et al., 2009; Wang et al., 2009; Vrana et al., 2014; Palta et al., 2015). Radiotherapy is also less likely to be used in old patients with estrogen receptor positive breast cancer (Rutter et al., 2015). To evaluate the role of radiotherapy in old patients, we compare the results of treatment between patients who received postoperative radiotherapy with those who underwent surgery alone.

Materials and Methods

In this study, we retrospectively reviewed and analyzed the characteristics, treatment outcome and survival of elderly women aged ≥60 years with newly histologically proven invasive breast adenocarcinoma that were treated and followed-up between 1993 and 2014. Patients with other epithelial pathologies such as squamous cell carcinoma, or non-epithelial tumors such as lymphomas and sarcomas were excluded. Tumor staging was performed using the seventh edition of American Joint Committee on Cancer TNM (AJCC) staging system. Clinical staging was carried out using imaging studies for

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all the patients before starting neoadjuvant treatments. Preliminary evaluation included comprehensive history and physical examination, bilateral mammography, chest radiography, echocardiography, complete blood cell count (CBC), and liver and renal function studies. Further investigation including whole body bone scintigraphy, CT scan of the chest, abdomen, and pelvis and brain MRI was performed in patients with stage III-IV and selected symptomatic cases. All patients but 4 underwent modified radical mastectomy (n=115) or conserving breast surgery (n=59). Adjuvant radiotherapy consisted of conventional external beam radiation using 6 MV megavoltage linear accelerator photons. The radiation portals were composed of the breast or chest wall fields in all patients and supraclavicular and posterior axillary fields in node positive cases. The patients received a total dose of 45-50.4 Gy with a daily fraction of 1.8-2 Gy, with five fractions per week. Adjuvant or neoadjuvant chemotherapy consisted of a median 6 (range 4-8) cycles of one of the following regimens: 1- 5-Fluorouracil (5-FU), methotrexate and cyclophosphamide (CMF regimen), 2- 5-FU, doxorubicin and cyclophosphamide (CAF regimen), 3- 5-FU, epirubicin and cyclophosphamide (CEF regimen), 4- doxorubicin and cyclophosphamide followed by paclitaxel (AC → P regimen) every three weeks. Patients with estrogen receptor (ER) and/or progesterone receptor (PR) positive breast cancer received hormone therapy with tamoxifen or letrozole for 5 years.

Results

Patients and tumor characteristics

One hundred and seventy-eight patients were enrolled in the study. Sixty patients (radiation group) received postoperative adjuvant radiation and remaining 118 patients (control group) not received adjuvant radiation. The median age of all patients was 74 years (range 60-95 years). Patients in radiation group were significantly younger than those in the control group (P value=0.004). The distribution of tumor stage was as follows: stage I-II 50 cases (83%) and stage III-IV 10 cases (17%) in radiation group; and stage I-II 104 cases (88%) and stage III-IV 14 cases (12%) in control group. We found a statistically significant difference regarding the node stage (P value<0.001) and disease stage (P=0.003) distribution between radiation and control groups. Patients in radiation group had more advanced node stage and disease stage compared to those in the control group. Additionally, patients in radiation group tended to have higher rate of grade II-III (P=0.031) and the use of neoadjuvant chemotherapy (P value <0.001) compared to those in the control group. The numbers of total dissected lymph nodes were similar between treatment groups. As well, there was a no statistically significant difference regarding the status of estrogen and progesterone hormone receptors and Her2 overexpression between radiation and control groups (Table 1).

Oncologic outcomes

After a median follow up of 38 (range 3-207) months for the surviving patients, the 5-year local control (LC), disease free survival (DFS) and overall survival (OS) rates were 82.6%, 67.7%, and 69.4%, respectively. The 10-year local control (LC), disease free survival (DFS) and overall survival (OS) rates were 74.6%, 32.8%, and 69.4%, respectively. On univariate analysis, node stage (log rank test, P<0.001), and stage of disease (log rank test, P=0.003) were found to be prognostic factors for LC, and DFS. Table 2 represents the univariate analysis of prognostic factors.

Figure 1. Kaplan-Meier Survival Analysis of Local Control Categorized According to the use of Adjuvant Radiation in 178 Elderly Patients with Stage I-II Breast Cancer
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Factors for 10-year local control rate in the 178 patients with breast cancer. Additionally, we found the same results using the stratified Log-Rank test of prognostic factors for 10-year local control rate (Table 3). Accordingly, we found a non-significant better local control rate in stage I-II compared to stage III-IV (79.2% vs. 73%, p=0.002).

Table 1. Clinical and pathological characteristics

| Variable                  | Adjuvant radiation Received | Adjuvant radiation Not received | P Value |
|---------------------------|-------------------------------|---------------------------------|---------|
| Total                      | 60                            | 118                             | 0.004   |
| Age (mean± SD)            | 72.5 ± 4.5 75.3 ± 6.5         | 0.737                           |
| Type of surgery           |                               |                                 |         |
| MRM                       | 41                            | 74                              |         |
| BCS                       | 19                            | 40                              |         |
| Tumor stage               |                               |                                 |         |
| T1-2                      | 50                            | 104                             | 0.486   |
| T3-4                      | 10                            | 14                              |         |
| Node stage                |                               |                                 | <0.001  |
| N0-1                      | 33                            | 98                              |         |
| N2-3                      | 27                            | 20                              |         |
| Dissected L.N (mean± SD)  | 15.6 ± 9.6 12.8 ± 9.5         | 0.082                           |
| Involved node (mean± SD)  | 4.9 ± 6.2 3.0 ± 6.8           | 0.104                           |
| Disease stage             |                               |                                 | 0.003   |
| I-II                      | 30                            | 86                              |         |
| III-IV                    | 30                            | 32                              |         |
| Tumor grade               |                               |                                 | 0.031   |
| I                         | 11                            | 43                              |         |
| II                        | 41                            | 58                              |         |
| III                       | 8                             | 17                              |         |
| Estrogen receptor         |                               |                                 | 0.372   |
| Positive                  | 41                            | 89                              |         |
| Negative                  | 19                            | 29                              |         |
| Progesterone receptor     |                               |                                 | 0.516   |
| Positive                  | 34                            | 74                              |         |
| Negative                  | 26                            | 44                              |         |
| Her2                      |                               |                                 | 0.553   |
| Positive                  | 10                            | 25                              |         |
| Negative                  | 44                            | 75                              |         |
| Unknown                   | 6                             | 18                              |         |
| Neoadjuvant ChT Received  | 15                            | 5                               | <0.001  |
| Not received              | 45                            | 113                             |         |

Table 2. Univariate analysis of prognostic factors for 10-year local control rate in the 178 patients with breast cancer

| Variable                  | 10-year local control rate (%) | P valuea | HR    | 95% CI |
|---------------------------|---------------------------------|----------|-------|--------|
| Age                       |                                 |          |       |        |
| ≤ 73 years                | 79.8                            | 0.42     | 1.38  | 0.63-3.02 |
| > 73 years                | 67.6                            |          |       |        |
| Tumor stage               |                                 |          |       |        |
| T1-2                      | 79                             | 0.163    | 1.92  | 0.76-4.81 |
| T3-4                      | 51.2                            |          |       |        |
| Node stage                |                                 |          |       |        |
| N0-1                      | 81.3                            | 0.001    | 4     | 1.81-8.86 |
| N2-3                      | 52.7                            |          |       |        |
| Dissected L.N ≤ 14        | 74.8                            | 0.594    | 1.27  | 0.52-3.07 |
| > 14                      | 82.9                            |          |       |        |
| Involved node ≤ 3         | 81.1                            | 0.638    | 1.26  | 0.47-3.37 |
| > 3                       | 73                              |          |       |        |
| Disease stage             |                                 |          |       |        |
| I-II                      | 82.4                            | 0.002    | 3.34  | 1.49-7.46 |
| III-IV                    | 58.4                            |          |       |        |
| Tumor grade               |                                 |          |       |        |
| I                         | 79.2                            | 0.222    | 1.75  | 0.70-4.38 |
| II-III                    | 72.7                            |          |       |        |
| Estrogen receptor         |                                 |          |       |        |
| Positive                  | 71.8                            | 0.772    | 1.14  | 0.47-2.75 |
| Negative                  | 80.4                            |          |       |        |
| Progesterone receptor     |                                 |          |       |        |
| Positive                  | 78                              | 0.439    | 1.35  | 0.62-2.95 |
| Negative                  | 69.2                            |          |       |        |
| Her2                      |                                 |          |       |        |
| Positive                  | 55.7                            | 0.489    | 1.93  | 0.48-7.64 |
| Negative                  | 69.3                            |          |       |        |
| Unknown                   | 86.7                            |          |       |        |
| Neoadjuvant ChT Received  | 85.5                            | 0.717    | 1.3   | 0.30-5.59 |
| Not received              | 74.3                            |          |       |        |
| Adjuvant RT               |                                 |          |       |        |
| Received                  | 74.5                            | 0.453    | 1.35  | 0.61-3.01 |
| Not received              | 75.7                            |          |       |        |
| Overall                   | 74.6                            |          |       |        |

Figure 2. Kaplan-Meier Survival Analysis of Local Control Categorized According to the use of Adjuvant Radiation in 178 Elderly Patients with Stage III-IV Breast Cancer

Figure 3. Kaplan-Meier Survival Analysis of Overall Survival Categorized According to the use of Adjuvant Radiation in 178 Elderly Patients with Breast Cancer
I-II in control group compared to radiation group (Figure 1); and a non significant better local control rate in stage III-IV in radiation group compared to control group (Figure 2). Regarding overall survival, tumor stage (log rank test, P=0.016), node stage (log rank test, P=0.001), and stage of disease (log rank test, P=0.013) were found to be prognostic factors for overall survival. However, adjuvant radiation did not have a significant impact on overall survival (Figure 3).

On multivariate analysis, only node stage was found to be independent prognostic factors for LC rate. Higher node (N2-3) stage [HR= 4.36, 95% CI=1.75-10.86, P=0.002] had a negative influence on LC rate. Regarding DFS, Her2 positivity (HR= 5.10, 95% CI=1.67-16.10, P=0.005), and higher node (N2-3) stage [HR= 3.55, 95% CI=1.75-10.86, P<0.001] had a negative influence on DFS. Additionally, higher node (N2-3) stage [HR= 3.69, 95% CI=1.67-8.14, P=0.001] was found to be an independent prognostic factors for OS. Accordingly, we did not find a prognostic impact for adjuvant radiation on oncologic outcomes in elderly patients with breast cancer.

### Table 3. Stratified Log-Rank test of prognostic factors for 10-year local control rate in the 178 patients with breast cancer

| Variable                  | With adjuvant RT | Without adjuvant RT | P valuea | HR  | 95% CI       |
|---------------------------|------------------|---------------------|----------|-----|--------------|
| Age                       |                  |                     |          |     |              |
| ≤ 73 years                | 81.8             | 79                  | 0.453    | 1.36| 0.60-3.10    |
| > 73 years                | 66               | 71.6                |          |     |              |
| Tumor stage               |                  |                     |          |     |              |
| T1-2                      | 78.2             | 79.4                | 0.37     | 1.56| 0.58-4.21    |
| T3-4                      | 56.3             | 50                  |          |     |              |
| Node stage                |                  |                     |          |     |              |
| N0-1                      | 78.3             | 82.3                | 0.001    | 4   | 1.67-9.59    |
| N2-3                      | 67.9             | 41.8                |          |     |              |
| Dissected L.N             |                  |                     |          |     |              |
| ≤ 14                      | 84               | 70                  | 0.44     | 1.43| 0.57-3.60    |
| > 14                      | 46.4             | 94.6                |          |     |              |
| Involved node             |                  |                     |          |     |              |
| ≤ 3                       | 78.4             | 82.4                | 0.006    | 3.07| 1.33-7.07    |
| > 3                       | 40               | 79.7                |          |     |              |
| Disease stage             |                  |                     |          |     |              |
| I-II                      | 77.4             | 84.3                | 0.019    | 1.94| 0.70-5.30    |
| III-IV                    | 69.3             | 54.4                |          |     |              |
| Tumor grade               |                  |                     |          |     |              |
| I                         | 83.3             | 79.9                | 0.057    | 1.3  | 0.51-5.31    |
| II-III                    | 74.8             | 72.6                |          |     |              |
| Estrogen receptor         |                  |                     |          |     |              |
| Positive                  | 65.2             | 75.6                | 0.204    | 1.67| 0.74-3.76    |
| Negative                  | 94.7             | 74.3                |          |     |              |
| Progesterone receptor     |                  |                     |          |     |              |
| Positive                  | 78               | 79.4                | 0.619    | 1.81| 0.51-6.41    |
| Negative                  | 71               | 69.6                |          |     |              |
| Her2                      |                  |                     |          |     |              |
| Positive                  | 64.3             | 60                  | 0.036    | 1.82| 0.39-8.40    |
| Negative                  | 79.7             | 68.1                |          |     |              |
| Unknown                   | 66.7             | 93.8                |          |     |              |

**Discussion**

Some studies confirmed that adjuvant systemic therapy including chemotherapy and/or hormone therapy significantly reduces locoregional recurrence rate in patients treated with breast-conserving surgery compared to those treated with conservative surgery alone; however, it is unclear whether this treatment strategy can replace the need for radiotherapy following conservative surgery alone (Fisher et al., 1996a; Fisher et al., 1996b; Dalberg et al., 1998). In NSABP trial B-13, adjuvant chemotherapy significantly reduced the eight-year local recurrence from 13.4% to 2.6% in women with node-negative, estrogen receptor negative invasive tumors compared to local treatment alone (Fisher et al., 1996b). In NSABP trial B-14, adjuvant hormone therapy using tamoxifen in women with node-negative, ER-positive tumors significantly reduced the rate of 10-year local recurrence from 14.7% to 4.3% compared to placebo arm (Fisher et al., 1996a). In addition, similar findings were observed in the Stockholm Breast Cancer Study Group. The ten-year local recurrence rate was significantly less
(3 versus 12 percent) in tamoxifen arm compared to placebo arm in women with node-negative breast cancer following conservative surgery (Dalberg et al., 1998). In another study in the German Breast Cancer Study Group (GBSG)-V trial, early stage low-risk breast cancer patients undergoing breast conserving surgery were randomly assigned to RT or not, and to tamoxifen or not. This study showed a benefit for both RT and tamoxifen in reducing local recurrence rates compared to conserving surgery alone; however, there was no significant difference between RT and tamoxifen in terms of local recurrence rate (5.3% for RT versus 7.5% for tamoxifen) (Winzer et al., 2010).

The omission of RT is particularly interesting subject in elderly women. Several randomized trials investigated the prognostic impact of adjuvant RT on oncologic outcome in elderly women with breast cancer following breast-conserving surgery. Overall, the findings of these studies support that in selected low risk elderly women (over the age of 70), treatment with adjuvant endocrine therapy alone provides a reasonable outcome (Fisher et al., 2002; Fyles et al., 2004; Poter et al., 2007)

Richard Poter et al. reported on 869 women with mean age of 66 years with favorable early stage breast cancer who randomly assigned to receive or not receive post-lumpectomy radiotherapy between 1996 and 2004. They found that breast radiotherapy plus tamoxifen or anastrozole results in significant reduction in local and overall recurrence. In that study all patients had estrogen or progesterone receptor positive tumors with 3 cm or less diameter (Poter et al., 2007).

Hughes et al reported on 636 patients (70 years of age or older) with stage one estrogen receptor positive breast cancer who received or not received post-lumpectomy radiotherapy plus tamoxifen. Although there was a significant difference between two groups regarding locoregional recurrence, the rates of mastectomy, distant metastases and overall survival were comparable in two groups (Hughes et al., 2004).

Vrana et al. suggested that omission of radiotherapy in a selected group of patients 70 years of age or older with breast cancer may be safe and results in a better quality of life (Vrana et al., 2014).

Cancer and Leukemia Group B 9343 study revealed a statistically significant better locoregional control with tamoxifen plus radiotherapy versus tamoxifen alone after lumpectomy in women with early stage breast cancer and ≥ 70 years of age. No clear benefit was found for addition of radiotherapy in that study regarding distant disease free and overall survival. Moreover, only 3% of patients died as a result of their cancer. The authors concluded that radiotherapy may be omitted after lumpectomy in old women (≥ 70 years) with stage one hormone receptor positive breast cancer (Hughes et al., 2013).

Our study showed no benefit for the addition of radiotherapy after surgery in old patients with breast cancer. Although in subgroup analysis those patients with higher stage of disease had a statistically non-significant better local control with radiotherapy, patients with early stage disease had no benefit with adjuvant radiotherapy. Despite the limitations of our study including the small number of patients and the heterogeneity in cases in terms of patients’ mean age, tumor stage, and ER and PR status, the findings of this study is consistent with previous large studies.

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