

Postoperative Radiotherapy in the Treatment of Male Breast Carcinoma: A Single Institute Experience

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Background: To evaluate the outcomes of radiation therapy treatment of male patients with breast cancer in our single institutional cohort and discover possible adverse prognostic factors.

Methods: We retrospectively evaluated 42 male patients (median age 55; range 33–77 years) with breast cancer. Patients were irradiated postoperatively in 2 Gy/fraction/day to chest wall ± lymphatics.

Results: Median follow-up was 29 months. Eleven patients had neoadjuvant and 36 patients had adjuvant Adriamycin®-based chemotherapy. Nine patients (21%) had local or regional, two (5%) had distant, and one (2.5%) had both local and distant disease at the time of analysis. The actuarial five-year Overall Survival (OS) was 77%, whereas the actuarial five-year Disease-Free (DFS), Locoregional Recurrence-free (LRRFS), and Distant Metastases-Free (DMFS) survival rates were 45%, 69% and 66%, respectively. Univariate analysis of variables, including patient characteristics, treatment modalities and factors, and tumor characteristics, failed to show an association with LRRFS and DFS except percent positive nodal involvement ≥30% and 50%.

Conclusion: Though radiotherapy seems quite effective in reducing local recurrence, we have revealed that male breast cancer patients in our cohort with extensive nodal involvement (PPNI >30% and 50%) appeared not to have had a significant benefit from postmastectomy irradiation and adjuvant CMF-based chemotherapy.

Key words: breast cancer ■ men's health ■ radiotherapy

INTRODUCTION

Male breast cancer (MBC) is a rare disease with no randomized trials. MBC accounts for approximately 1% of all breast cancers.^{1,2} Treatment recommendations have been extrapolated from results of retrospective and prospective trials and experience in female patients. However the incidence of male breast cancer is rising,³ and as a result there is increasing interest in this disease. Here, we would like to share our single center clinical experience of male breast cancer patients treated with postoperative radiotherapy.

MATERIALS AND METHODS

Patients

A search of the database maintained by the Department of Radiation Oncology in Hacettepe University Oncology Institute was performed to identify male patients with invasive breast carcinoma treated with postoperative radiotherapy between July 1994 and August 2001. Patients had pathologic confirmation of their diagnoses performed at our center. This search identified 42 patients with stage-I–IIIC invasive ductal carcinoma of the breast.

Staging and Treatment

Patients were retrospectively staged according to the American Joint Committee for Cancer Staging System (AJCC) 2002 tumor-node-metastasis (TNM) staging system.⁴ All patients were irradiated postoperatively in 2 Gy/fraction/day to chest wall ± lymphatics to a total median dose of 50 Gy (range, 46–60 Gy). Prescription of chemotherapy varied as neoadjuvant or adjuvant due to initial tumor burden and referral centers. In general, adjuvant chemotherapy (mainly CMF) was offered to those patients with breast tumors measuring >1 cm and to those patients with lymph node involvement. Neoadjuvant chemotherapy was mainly offered to T3 and T4 tumors.

Late Effects

The Radiation Therapy Oncology Group (RTOG)

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“late radiation morbidity scoring schema” was used in our review to grade severe complications.

Statistical Analysis

Actuarial survival time (overall survival: OS, disease-free survival: DFS, locoregional relapse-free survival: LRRFS, distant metastasis-free survival: DMFS) was calculated from the date of initiation of radiotherapy. Actuarial survival analyses were performed using the Kaplan-Meier method.⁵ A Chi-squared test was used to assess differences in patient distribution between groups.

Prognostic factor analysis was performed with stratification of patients receiving neoadjuvant chemotherapy or not. Prognostic factors evaluated in this retrospective analysis were tumor size (≤ 5 cm vs. > 5 cm), metastatic nodal involvement (LN- vs. LN+), number of metastatic nodal involvement (0 vs. 1–3 vs. > 4 LN), percent positive nodal involvement (PPNI: metastatic nodes \times 100/total nodes; 0% vs. $\leq 25\%$ vs. 26–50% vs. $> 50\%$), PPNI-30 (0– $\leq 30\%$ vs. $> 30\%$), PPNI-50 (0– $\leq 50\%$ vs. $> 50\%$), AJCC 2002 staging (stage I–II vs. III), type of surgery (biopsy, excision, mastectomy), surgical margin status (negative versus positive), neoadjuvant chemotherapy (present versus absent), adjuvant chemotherapy (present versus absent), and grade (grade I vs. grade II vs. grade III/IV) were analyzed using the univariate log-rank method and the multivariate Cox regression analysis.⁶ A p value < 0.05 was considered statistically significant.

RESULTS

Patients

Forty-two patients formed the study cohort. The median and mean ages were 55 and 54 years, respectively (range 33–77 years). None of the patients had previously noted testicular abnormalities or exposure to chest wall radiotherapy.

The median follow-up after radiotherapy was 29 months (range 4.5–118 months). All the surviving patients had completed treatment at least 48 months prior to the analysis, and two surviving patients were lost to follow-up during the first two years.

The presenting symptoms were painless subareolar lump (37 patients), nipple retraction (four patients) and bleeding from the nipple (one patient). Disease was left-sided in 27 patients (64.3%), right-sided in 14 patients (33.3%) and bilateral in one patient (2.4%). The surgical treatment consisted of radical mastectomy in 10, modified radical mastectomy in 29, simple mastectomy without axillary node dissection in one and lumpectomy in two patients. TNM staging was recorded as stage I, one (2.4%); stage IIA, 11 (25.9%); stage IIB, eight

(18.9%); stage IIIA, six (14.3%); stage IIIB, seven (16.7%); and stage IIIC, nine (21.4%). Patients were categorized as T3 and T4 in, respectively, 29% and 10.5% of the cases. Median number of axillary dissected lymph nodes was 18, and 16 patients had no nodal metastasis (N0, 38%). Node positive (N+) status was as follows: 1–3 N+: 8 (19%) and > 3 N+: 18 (43%). Percent positive nodal involvement was $< 26\%$ in 8, 26–50% in 7 and $> 50\%$ in 11 patients.

Examination of the hormone receptors was documented positive in 19 patients (estrogen receptor alone, ER: 14; estrogen and progesterone receptor, ER+PR: 5).

Eleven patients had neoadjuvant and 36 patients had adjuvant chemotherapy.

Pathological analysis of the specimens revealed infiltrating ductal carcinoma in 37 patients (88%), infiltrating lobular carcinoma in one (2.4%), infiltrating lobular and ductal carcinoma in three (7.1%) and medullary carcinoma in one (2.4%) cases. Grading according to the Scarff–Bloom–Richardson system was as follows: grade I: 26 (62%); grade II: nine (21.5%); grade III: five (12%); unknown: two (5%) patients.

Locoregional Relapse-Free Survival

Local control. The two- and five-year actuarial local control rates were 81.1% and 77.4%, respectively. Six of the total eight local recurrences occurred within two years after the end of radiotherapy. The two- and five-year actuarial regional control rates were 91% and 85.3%, respectively. Three of the total five regional recurrences occurred within two years after the end of radiotherapy.

The two- and five-year actuarial locoregional control rates were 73.6% and 65.4%, respectively. Univariate analysis of variables, including patient characteristics, treatment modalities and factors, and tumor characteristics, failed to show an association with LRRFS, except PPNI-30 and PPNI-50, in patients without neoadjuvant chemotherapy. The crude failure rate was 4/21 patients for PPNI $\leq 30\%$ and 5/10 patients for PPNI $> 30\%$. The two- and five-year actuarial control rates were 94.4% and 87.7%, respectively, for patients PPNI $\leq 30\%$ and 36.0% and 18% for patients PPNI $> 30\%$ ($p=0.0088$). Cox regression multivariate analysis revealed no significant prognostic factor for LRRFS.

Distant Metastasis-Free Survival

The two- and five-year actuarial DMFS rates were 72.2% and 63.2%, respectively. Nine of the total 12 distant metastasis occurred within two years after the end of radiotherapy. Univariate analysis failed to show an association with DMFS except tumor size (≤ 5 cm vs. > 5 cm) in patients without

neoadjuvant chemotherapy. The crude failure rate was 4/18 patients for tumors ≤ 5 cm and 4/10 patients for tumors > 5 cm. The two- and five-year actuarial control rates were 87.2% and 78.5% for tumors ≤ 5 cm and 44.4% and 22.2% for tumors > 5 cm ($p=0.0178$). Cox regression multivariate analysis revealed no significant prognostic factor for DMFS.

Disease-Free Survival

The two- and five-year actuarial DFS rates were 56% and 42.1%, respectively. Sixteen of the total 23 events occurred within two years after the end of radiotherapy. Univariate analysis failed to show an association with DFS except tumor size (≤ 5 cm vs. > 5 cm), PPNI-30 and PPNI-50 in patients without neoadjuvant chemotherapy. The crude failure rate was 8/18 patients for tumors ≤ 5 cm and 5/10 patients for tumors > 5 cm. The two- and five-year actuarial control rates were 81.0% and 64.8% for tumors ≤ 5 cm and 39.5% and 19.8% for tumors > 5 cm ($p=0.0298$). The crude failure rate was 8/21 patients for PPNI $\leq 30\%$ and 8/10 patients for PPNI $> 30\%$. The two- and five-year actuarial control rates were 81.9% and 60.0% for patients PPNI $\leq 30\%$ and 26.3% and 13.1% for patients PPNI $> 30\%$ ($p=0.0115$). The crude failure rate was 9/22 patients for PPNI $\leq 50\%$ and 8/9 patients for PPNI $> 50\%$. The two- and five-year actuarial control rates were 81.9% and 60.0% for patients PPNI $\leq 50\%$ and 25.9% and 13.0% for patients PPNI $> 50\%$ ($p=0.0106$). Cox regression multivariate analysis revealed no significant prognostic factor for DFS.

Overall Survival

The two- and five-year actuarial OS rates were 86% and 77.4%. Five of the total 12 events occurred within two years after the end of radiotherapy. Only one patient died without disease, but two (5%) with local, six (14%) with distant and three (5%) with local + distant disease. Univariate analysis failed to show an association with OS. Cox regression multivariate analysis revealed no significant prognostic factor for DFS.

Second Primary Tumors

Two patients in this cohort developed second primary breast cancer in the contra lateral breast.

Late Effects

No grade-3 and -4 late morbidities were noted.

DISCUSSION

Recent reports from large prospective trials in female breast cancer patients showed superior locoregional control, disease-free survival and overall survival with the use of radiotherapy after mas-

tectomy and chemotherapy.⁷⁻⁹ It is therefore imperative to identify those patients at significant risk of recurrence who are most likely to realize the benefit of adjuvant irradiation. Since male breast cancer is a rare disease and no randomized trials have been possible for the management and prognostic factors of localized disease, we evaluated our limited number of patients to perceive any possible clues for patient selection criteria. Here, we demonstrate poor locoregional failure-free survival and disease-free survival in patients with PPNI $> 30\%$.

Although breast cancer in male patients has been reported ranging in age from 5–93 years,¹⁰ mean age at diagnosis is 67 years, five years older than the average age for women.³ Our patients were somewhat younger. The most common presenting symptom in our cohort was painless subareolar lump, in accordance with the other series.¹¹⁻¹³ There was a preponderance of left-sided disease such as female breast cancers, which is similar to other reports.¹⁴

The etiology of male breast cancer is unclear. However, patients with testicular abnormalities and benign breast conditions, such as a history of breast trauma and nipple discharge, are at increased risk of developing breast cancer.^{11,15-17} Similar to female breast cancer, a family history of breast cancer or prior radiation exposure to chest wall for Hodgkin's disease increase the risk of developing breast cancer.^{15,18} None of the patients in this series had previously noted testicular abnormalities or exposure to chest wall radiotherapy. However, a family history of a female breast cancer relative and a history of benign breast conditions could not be properly evaluated from this retrospective review. *BRCA1* mutations causing breast cancer susceptibility, on the other hand, have also been reported in men with breast cancer, although no consistent correlation could be found.¹⁹⁻²⁴ Because the study is a retrospective analysis, we cannot make a comment on this issue in our series of patients.

The ranges of histologic subtypes for invasive carcinomas representing female and male breast cancer were reported to be similar with variations of the relative distributions.³ A population-based study evaluating $> 2,000$ male patients demonstrated that 93.7% is ductal or unclassified, 2.6% is papillary, 1.8% is mucinous and only 1.5% is lobular,³ in contrast to extent in female breast cancer, where approximately 12% of cancers are lobular. Our series had a predominance of infiltrative ductal carcinoma as expected, with a 2.4% incidence of lobular carcinoma and a 7.1% incidence of combination of infiltrative ductal and lobular carcinoma. None of our patients had ductal or lobular carcinoma in situ, while previous series detected ductal carcinoma in situ (DCIS) in up to 10% of breast cancers in men.^{3,25}

Due to the substantial risk of recurrence and death from breast cancer, most of our patients also received adjuvant chemotherapy. As adjuvant chemotherapy has a solid role for women with breast cancer,²⁶ reliable and widespread data supporting adjuvant chemotherapy for men is lacking. The NCI published results of a prospective study of adjuvant chemotherapy in a series of 24 male patients with stage-II breast cancer treated with adjuvant cyclophosphamide, methotrexate and fluorouracil (CMF) and demonstrated a projected five-year survival rate of >80%.²⁷ Retrospective studies evaluating male breast cancer patients have also shown a decrease risk in recurrence with adjuvant chemotherapy.^{17,28,29} Therefore, the suggestive evidence in men and the documented gain in women for adjuvant chemotherapy prompted us to use adjuvant chemotherapy in our cohort.

The indications for adjuvant radiation therapy in male patients depended on limited data, but postmastectomy radiotherapy was generally more inclined in men than women, owing to the fact of probable nipple or skin involvement.¹⁴ To date, no potential survival benefit of radiation therapy could be demonstrated besides its effectiveness in preventing local recurrences in male patients.^{1,30-32} Tumor size and lymph node involvement are recognized to be two clear prognostic factors for male patients with breast cancer.³ As tumors measuring 2–5 cm displayed a 40% higher risk of death in comparison to tumors <2 cm, positive nodal involvement also increased risk of death 50%.³ Tumor size >5 cm predicted for poorer distant metastasis and disease-free survival in our series in univariate analysis; however, this was not manifested in multivariate analysis. Guinee et al. assessed the increasing number of involved axillary lymph nodes in a large series of 335 patients and remarked the correlation with a poorer prognosis.³³ We have analyzed our patients to differentiate their outcome in case of “a heavy axillary tumoral involvement.” We have detected a persistent unfavorable effect of increasing percentage of positive axillary nodal involvement in the LRRFS and DFS. As expected, this finding was not projected to multivariate analysis, possibly due to the limited number of patients. Male patients with breast carcinoma treated without radiation therapy have also been evaluated to define the predictors of local-regional failure,³⁴ and Perkins et al. pointed out the major factors for locoregional failure as margin status, tumor size and the number of involved axillary lymph nodes in his series of 142 male patients.³⁴ The projection of this MD Anderson Cancer Center data supports our findings related with the effect of increased PPNI and tumor size in LRRFS and DFS. Our findings suggest that patients with extensive nodal involvement (PPNI >30% and 50%) do not benefit adequately from post-

mastectomy irradiation and adjuvant CMF-based chemotherapy. Since there is growing evidence that anthracycline-based chemotherapy is superior for women with node-positive breast cancer,³⁵ we might speculate that male patients with extensive nodal involvement would gain advantage with an anthracycline- or taxane-based regimen.

Male breast cancer survivors are known to have an increased risk of developing second primary cancers. While the Swedish Cancer Database data demonstrated a 93-fold greater risk of developing contralateral breast cancer in male breast cancer patients,³⁶ the SEER cancer registry database reported a 30-fold greater risk in comparison to male with no breast cancer history.³⁷ Two out of 42 patients in our series developed a contralateral breast cancer.

CONCLUSION

We demonstrate that male breast cancer patients with extensive nodal involvement (PPNI >30% and 50%) did not benefit significantly from postmastectomy irradiation and adjuvant CMF-based chemotherapy. More effective treatment options such as new chemotherapy regimens and hormonal manipulations may add further benefit. We suggest that this observation warrants further research that will provide valuable insight into the optimal treatment strategy for this disease and strengthen this emerging literature.

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