

## BREAST CANCER PATIENTS WITH 10 OR MORE INVOLVED AXILLARY LYMPH NODES TREATED BY MULTIMODALITY THERAPY: INFLUENCE OF CLINICAL PRESENTATION ON OUTCOME

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**Purpose:** To analyze tumor control and survival for breast cancer patients with 10 or more positive lymph nodes without systemic disease, treated by adjuvant radiation alone or combined-modality therapy.

**Methods and Materials:** We reviewed the records of 309 consecutive patients with these characteristics who received locoregional radiotherapy (RT) at our institution. The majority of patients had clinical Stage II or IIIA–B disease (43% and 48%, respectively). The median number of positive axillary lymph nodes was 15 (range, 10–78). Adjuvant therapy consisted of RT alone, with or without chemotherapy, tamoxifen, and/or ovarian castration.

**Results:** The overall 5-year and 10-year disease-free survival (DFS) rates were 20% and 7%, respectively. Median DFS was higher for patients with Stage I–II compared with those with Stage IIIABC (28 vs. 19 months;  $p = 0.006$ ). Median DFS for patients aged  $\leq 35$  years was lower than that of older patients (12 vs. 24 months;  $p < 0.0001$ ). Patients treated with a combination therapy had a higher 5-year DFS rate compared with those treated by RT alone (26% vs. 11%;  $p = 0.03$ ). In multivariate analysis, clinical stage (III vs. I, II; relative risk = 1.8,  $p = 0.002$ ) and age ( $\leq 35$  vs. others; relative risk = 2.6,  $p < 0.001$ ) were found to be independent variables for DFS. **Conclusion:** This retrospective data analysis identified young age and advanced clinical stage as pertinent and independent clinical prognostic factors for breast cancer patients with advanced axillary disease (10 or more involved nodes). These factors can be used for further prognostic classification. © 2007 Elsevier Inc.

Breast cancer, Advanced disease, Clinical presentation.

### INTRODUCTION

Despite increased awareness and early detection campaigns, many patients with breast cancer still present with locally and regionally advanced disease. In patients with breast cancer, the risk of axillary lymph node involvement is directly related to the size of the tumor; however, the number of involved axillary lymph nodes is relatively independent of tumor size and location within the breast (1). It has been widely accepted that the presence of positive axillary metastases is the most important prognostic factor in breast cancer (2, 3). Within the group of patients with positive axillary lymph nodes, those who have a higher number of involved nodes have a worse outcome (1, 3, 4). In view of this, several studies have identified separate clinical prognostic groups based on the number of involved axillary lymph nodes (e.g.,  $<3$ , 4–7,  $>7$ ) and proposed

adjuvant treatment strategies to fit this risk classification (2, 5, 6). Recognizing the high risk of recurrence for patients with more than 10 positive axillary lymph nodes, several research groups have investigated aggressive treatment approaches, such as intensified chemotherapy regimens with stem cell support for this patient population (7–12). Unfortunately, these aggressive approaches did not result in an unequivocal clinical benefit, and the quest for an appropriate adjuvant therapy for these high-risk patients remains ongoing (13).

Over the years, clinical investigations of breast cancer have identified important prognostic factors and developed different chemotherapy regimens, drug combinations, and strategies, with or without hormonal therapy, and with or without locoregional radiotherapy (LRRT) to address the individual risk of recurrence. Whereas early studies considered LRRT a potentially harmful treatment owing to exces-

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sive non-cancer-related deaths (14), the publication of two prospective, randomized trials later demonstrated that post-mastectomy radiotherapy (RT) reduces both locoregional recurrence and mortality from breast cancer in patients with high risk of recurrence (15, 16). The actual contribution of LRRT for patients with advanced breast cancer was also evaluated by Strom *et al.* (17), who reported on 376 patients with advanced breast cancer treated by surgery and RT without chemotherapy between 1955 and 1984. They observed a 5-year disease-specific survival (DSS) rate of 48% and 30% for patients with stage IIIA and IIIB, respectively, indicating that LRRT contributes to a survival benefit in this group of patients because a reasonable proportion of patients can be cured by locoregional therapy alone.

Few studies have examined locoregional therapies in breast cancer patients with 10 or more positive axillary lymph nodes. Donegan and Lewis (4) have demonstrated that patients with more than 10 involved lymph nodes, treated with radical mastectomy alone, had a locoregional recurrence rate of 50% and a 10-year survival rate of 10%. Diab *et al.* (18) analyzed 618 breast cancer patients with  $>10$  positive axillary lymph nodes and reported a survival advantage in those patients receiving postmastectomy RT. Similar results were reported by Jabro *et al.* (19), who analyzed the outcome of 55 patients with 10 or more positive axillary lymph nodes treated by intensive chemotherapy, including high-dose chemotherapy and stem cell transplantation with or without LRRT. Although the addition of systemic therapy and LRRT has improved the prognosis of these high-risk patients, the optimal integration, intensity, and relative benefit of the various therapeutic options remains unclear.

In this study, we review the results of breast cancer management in patients with  $\geq 10$  positive axillary nodes and without systemic disease at our institution. Particular attention is focused on the respective role of each adjuvant treatment modality and on potential prognostic factors within this group of high-risk patients.

## METHODS AND MATERIALS

### Patient population

The medical records of all patients with node-positive breast cancer, referred for RT at our institution between 1966 and 1997, were reviewed. A total of 309 patients had 10 or more positive axillary lymph nodes without evidence of distant metastases and were included in the analysis. Data were retrospectively collected on clinical characteristics, clinical and surgical staging, RT parameters, adjuvant chemotherapy, and hormonal therapy, including ovarian castration. Demographic and follow-up information and data on time and sites of recurrence were obtained by direct review of the medical records performed by the investigators.

### Treatment methods

All patients underwent surgery. Modified radical mastectomy was performed in 181 patients (59%), radical mastectomy in 116 (38%), partial mastectomy in 8 (2%), and simple mastectomy in 4 patients (1%). Adjuvant therapy consisted of RT alone in 94

Table 1. Patient and treatment characteristics

Parameter	Number (percentage)
Age $<50$ y	169 (55)
Age $\geq 50$ y	140 (45)
Stage	
I	8 (3)
II	132 (43)
IIIAB	149 (48)
IIIC	19 (6)
Pathologic types	
Invasive ductal Ca	288 (93)
Invasive lobular Ca	8 (3)
Scirrhus Ca	10 (3)
Medullary Ca	3 (1)
Pathology grade	
High	111 (36)
Intermediate	53 (17)
Low	8 (3)
Not specified	137 (44)
Type of surgery	
Radical	116 (38)
Modified radical	181 (59)
Simple	4 (1)
Partial	8 (2)
Adjuvant therapy	
Radiation alone	94 (30)
RT/ovarian castration alone	15 (5)
RT/tamoxifen alone	17 (6)
RT/chemotherapy	183 (59)
Chemotherapy regimens	
CMF	41 (22)
FAC	68 (37)
Other	74 (41)

*Abbreviations:* Ca = carcinoma; RT = radiotherapy; CMF = cyclophosphamide-methotrexate-5-fluorouracil; FAC = 5-fluorouracil-adriamycin-cyclophosphamide.

*Note:* Patients aged  $>50$  years were arbitrarily considered postmenopausal.

patients (30%), RT with ovarian castration and no chemotherapy in 15 (5%), RT with tamoxifen and no chemotherapy in 17 (6%). A total of 183 patients (59%) received adjuvant chemotherapy, which consisted of CMF (cyclophosphamide-methotrexate-5-fluorouracil) in 40 patients (13%), FAC (5-fluorouracil-adriamycin-cyclophosphamide) in 30 patients (10%), or other types of single or multiagent chemotherapy in 113 patients (37%), with or without ovarian castration or tamoxifen. The decision to deliver ovarian castration depended on the physician and the time period during which the patient was treated. A total of 51 patients (17%) received radiotherapeutic ovarian castration with a median pelvic radiation dose of 24 Gy (range, 14–25 Gy) (Table 1). Adjuvant RT was delivered to the entire chest wall, ipsilateral axillary and supraclavicular (SCV) regions, and internal mammary nodes (IMN). The radiation technique was quite uniform, using opposed tangents to treat the chest wall and a single appositional field to treat both the IMN and SCV nodes. The large majority of the patients (302; 98%) received RT to all four volumes (chest wall, axilla, IMN, and SCV region); in 4 patients (1%) the SCV region was omitted; and in another 3 patients (1%) the chest wall was omitted. The median dose to the chest wall was 56 Gy (range, 44.6–68 Gy) delivered at 2 Gy per fraction using  $\text{Co}^{60}$  photons. The median doses to different target volumes were as follows: SCV region, 55 Gy

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