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ScienceDirect
THE BREAST
The Breast 17 (2008) 263–269
www.elsevier.com/locate/breast

Original Article

Prognostic factors in node negative premenopausal women treated with breast conserving therapy without adjuvant systemic therapy

Ashwini N. Budrukkar[a], Rajiv Sarin[a], Roshan F. Chinoy[b], Rajendra Badwe[c], Shyam Kishore Shrivastava[a], Ketayun A. Dinshaw[a,*]

[a]*Department of Radiation Oncology, Tata Memorial Hospital, Parel, Mumbai 400012, India*
[b]*Department of Pathology, Tata Memorial Hospital, Parel, Mumbai 400012, India*
[c]*Department of Surgery, Tata Memorial Hospital, Parel, Mumbai 400012, India*

Received 13 January 2007; received in revised form 10 September 2007; accepted 12 October 2007

Abstract

Purpose: To study the prognostic factors in node negative premenopausal women treated with breast conserving therapy (BCT) without any adjuvant systemic therapy.
Methods: Of the 1022 women treated with BCT at Tata Memorial Hospital, there was a cohort of 175 women who were premenopausal, node negative and had not received any adjuvant systemic therapy. BCT consisted of wide excision, complete axillary clearance, whole breast radiotherapy (45 Gy in 25 fractions) with 6 MV photons plus tumour bed boost either with brachytherapy or electrons.
Results: The median age at presentation was 38 years (range 22–51 years) and the median pathological tumour size was 3 cm (1–5 cm). The 5-year actuarial local control rate was 89.5% and the overall survival (OS) was 88%. On univariate analysis, lymphovascular invasion (LVI) was the only prognostic factor affecting all failures and disease-free survival. The 5-year local control rate in absence of LVI was 93.5% in contrast to 76.5% ($p = 0.0098$) when LVI was present. Similarly, the OS in absence of LVI was 91% in contrast to 74% in presence of LVI ($p = 0.02$). On multivariate analysis, LVI was the independent prognostic factor affecting the disease-free survival ($p = 0.001$; 95% CI: 1.46–4.96).
Conclusion: LVI emerged as the most important prognostic factor for node negative premenopausal women not receiving adjuvant systemic therapy. There is a need to take into consideration the presence of LVI while deciding adjuvant systemic therapy in T1N0 patients.

Keywords: Breast conservation; Node negative; Premenopausal; Prognostic factors; Lymphovascular invasion

Introduction

Various host-related and disease-related factors are known to affect the prognosis in women with breast cancer. Tumour size and axillary lymph node status are well established prognostic factors affecting local control and survival.[1–7] Apart from these two factors, various other factors like age, tumour grade, presence of extensive intraductal carcinoma (EIC), perinodal extension, lymphovascular invasion, cut margin status have been studied with varying results.[8–17] As axillary lymph node status is one of the most important prognostic factors, in absence of axillary node metastasis other prognostic factors may play an important role. However in this era, where adjuvant chemotherapy is generally recommended for tumour size of more than 1 cm, the effect of these prognostic factors may be masked by the improved outcome achieved by the adjuvant therapy.

Breast conserving therapy (BCT) was started at our hospital in 1980. Over a period of 25 years, we have treated a large number of women with BCT. Early results of the cosmetic outcome and the therapeutic factors have been published.[18,19] We have also reported our results of prognostic factors in women treated with BCT in which

*Corresponding author. Tel.: +91 22 24139318, +91 22 24146750; fax: +91 22 24168440, +91 22 24146937.
E-mail address: dinshaw.tmc@vsnl.com (K.A. Dinshaw).

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doi:10.1016/j.breast.2007.10.012

lymphovascular invasion (LVI) was found to be the most important prognostic factor affecting local control (LC), disease-free survival (DFS) and overall survival (OS).[20] During the 1980s and early 1990s, chemotherapy was considered for node positive women or women with T3 tumours. Hence, we have a subset of premenopausal women who had negative axillary lymph node status and were not considered for any adjuvant systemic therapy. In this report, we have studied the prognostic factors for this subset of women.

Materials and method

During a two-decade period from 1980 to 2000, 1094 women with pathological stage I and II breast cancer were treated with breast conserving surgery and radiotherapy with or without systemic therapy at the Tata Memorial Hospital, Mumbai, India. Of these 1094 patients, 72 women were excluded as they had received neoadjuvant chemotherapy prior to surgery (49 patients); or were treated with suboptimal radiation technique and fractionation at the very beginning of our BCT programme (23 patients). Thus, 1022 women with pathological stage I and II breast cancer had received standard treatment with breast conserving surgery and radical radiation therapy with or without systemic therapy.[21,22] Of these 1022 women, there were 175 premenopausal women who had not received any adjuvant systemic therapy due to the prevailing practice at that period of time. This forms the cohort for the current study.

All patients underwent wide excision of the primary tumour and complete axillary dissection. A detailed histopathological review was carried out on all these patients by a breast pathologist. The standard Hematoxylin and Eosin (H and E) stained sections were studied without recourse of immunohistochemistry for features like micro metastasis or angiogenesis. Primary breast tumour was typed according to the American Joint Committee histopathologic classification of the tumours of the breast.[23] The pathological evaluation included documentation of the tumour size, type of the tumour, grade of the tumour, presence of in situ carcinoma, EIC, LVI, desmoplasia, cut margins, axillary lymph node status, perinodal extension and apical nodal status. Lymphatic and vascular invasion was carefully looked for in the H and E stained sections. For identification of LVI, the criteria suggested by Orbo et al. was used.[24] Tissue spaces containing tumour tissue were diagnosed as lymphatic vessels if they had an apparent endothelial lining and a thin non-muscular wall, contained no erythrocytes and showed a perivascular pattern. Emboli in these lymphatics within and outside the tumour area were recorded as LVI. Hormone receptor status was evaluated by dextran charcoal ligand binding method or by immunohistochemistry.

Revision excision was considered whenever possible for women with positive margins. All patients received standard radiation therapy to the entire breast to a dose of 45 Gy in 25 fractions over 5 weeks and a 10–20 Gy boost to the tumour bed with electrons or a low dose rate or high dose rate Iridium 192 interstitial implant.[16–18] Higher boost dose of 20 Gy was considered in women with positive margins. After completion of the treatment patients were followed up 3–6 monthly for first 5 years and annually thereafter. At each follow up, assessment was done with respect to disease control, complications and cosmesis. Local recurrence was defined as cytologically or histologically confirmed tumour recurrence in the ipsilateral breast parenchyma or overlying skin. Locoregional recurrence was defined as recurrence in the ipsilateral axillary, supraclavicular or internal mammary nodes or recurrence within the breast. Any local, regional or distant metastasis was considered as an event for calculating the DFS. Death due to any cause was considered as an event for OS.

The statistical analysis was performed using SPSS software for Windows. The survival analysis was done by Kalpan–Meier method and various groups were compared using log rank test.[25] The p-value of 0.016 was considered as significant as per the Bonferroni correction for the subset analysis of univariate analysis. Multivariate analysis was done using Cox proportional Hazard model using forward conditional method. The p-value of 0.05 was considered as significant for multivariate analysis.

Results

The median age at presentation was 38 years (range 22–51 years). The most common site of involvement was the upper outer quadrant (83 patients), followed by upper inner quadrant (51 patients), lower outer quadrant in 19, lower inner quadrant in 15 and central and other locations in 7 patients. Family history of breast cancer was noted in 23 patients.

The pathological characteristics are shown in Table 1. The median pathological tumour size was 3 cm (range 1–5 cm). The tumour type was infiltrating duct carcinoma (IDC) in 153 (87.5%), ILC in 3 (2%) and others in 19 (10.5%) patients. The grade of the tumour was grade III as per Modified Richardson Bloom scoring in 109 (62%) women. The final inked margins were involved with either invasive or in situ carcinoma in 7 (4%) and EIC was present in 9 (5%) patients. LVI was present in 42 (24%) patients. All patients in this subset had pathologically negative axillary nodes. Oestrogen and progesterone receptor status was known only in 25% patients. Oestrogen receptor status was positive in 13 women while progesterone receptor status was positive in 9 women.

At a median follow up of 72 months, the actuarial local control rate was 89.5% at 5 years and 84% at 10 years (Fig. 1). The actuarial DFS was 76% at 5 years and 67% at 10 years. The actuarial OS was 88% at 5 years and 80% at 10 years (Fig. 1). The effect of various prognostic factors like age, tumour size, grade of the tumour, cut margin and LVI was studied in this subgroup (Table 2). The effect of EIC and ER/PR status could not be studied as the