Estrogen Receptor Negative Breast Cancer in India: Do We Really Have Higher Burden of this Subtype?

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Abstract ER negative and Triple negative breast cancers carry a poorer prognosis and are not amenable to hormone therapy. It has been previously observed that Indian patients with breast cancer have a higher tendency to have these tumours. Whether this is due to inherent biological differences in the tumours of our patients is a matter of much debate. We have analysed 250 patients of breast cancer for hormone receptor status, compared them with western series, and attempted to support the hypothesis that the higher ER negativity and triple negativity is indeed due to different tumour biology.

Keywords Breast cancer · Estrogen receptor · Triple negative

Introduction

Estrogen receptor (ER) is an important prognostic and predictive marker in breast cancer. Data from the west show not more than one-third of all breast cancers to be ER

negative when corrected for age, and about half of that proportion (15%) to be Triple negative (TPN), i.e. lacking ER, progesterone receptor (PR) as well as HER-2 receptors [1]. Previous data from India show higher proportion of ER negative breast cancer compared to the west [2–4]. This higher burden of ER negative disease has been attributed to several factors, including technical failures at detection of ER positivity, younger age of patients, and advanced stage at presentation – all of which can increase the proportion of ER negative tumours [2]. Our study aims to evaluate ER negative breast cancer in a South Indian cohort of patients, and compares data with the SEER database.

Materials and Methods

Our data is from an ongoing prospective longitudinal observational study looking mainly at molecular markers in female patients with Primary Breast Cancer, and the study has been cleared by the hospital ethical review board. The study is a collaborative effort of the Department of Surgical Oncology, St. John's Medical College Hospital, and the Division of Molecular Medicine, St. John's Research Institute, Bangalore. The study began in October 2006, and analysis was started after enrolling the 250th patient in June 2010.

Details of the immunohistochemistry (IHC) for ER, PR and HER-2 were obtained from histopathology records for each case. Information on breast cancer for the western population was collected from the SEER (Surveillance, Epidemiology and End Results) database [1], which is a source of information on cancer incidence and survival from population based cancer registries in the USA. Sorting the data and analysis was done using Microsoft Excel worksheet and SPSS software version 11.6.

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Fig. 1 ER -ve 127 of 250

Fig. 2 TPN 62 of 250

The technique of (IHC) at our centre is as follows: We use the polymer technology which is more sensitive than the more routinely performed avidin-biotin complex (ABC) method. Tissue fixation is in 10% neutral buffered formalin overnight. The primary antibody is 1D5 for ER receptor, PGR636 for PR receptor, and PN2A for the HER-2 receptor (all from DAKO company, Glostrup, Denmark). Antigen retrieval is done by EDTA for ER and PR receptors and pressure cooking for ten minutes, and by citrate for HER-2. Human endometrial tissue is used as positive external

control for all cases. There is no lower limit of cut-off for positivity, and any ER staining is considered as positive.

Results

In our series, 127 of 250 (50.8%) patients were ER negative and 123 (49.2%) were ER positive. Overall proportion of ER negativity was found to be more than double that of breast cancers from the SEER data (50.8% versus 23.4%) (Fig. 1). Sixty two patients (24.8%) had TPN tumours, compared to 15% in the SEER (Fig. 2). The mean age of our patients was 53.0 years (Standard Deviation {SD} 11.38), with 76.4% (191 of 250) being less than 60 years of age. ER negative disease occurred at a younger age, at a mean of 50.2 years (SD 10.28), whereas the mean age of ER positive disease was 55.7 years (SD 11.38) (Fig. 3). The younger the age of the patient, the greater were the chances of the cancer being ER negative, with 63.5% of patients (73 of 115) under 50 years of age having ER negative tumours, and 33% of patients (38 of 115) under 50 years of age having TPN tumours (Fig. 4). As the age of the patient increased, likelihood of ER negativity also decreased (Fig. 5). However, even in the 7th decade, the incidence of ER negative and TPN tumours did not fall below 45% and 12.5% respectively (Fig. 5). Higher ER negativity rates were seen across all age groups when our data was compared with SEER data (65% versus 34% under 50 years, 42% versus 24% between 50 and 64 years, and 38% versus 16% in patients over 65 years) (Fig. 6). When the ER negativity was plotted against the Grade of tumour, it was found that highest proportion of ER negativity was found in

Fig. 3 Age distribution: ER positive vs ER negative

Fig. 4 Relative age distribution: Total cases, ER –ve, Triple –ve

Grade III tumours (63.1%) and lowest in Grade I tumours (42.8%). Again, when compared to SEER data, ER negativity rates among our patients were higher across all stages (Fig. 7).

Discussion

ER receptor predicts response to hormone therapy in breast cancer, and is an independent prognostic factor as well. Hormone therapy is a safe and effective therapy and usually administered orally on an outpatient basis. Importantly, it is inexpensive, which is relevant in countries with low economic resources. However, hormone therapy is effective only in patients whose tumours exhibit hormone receptor positivity, and completely ineffective in receptor negative disease [5]. At the same time, any degree of ER staining renders a patient suitable for hormone therapy [5].

Previous Indian studies have documented that rates of ER negativity is high among breast cancers in Indian women [2–4]. It has been suggested that factors contributing to this high ER negativity could be technical failures of detection of ER, younger age of patients, and advanced

Fig. 6 Age-wise comparison: ER –Ve St. John's vs SEER

stage at presentation – all of which can increase the proportion of ER negative tumours [2].

The need for quality assurance has been shown in previous studies [6–10]. Unless standardized techniques are used for detecting ER receptor, the likelihood of false negative results remains. This is especially true with regard to the tissue fixation time [6], antibody retrieval techniques [7, 8], and hormone receptor detection methods used [8, 9]. An Indian study [10] has previously attributed higher incidence of ER negative breast cancer to suboptimal assays. In fact, Shet et al [2] have highlighted the experience of a single Indian institution in which the ER negative and PR positive tumours in an earlier study was due to underreporting of ER positivity [2, 11]. To this end, we standardized our technique prior to commencing the study. Our technique, as explained previously, has been carefully designed using standard fixation technique and duration, optimal antigen retrieval methods, and use of a standard set of antibodies for receptor detection. These steps minimize false negatives. In addition, we have also used an external positive control of human endometrial tissue in all cases. Further, we have kept no lower limit of cut-off for ER positivity, and considered any ER positivity

Fig. 5 Age specific incidence by ER & TPN

Fig. 7 Stage-wise comparison:
ER –Ve St. John's vs SEER

as positive. This is in accordance with the recommendation of the 2001 consensus development panel of the NIH, that any ER staining in breast cancers is sufficient to consider a tumour ER positive [5].

The second hypothetical reason often given for high ER negativity is the younger age of Indian breast cancer patients. On an average, our patients are about one decade younger than those in the west [2, 12]. This has been suggested as a factor which contributes to high ER negativity as younger patients tend to have more ER negative and more triple negative tumours. However, even when patients of similar age were compared, we found that across every age group the ER negativity rates of our patients are higher than patients from SEER data. Thus it is unlikely that overall high ER negativity is due to a greater proportion of younger patients in Indian series.

A third argument which seeks to explain overall high ER negativity is that our patients often present at advanced stage of breast cancer, in which ER negativity is likely to be higher [2]. A higher proportion of advanced (stage III of IV) cancers may contribute to overall higher percentage of ER negative tumours. But, when we compare ER negativity among corresponding stages, again our patients have higher ER negativity across all stages. Thus, even though our proportion of advanced cancers is much higher than in the west, overall ER negativity is high even when corrected for stage.

Conclusions

There is a high proportion of ER negative as well as Triple negative breast cancer in Indian patients, as compared to western patients. In our series, among patients younger than 50 years of age, two-thirds have ER negative and one-third have Triple negative disease. This trend of higher ER negativity is seen even when IHC techniques are standardized, and is seen across all age-groups of patients and across all stages of the disease. Thus it is a result of tumour biology rather than poor IHC

technique or demographic factors like age and advanced stage at presentation.

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