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Commentary: Eight Year Survival Analysis of Patients with Triple Negative Breast Cancer in India

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Breast cancer is the most common cancer in women worldwide and remains an important global health issue. Its incidence is increasing particularly in developing countries where the majority of cases are diagnosed in late stages[1]. Although breast cancer is considered to be a disease of the developed world, almost half of total breast cancer cases and 58% of deaths take place in less developed countries[1]. The literature shows that breast cancer is one of the most heterogeneous and complex diseases in terms of tumor histology, cellular origin, molecular subtypes, gene mutations, metastasis, disease progression, therapeutic response, and clinical outcome[2].

Triple-negative breast cancer (TNBC) is clinically defined by the lack of expression of estrogen receptor, progesterone receptor and no overexpression of human epidermal growth factor receptor-2 (HER2). It accounts for approximately 15-25% of newly diagnosed breast cancer cases[3]. TNBC is an aggressive disease with outcomes inferior to those of other breast cancer subtypes. This group of breast cancer is only partially responsive to chemotherapy and presents a lack of targeted therapies.

Compared to other types of breast cancer, TNBC is seen more in premenopausal women than older women. In the article, the median age at the time of diagnosis was 49 years[4] which may be considered as younger age and is comparable to many other Indian studies[5]. However, the majority of patients considered in this study were postmenopausal. This shows that TNBC is affecting younger population and most likely reflects the general trend of breast cancers occurring a decade earlier. This leads to another finding that menopause has been reached early in the women considered in this study. This is in line with the existing literature, the average age of menopause of an Indian woman is 46.2 years and is much less than their Western counterparts (51 years)[6]. Clinically stage II was the commonest stage at presentation. This reflects the awareness among population presenting to a private tertiary cancer care center located in a metropolis. Age group wise comparison showed that the pathological tumor size > 5 cm was observed more commonly in the patients with age group less the 50 years while patients > 50 years of age had a higher predominance of tumor size < 5 cm.

Interestingly, compared to the older patients' group, the younger age (<50 years) group showed better overall survival (OS) despite having decreased relapse-free survival (RFS). Surprisingly, enhanced RFS was observed in patients with higher tumor grade and presence

of lymph-vascular invasion (though not significant), while the reverse is expected concerning the observed trend. Similarly, improved OS was seen in patients with premenopausal status, higher tumor grade and presence of lymph-vascular invasion. Such findings are not usually found in the literature. This may indicate towards the heterogeneity of this disease. The subgroup of patients with no axillary lymphnode involvement showed better RFS (69%; p-value 0.001) as well as OS (86%; p-value 0.001) in comparison with the sub-group of patients with positive axillary lymphnodes.

Molecular profiling has provided biological evidence for heterogeneity of breast cancer through the identification of intrinsic subtypes. These subtypes consist of Luminal A, Luminal B, HER2 expressing, basal-like (BL) and normal breast-like. Further, it has also been observed that heterogeneity exists within TNBC. The majority of TNBCs show the expression of basal markers on gene expression profiling and most authors accept TNBC as BL. However, a smaller fraction lacks a BL phenotype despite being TNBC. Lately, the literature has reported that TNBC can be classified into 7 subtypes (6 defined subtypes and an unstable group) by gene expression microarray[7,8]. The subtypes were characterized as BL 1, BL 2, immunomodulatory, mesenchymal, mesenchymal stem-like, luminal androgen receptor and unstable. These studies show that significant biological heterogeneity exists within a group of patients detected with TNBC.

The bias towards modified radical mastectomy (MRM) was highly significant in this study with all patients of neo-adjuvant chemotherapy undergoing only MRM. This reflects the social and cultural differences in the Indian population. No significant difference could be seen between RFS of surgical procedure groups, i.e., MRM vs. breast conservation surgery. Similarly, OS of surgical procedure groups showed no considerable difference. These observations are in collaboration with the known literature. The study observed that eight-years RFS and OS was 58% and 75%, respectively. Literature has pointed out that TNBC has higher chances of early recurrences and poor survival outcomes followed by treatment. Our results also represent this phenomenon, though the OS is better keeping in view the number of recurrences.

The current study has presented comprehensive eight-years survival data on the most aggressive type of breast cancer. There are many studies in the Western literature on the same, but the reliable data in the Indian setting on TNBC survival are scarce. TNBC have aggressive clinical behavior, distinct metastatic pattern and poor prognosis[9] despite responding to conventional neoadjuvant and chemotherapy[3]. The main limitation of this study was the lack of testing for basal cytokeratins. Identification of basal markers positivity within this group of TNBC could identify a subgroup of tumors, BLBC. It has been shown that BLBC consistently over expresses HER1 or epidermal growth factor receptors (EGFR), hence EGFR inhibitors may have a role in the treatment of this tumor subtype[10].

Prevalence of TNBC in India is considerably higher compared with Western populations[11]. The Triple-negative disease could affect one in three women with breast cancer[11]. This finding has significant clinical relevance as it may lead to poor outcomes in patients with breast cancer in India[11]. Further research is required to understand the determinants of TNBC in India. Identification of newer targets and development of targeted therapies are the need of the hour.

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