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Overview

Breast Cancer Demographics, Types and Management Pathways: Can Western Algorithms be Optimally used in Eastern Countries?

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Abstract

Over the past decade, breast cancer has overtaken cervical cancer to become the most common cancer among women in India, as in most Western nations. In addition to the high incidence, the morbidity and mortality associated with this malignancy are disproportionately higher in India. Although some efforts are being made to increase awareness about this disease, a large majority of Indian patients present with advanced disease. Here, important institutional data and treatment outcomes are reviewed and compared with data from the West. Additionally, we highlight recent efforts in setting up collaborative multicentre trials in breast cancer in India and suggest some ways forward to improve outcomes.

Keywords: Breast cancer; breast surgery; hypofractionation; immunohistochemistry; India; UK

Burden of Breast Cancer

As in all developed Western nations, breast cancer is the most common of all cancers in urban women in India. Here we compare and contrast the patient demography, pathology, treatment acceptability and research options available to Indian breast cancer patients as opposed to those available in Western countries. Although the annual age-standardised incidence of breast cancer is 25.8 per 100 000, which is a quarter of the incidence observed in the UK, mortality from breast cancer is disproportionately higher in India, with an annual age-standardised rate of 12.7 per 100 000 as compared with 17.1 per 100 000 in the UK https://paperpile.com/c/epy1Ik/EPVA+aUVQ [1,2]. This implies that nearly a half of the incident cases in India will die of breast cancer compared with one-fifth in the UK. Breast cancer is also the second highest cause of cancer associated with disability-adjusted life years (DALY) in India https://paperpile.com/c/epy1Ik/RMIh [3].

Epidemiology and Screening

Population-based screening strategies form an integral part of many Western healthcare systems https://paperpile.com/c/epy1Ik/Qzup [4], allowing the detection of early cancers and possible improvements in survival https://paperpile.com/c/epy1Ik/mCNy [5]. Most breast cancer patients present with clinically palpable disease in the primarily unscreened Eastern countries, like India. The reasons for delayed presentation are multifactorial, including lack of awareness, cultural inhibitions, poor access to effective healthcare, negligent health-seeking behaviour in women of low socioeconomic and educational status, as well as a lack of health insurance coverage https://paperpile.com/c/epy1Ik/zvNV [6]. There is also a high burden of out of pocket expenditure due to limited health insurance coverage https://paperpile.com/c/epy1Ik/LqQt [7]. Existing insurance systems in India do not reimburse or provide cover for diagnostic tests in the absence of treatment https://paperpile.com/c/epy1Ik/ZNuR [8]. More importantly, the publicly funded healthcare systems are already overstretched and earlier detection may not necessarily

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translate into an early and appropriate treatment of breast cancer https://paperpile.com/c/epy1Ik/Pykj [9], making screening tests difficult to roll out as a nationwide policy https://paperpile.com/c/epy1Ik/H2x9 [10]. Moreover, whether mammographic screening is cost-effective for low resource countries like India remains to be proven and alternative strategies to increase cancer awareness and clinical examination of the breast have been tried with some effect https://paperpile.com/c/epy1Ik/mQY1+Xe2D [11,12]. Indian patients present at an earlier age with breast cancer https://paperpile.com/c/epy1Ik/QOw2+VwZB+ZRSt [13–15]; the reasons for this are not clear, but could be related to their early menarche and menopause. Given the younger age profile of Indian breast cancer patients, the efficacy of mammographic screening for dense breast could also be less. Recently, the National Health Mission started a programme of community-based assessment of all women and men above the age of 30 years, with the goal of screening for non-communicable diseases. This unique programme, led by community health workers using a uniformly standardised tool known as the Community Based Assessment Checklist, which includes questions on early warning signs of breast cancers, may increase the diagnosis of clinically relevant breast cancers https://paperpile.com/c/epy1Ik/zxv1 [16]. Therefore, in the foreseeable future, the incidence of breast cancer in India will probably increase, due to increased awareness coupled with an ageing population. Hence, there is an urgent need to evaluate if the breast cancer phenotype is the same in India as in the West and if Western management strategies are implementable in the Indian setting.

Histopathology

It was believed that the molecular phenotype of breast cancers presenting in India is different from that in the West. For example, a meta-analysis of studies reporting the prevalence of triple-negative breast cancers (TNBC) in India reported a combined prevalence rate of 31% (95% confidence interval 27–35%) https://paperpile.com/c/epy1Ik/CoJA [17]. However, in this study, the authors reported significant heterogeneity between reporting centres. Not only were some studies conducted in small populations https://paperpile.com/c/epy1Ik/p8D8 [18], but also a degree of referral bias may have been expected in studies reported from large referral centres https://paperpile.com/c/epy1Ik/bBAW [19]. Furthermore, technical issues related to the immunohistochemistry (IHC) process are important https://paperpile.com/c/epy1Ik/JOuo+TNVL [20,21]. For example, most centres used manual IHC techniques and failed to report the antibodies used, the pre-analytical methodology, such as the cold ischaemia time, and the appropriateness of the fixation of the tumour specimen. In most of these studies, IHC was carried out on manually fixed specimens. The use of improved quality-assured antibodies has improved the detection threshold of oestrogen and progesterone receptors https://paperpile.com/c/epy1Ik/GUyw [22]. Finally, IHC carried out on lumpectomy or mastectomy specimens rather than core biopsies, as in many of the Indian centres, may lead to 9% false-negative oestrogen receptor results.

In contrast to these results, overall rates of TNBC in the Tata Medical Center [23] were 12.5%, with 15.5% for those with locally advanced tumours. Similar to the results in the UK, nearly 75% of our patients had oestrogen receptor/progesterone receptor-positive disease https://paperpile.com/c/epy1Ik/VwZB [14]. For all patients in our series, IHC was carried out on mostly core biopsies using automated, approved and peer-reviewed methods, with appropriate internal and formal external quality assurance. These results have now been replicated in other centres that have participated in the Pathology External Quality Assurance Scheme conducted by the National Cancer Grid of India https://paperpile.com/c/epy1Ik/HcK1 [24]. The high reported prevalence of TNBC in India could largely be attributed to methodological issues with sample processing and referral bias rather than a true difference in the phenotype.

Surgery

Although surgery is the mainstay of treatment for breast cancer, increasing emphasis has been placed on avoiding axillary dissection in the routine management of breast cancer in the West https://paperpile.com/c/epy1Ik/WnUy [25]. Current guidelines recommend axillary node dissection if the sentinel lymph node biopsy (SLNB) is positive https://paperpile.com/c/epy1Ik/60EZ [26]. The results from the ACOSOG Z0011 trial suggest that the use of axillary lymph node dissection may not be required in all patients with one to two sentinel node macrometastases https://paperpile.com/c/epy1Ik/fKwP [27]. Moreover, increasingly, nomograms are being used to tailor axillary lymph node dissection when sentinel lymph nodes are positive https://paperpile.com/c/epy1Ik/odqB [28]. The recent American Society of Clinical Oncology guidelines for SNLB suggest that axillary dissection may be avoided in patients with one to two positive nodes, with those patients receiving adjuvant radiotherapy for the whole breast https://paperpile.com/c/epy1Ik/VbK9 [29].

However, the results of the Z0011 trial may not be directly applicable in an unscreened population, as seen in India. The prospectively collected results of the SNLB procedure from the Tata Medical Center Kolkata suggest that 35% of all SLNBs are positive https://paperpile.com/c/epy1Ik/MQcj [30]. Of 109 such women in whom SLNB was carried out between 2012 and 2016 at the Tata Medical Center, 72 patients (66%) had one to two positive nodes and were therefore suitable for avoiding axillary nodal dissection, as per the American Society of Clinical Oncology recommendation. However, when compared with the Z0011 trial cohort, our patients had a higher proportion of clinically T2 disease (79% versus 32%), a higher nuclear grade (47% versus 22%) and an increased presence of lymphovascular emboli (82% versus 31%). Most concerning was that almost 44% of these patients had a positive non-sentinel node on axillary dissection, as compared with

23% in the Z0011 trial https://paperpile.com/c/epy1Ik/MQcj [30]. In light of the above findings, the safety of omitting further axillary dissection in patients with positive SNLB remains to be confirmed in our setting. Furthermore, direct use of nomograms that predict the risk of further axillary nodal metastases is possibly not universally applicable for our population https://paperpile.com/c/epy1Ik/4wqz [31]. This was shown by Syed *et al.* [32], who found that the Memorial Sloan Kettering Cancer Center nomogram was associated with an AUC of only 0.66 in a UK cohort of breast cancers. Hence, the current National Cancer Grid guidelines continue to recommend completion axillary clearance in patients with a positive SNLB https://paperpile.com/c/epy1Ik/7Urm [33].

As an alternative to SLNB in the resource-poor setting, low axillary sampling has been used. In a study by Parmar *et al.* [34], low axillary sampling had similar false-negative rates as SNLB carried out in a series of patients (10.5% versus 12.7%). However, the efficacy in terms of reducing shoulder morbidity and arm lymphoedema remains to be established.

With locally advanced breast cancers accounting for a large majority of breast cancers at presentation, it is no surprise that nearly 40–50% of breast cancer patients in India undergo mastectomy, even in tertiary cancer centres https://paperpile.com/c/epy1Ik/VwZB+zNCG [14,35]. As reported by Nair *et al.* [35], in their series, only 1–2% of patients underwent whole breast reconstruction after mastectomy. Shaikh *et al.* [36] reported rates of 18% and in most of these patients immediate reconstruction using a transverse rectus abdominis myocutaneous or latissimus dorsi flap was carried out. The consensus report of the Association of the Breast Surgeons of India suggests that most breast cancer surgeons prefer immediate reconstruction after mastectomy https://paperpile.com/c/epy1Ik/U9FG [37].

Systemic Therapy

The receipt of systemic chemotherapy in the adjuvant and neoadjuvant settings is poorly reported in India. Parmar *et al.* [38] reported the response rates in patients with locally advanced breast cancer receiving neoadjuvant chemotherapy (NACT) and showed that a pathological complete response was obtained in 8.3% of patients. These results may be due to the sparse use of anti-HER2 therapy, as well as using anthracycline-based chemotherapy only in many patients. Similar low rates of pathological complete response have been reported by Raina *et al.* https://paperpile.com/c/epy1Ik/DCXR [39]. By contrast, results from a series reported from the Tata Medical Center of all patients receiving NACT using anthracyclines and taxanes, showed that a pathological complete response was observed in 23% of patients https://paperpile.com/c/epy1Ik/5snx [40]. This rate is again similar to that in a series of patients with locally advanced breast cancer who received NACT in the US, where the reported pathological complete response was 25% https://paperpile.com/c/epy1Ik/cLiw [41].

A closer look at the data shows that the high rates of pathological complete response reported in Western literature were primarily driven by HER2-positive tumours, which had a pathological complete response of 48%. It should be noted that in this series, anti-HER2 therapy was received by 100% of the HER2-positive patients https://paperpile.com/c/epy1Ik/hgBd [38]. Limited access to anti-HER2 therapy has been reported by several centres in India. In an analysis of patients treated between 2011 and 2013, it was observed that NACT with trastuzumab could be delivered to only 24% of patients https://paperpile.com/c/epy1Ik/5snx [40]. Similarly, studies reported from other Indian centres showed that anti-HER2 therapy was given to 10–20% of eligible patients with HER2-positive disease https://paperpile.com/c/epy1Ik/x9S7+r1br [42,43].

Limited access to anti-HER2 therapy is a significant concern, although the situation has improved in recent years with the availability of biosimilars. A recent survey of Indian oncologists has shown that nearly two-thirds of oncologists prescribe biosimilars. The study reported that in practice about 60% of patients could afford to take trastuzumab and of them 70% received the drug for a period of 1 year https://paperpile.com/c/epy1Ik/AcoC [44]. Active philanthropic support in recent years has enabled the use of trastuzumab even in public sector hospitals, with nearly 60% of patients getting access to at least 12 weeks of the drug https://paperpile.com/c/epy1Ik/jPIW [45].

Outcomes of patients undergoing NACT have been reported from major centres. Parmar *et al.* [46] reported outcomes of NACT followed by surgery and showed that after a median follow-up of 30 months, the local-only relapse rate was 8% after breast conservation therapy and 10% after mastectomy. These rates are quite similar to the local recurrence rate reported after NACT in the Early Breast Cancer Trialists' Collaborative Group meta-analysis, where a 5-year local recurrence risk of 10% was reported in patients undergoing surgery https://paperpile.com/c/epy1Ik/vhPj [47]. Recently reported locoregional recurrence rates from the Tata Medical Center at a median follow-up of 22 months, for patients undergoing breast conservation therapy and mastectomy after NACT, were 2.7 and 6.5%, respectively https://paperpile.com/c/epy1Ik/VwZB [14].

Use of dual HER2 blockade has translated into an improvement in the 4-year disease-free survival of 1.7%, with an absolute improvement of 3.2% in patients with node-positive disease https://paperpile.com/c/epy1Ik/qr3l [48]. The regimen has not shown an improvement in overall survival at 4 years. Dual HER2 blockade has been approved for both neoadjuvant and adjuvant therapy in the UK and USA. The UK approval is, however, restricted to patients with node-positive disease and conditional to a UK-specific commercial agreement with the manufacturer, together with the use of trastuzumab biosimilars. The combination of drugs met the UK cost-effectiveness threshold of £20 000 after taking into account these considerations https://paperpile.com/c/epy1Ik/ildW [49].

In order for this regimen to be cost-effective in India, the cost of pertuzumab has to be reduced substantially. The current cost of dual HER-based adjuvant therapy in the

Indian market, with available patient assistance from the manufacturers and generic trastuzumab, is approximately INR 3 000 000 (£33 177), which is approximately six times the annual per capita income adjusted for purchasing power (£5459). The cost-effectiveness threshold in India, in keeping with the World Health Organization-Choice guidelines, requires the cost per DALY saved to be less than INR 352 281 (£3895) https://paperpile.com/c/epy1Ik/KwK5 [50]. This is significantly lower than the UK threshold https://paperpile.com/c/epy1Ik/60EZ [26]. Therefore, improved patient access programmes are needed in the Indian setting before routine recommendation of dual Her 2 blockade is considered.

Endocrine Therapy

Adjuvant hormonal therapy protocols in India are similar to those of the West https://paperpile.com/c/epy1Ik/60EZ+7Urm [26,33]. Patients who are postmenopausal are offered treatment with aromatase inhibitors, whereas premenopausal women are offered treatment with tamoxifen. Increasingly, oncologists agree that patients with high-risk factors could be offered extended endocrine therapy https://paperpile.com/c/epy1Ik/hUwG [51], whereas in premenopausal women, combined ovarian suppression could be considered. Interestingly, India recruited nearly a quarter of the patients in the ATLAS trial, which was one of the major trials that showed the advantage of extended endocrine therapy https://paperpile.com/c/epy1Ik/2nQR [52]. It is to be noted that the cardiovascular effects of long-term endocrine treatment have been poorly studied in India. This needs further study, especially in light of the higher baseline risk of cardiovascular events in the population https://paperpile.com/c/epy1Ik/6Ox3 [53].

Radiotherapy

Breast cancer radiotherapy schedules have traditionally followed US standards of conventionally fractionated radiotherapy. In a practice survey of Radiation Oncologists of India between 2006 and 2008, nearly two-thirds of the surveyed radiation oncologists practised the conventionally fractionated 50 Gy/25 fraction regimen https://paperpile.com/c/epy1Ik/GTV2 [54]. The use of hypofractionated regimens was infrequent and was part of institutional practice for very few centres https://paperpile.com/c/epy1Ik/jpPi [55]. This has changed over the past few years, after the publication of mature data from the START trial and Canadian trials https://paperpile.com/c/epy1Ik/LtN5+ytnO [56,57]. Combined analysis of these major trials showed that subgroups of patients with younger age, node positivity, as well as those who had had a mastectomy did not have any significant detriment in outcomes with the use of a 3-week hypofractionated course of adjuvant radiotherapy https://paperpile.com/c/epy1Ik/ytnO [57]. Our group subsequently published the results of our institutional experience with the use of hypofractionated radiotherapy in breast cancer. Between 2011 and 2013, 925 consecutive patients with breast cancer received hypofractionated adjuvant radiotherapy to a dose of 40 Gy in 15 fractions over 3 weeks followed by a sequential boost https://paperpile.com/c/epy1Ik/VwZB [14]. Thirty-five per cent of the patients received NACT, whereas nearly a half had undergone a mastectomy. TNBC patients accounted for about 12% of our overall population. Over a median follow-up of 22.9 months, we showed that the overall survival, disease-free survival and locoregional recurrence-free survival were 93, 86.9 and 97.1%, respectively. These outcomes were in line with the results obtained in the previous studies reported. Interestingly, we failed to identify a difference in the local control as per the tumour subtypes https://paperpile.com/c/epy1Ik/VwZB [14]. This was further validated in our recent analysis of the outcomes of 350 patients with TNBC (who had been subtyped based on automated IHC), where we showed that the 5-year overall locoregional recurrence rate was 5.2% https://paperpile.com/c/epy1Ik/pZlD [58].

Similarly, centres like Tata Memorial Hospital, Mumbai, which have adopted hypofractionated radiotherapy later, have also reported outcomes of their patients receiving postmastectomy radiotherapy as compared with a historical cohort who received a more conventional dose of 45 Gy in 20 fractions. This retrospective audit of 549 patients with a median follow-up of 38 months failed to identify any difference in locoregional control (83% versus 84.2%) and overall survival (87% versus 93.5%) in patients receiving hypofractionated radiotherapy following the START schedule https://paperpile.com/c/epy1Ik/fuUs [59]. Similar outcomes in terms of locoregional recurrence rates have been reported in another series of postmastectomy patients receiving hypofractionated radiotherapy from northern India https://paperpile.com/c/epy1Ik/jpPi [55].

The uptake of hypofractionated radiotherapy has increased recently and in a survey conducted in 2016 we found that nearly 20% of the responding institutes ($n = 82$) across India have started using 3-week hypofractionated breast radiotherapy in their routine practice. For a nation like India, with limited access to radiotherapy, use of a 3-week regimen allows treatment of one extra patient for every two patients treated as compared with a conventional 5-week regimen. More importantly, as patients often have to travel far for treatment, this is associated with significant logistical advantages and possibly may be associated with improved compliance https://paperpile.com/c/epy1Ik/sIjI [60].

Standard breast cancer radiotherapy is associated with an increased radiation dose to the heart when left-sided breast cancer radiotherapy is being planned. The UK Heartspare study is a prospective study that is aiming to standardise the adoption of voluntary breath-hold radiotherapy across the UK https://paperpile.com/c/epy1Ik/2vuc [61]. Voluntary breath-hold radiotherapy is, however, implemented non-uniformly in India and needs standardisation. We have adopted a uniform policy of treating all left-sided breast cancer patients with deep-inspiration breath-hold and currently mean cardiac doses of less than 2 Gy are routinely achieved with breath-hold plans. The use

of breath-hold radiotherapy is associated with an increased resource requirement, with an approximate requirement of 7.13 person-hours per patient. However, this increased workload is extremely cost-effective in the Indian setting, as the excess cost incurred to save one DALY due to ischaemic heart disease is INR 20 975, which is only 0.18 times the annual per capita gross domestic product of India https://paperpile.com/c/epy1Ik/KwK5 [50]. These data should spur the utilisation of breath-hold techniques in other Indian centres.

With a high proportion of patients with screen-detected breast cancers, radiotherapy after breast conservation therapy may be omitted in certain select populations of breast cancer, as shown in the PRIME II trial https://paperpile.com/c/epy1Ik/nzh5 [62]. Although the trial failed to meet its primary end point, the overall low risk of recurrence in the population of elderly (70 years or more) breast cancer patients, who were oestrogen receptor positive, node negative and had grade 1–2 disease, may mean that this group of patients can avoid adjuvant radiotherapy. However, in India, patients with breast cancer present almost a decade earlier than in the West and have a higher proportion of grade 3 disease. Thus, fewer patients can avoid radiotherapy. However, this can be discussed with an individual patient when treated in a tertiary cancer centre with a dedicated breast multidisciplinary team.

Frontier Forward

As the above results show, Indian breast cancer patients can achieve good outcomes with standardised multidisciplinary care with quality controlled pathology and appropriate therapy. The key challenges in India are improving access to this kind of quality care and increasing awareness regarding the disease so that early detection is possible. The large pool of technological talent available in India also needs to be tapped and methods to automate diagnostic workflows are sorely needed in order to ensure that standardised evaluation is possible. A small step has been taken in this regard in the automation of the process of Ki-67 reporting using IHC using deep learning. The methodology has shown a precision of 93% for automated scoring of Ki-67 on IHC https://paperpile.com/c/epy1Ik/UJXj [63]. Similar approaches to utilising machine learning in standardising reporting of radiology and pathology will go a long way towards improving access to quality care in India. As Ki-67 testing using IHC is associated with significant variability https://paperpile.com/c/epy1Ik/JOsE [64], such automated scoring techniques have a significant impact in our setting, where centralised testing of specimens is very difficult to achieve. The Tata Medical Center has participated in an international phase III study led by the Royal Marsden Hospital to standardise Ki-67 scoring, which met the pre-specified criteria of success of scoring reproducibility https://paperpile.com/c/epy1Ik/hXqM [65]. Ki-67 scoring results from any centre will need further validation against reference laboratory results with stringent quality assurance procedures. This will require an Indian national consensus and an international collaborative effort.

Research studies that reduce the burden on healthcare need to be encouraged and one of the ways to advance this is to look for treatment measures that can retain or improve efficacy at a reduced cost. Towards this end, a multicentric study is being initiated among four large cancer centres, where a 1-week course of adjuvant radiotherapy will be tested against a 3-week course of radiotherapy (HYPORT Adjuvant, NCT03788213). This large prospective multicentric trial will not only test a 1-week logistically efficient course of radiotherapy similar to the FAST FORWARD trial https://paperpile.com/c/epy1Ik/vpYG [66], but will also enable quality assurance of the radiotherapy treatment process across participating centres https://paperpile.com/c/epy1Ik/wwt2 [67]. This study will be important as most of our patients often present with larger tumours and need regional nodal radiation. Another study of note is the PMRT-NNBC (NCT02992574) study, which is attempting to answer the question if postmastectomy radiotherapy can improve disease-free survival in node-negative breast cancer patients.

Finally, locally advanced breast cancer is a problem that is more common in developing nations and preferably needs home-grown solutions. One exciting way by which control rates can be improved in these tumours is preoperative radiotherapy and one centre in India (Cancer Institute [WIA] Adayar, Chennai) has been practising this treatment modality for several decades. They have reported a case series of more than 1000 patients where neoadjuvant concurrent chemoradiotherapy resulted in a local recurrence rate of only 7% with a 5-year survival of nearly 75% https://paperpile.com/c/epy1Ik/2s4h [68]. Encouraging results following neoadjuvant radiotherapy have been published from the West https://paperpile.com/c/epy1Ik/vGqZ+P8cZ [69,70]. More than seven prospective studies evaluating various strategies of neoadjuvant radiotherapy, of which three are prospective phase II trials, are enrolling or have completed recruitment https://paperpile.com/c/epy1Ik/EBKR [71]. Studies looking at neoadjuvant radiotherapy are needed in the Indian context to appropriately address the poor outcomes associated with locally advanced breast disease.

Conclusion

The management of breast cancers is evolving in India as we come to grips with the increasing burden of this disease. Greater emphasis on awareness and early detection is needed to reduce the burden of mortality. At the same time, emphasis should be placed on standardising pathological testing and reporting so that patients can get appropriate treatment. Standardisation of surgical, radiation and medical oncological approaches is also needed. Innovative and cost-effective solutions using our huge human talent pool should also be investigated. With standardised management, outcomes similar to those seen in the West can be expected.

Interestingly, there seems to be more published breast cancer outcome data available from Eastern countries, like India, and an increase in quality research. However, the breast groups in developed countries like the UK have over the last few decades established a strong collaborative research network. It will be very useful if countries like India could join in collaborative discussion groups and participate in mutually beneficial research.

Conflict of Interest

The authors declare no conflict of interest.

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