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Review Article

Breast cancer: An overview of published Indian data

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Abstract

The Incidence of breast cancer has been steadily increasing in the last two decades, more so in urban areas of the sub-continent. Cancer ceters across the country have large numbers of patients being treated with multiple publications in this field. Inspite of paucity of prospective data and randomised clinical trials from India, there are large number of retrospective publications on various aspects of the disease including pathology, radiology, surgery, chemotherapy, radiation, palliative care and alternatitive treatment modalities. These published data provide an insight into the trends of breast cancer in the country and this comprehensive data review of Indian data will provide a basis for designing trials relevant to our population and planning health care.

Key words: Breast cancer, carcinoma breast, Indian data

Introduction

Epidemiology

For decades together, cervical cancer was the most common cancer in women in India, and more deaths in women in India were attributed to cervical cancer than any other cancer.[1] However, over the last 10 years or so, breast cancer has been rising steadily, and for the first time in 2012, breast cancer was the most common cancer in women in India, a way ahead of cervical cancer.[2] This is partly due to an actual decrease in the incidence of cervical cancer. However, mostly due to a rapid rise in the number of breast cancer cases, the incidence of this disease has been consistently increasing, and it is estimated that it has risen by 50% between 1965 and 1985. The annual percentage change in the incidence ranged from 0.46 to 2.56 for breast cancer. In 2015, there will be an estimated 155,000 new cases of breast cancer and about 76,000 women in India are expected to die of the disease.[3] Breast cancer seems to be more common in the younger age group in India and 52% of all women suffering from breast cancer in Mumbai are between 40 and 49 years of age. A significant number of patients are below 30 years.[4] The population-based registries show a significant rural/urban division in the breast cancer incidence. However hospital based registries may be biased due to varying reference patters/socoieconomic and other factors.

Pathology of Breast Cancer in India: Is Anything Different?

Pathology forms our basis for understanding of a disease like cancer; however, in our country, it is the least reported data that exist in literature.

Are the breast cancers seen in India are different from the Western literature if we ignore the advanced stage at which they present?

Answer is clearly no! However, the proportion of various cancer distributions is different in the Indian continent. Protocols for tumor sampling are often incomplete as economics drives sampling and hence, adequate representation of features such as extensive intraductal component (EIC) and emboli are lacking in many specimens. Some differences are as follows:

1. Tumor grade: An interesting socioeconomic pattern affects the tumor grade in our patient population given the wide economic gap. Thus, while large referral institutes like ours observe 80% of Grade III cancers, in private hospitals, Grade II cancers dominate with equal number of Grade II and Grade III cancers. Grade I tumors form 9.5% to 20% across varying populations in our country with lower incidence in lower socioeconomic status[5]
2. Tumor subtypes 1: Though the subtypes are histologically

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same as seen in the West, an overall paucity of subtypes is seen in our population. Infiltrating lobular carcinomas form 2% to 7% of the total breast cancers and mucinous carcinomas form 2% to 3% of the special types of cancers. Within the mucinous carcinomas, however, the type A or micropapillary variant is more common in our patients versus type B (solid variant of papillary carcinoma). Western literature and this result in more aggressive behavior of mucinous carcinomas of the breast[6-8]

3. Molecular subtypes: In the absence of uniform standardization of basic procedures such as fixation and processing, there is a nonuniform reporting of molecular subtypes of breast cancer. Economics drives testing protocols, hence the results of even HER2/neu testing across states are not uniform. In fact, many labs still report a lower incidence of hormone receptors. The overall hormone receptor positivity in our institute has jumped from 56% to 70% in the past 5 years.[7] Various percentages reported for luminal A – 25–67% and luminal type B vary from 14.8% to 20%. Triple-negative cancers likewise range from 15% to 20%.[6-7] The HER2/neu positivity result also range at a maximum from 16% to 28%.[9-11]
4. Ki-67 testing: Indian context – "As is the West so is the East" policy has resulted in random ordering of Ki-67 across the country without realizing the fact that many of our cancers are high grade. The range of Ki-67 in Grade III cancer ranges from 25% to 100% (unpublished observations). Hence, Ki-67 should be ordered by reviewing the mitotic count within the tumor in Grade III cancers. In addition, such testing should be performed on well-fixed tissues.

Surgical Advances: Indian Experience

Surgery for breast cancer has undergone a paradigm shift over the last few decades, from the early Halstedian era of radical surgery to Fishers' theory of breast cancer being a systemic disease at inception. However, the foundation of locoregional therapy still stands on complete eradication of all malignant cells from the breast and the draining nodal basin.

Breast conservation therapy

The NSABP B-06 study, published in the 1980s, heralded the era of breast conservation surgery.[12] Following those results, the Tata Memorial Hospital (TMH) published their results of women who had undergone breast conservation therapy (BCT) from 1980 to 2000.[13] One thousand twenty-two women with Stage I/II breast cancer underwent BCT (wide excision, complete axillary clearance, whole breast radiotherapy with 6 MV photons plus tumor bed boost, and ± systemic therapy). The 5- and 10-year actuarial overall survival (OS) was 87% and 77% and disease-free survival (DFS) was 76% and 68%, respectively. Actuarial 5-year local and locoregional control rates were 91% and 87%, respectively, with good-to-excellent cosmesis in 78% of the women. Risk factors for local or locoregional recurrence (LRR) were age <40 years, axillary node metastasis, lymphovascular invasion, adjuvant systemic therapy, inner quadrant tumor, and axillary node metastasis. They concluded that compared to the Western literature, Indian women undergoing BCT were younger, had larger tumors of higher grade, and they were of receptor-negative tumors. Furthermore, various reports on the quality of life (QOL) of women undergoing surgery for breast cancer have been published, most of which indicate no significant change in overall QOL immediately after the surgery and a significantly better QOL among women undergoing BCT compared with mastectomy.[14,15]

However, despite these favorable results, BCT is not universally practiced across India due to resource constraints. The need for a preoperative mammography is one of those limitations. Its limited availability in developing countries has discouraged surgeons in rural areas from practicing breast conservation. Nadkarni *et al*.[16] analyzed the database of breast surgeries at their institute to investigate if BCT could be safely performed based on clinical feasibility alone. They reported that of the 735 women who underwent surgery, 38 would have been wrongly planned for BCT based on clinical findings alone. Of those 38, 13 had impalpable mammographic multicentricity and 25 had extensive microcalcifications. They concluded that although mammography cannot be totally excluded from the treatment algorithm for palpable breast cancer, BCT could be offered in clinically suitable cases in the absence of a preoperative mammography, as these lesions can be identified at the time of radiation planning.

In addition to the disparity in the number of women being offered breast conservation, another problem we encounter is patients with incompletely performed mastectomies. Thorat *et al*.[17] addressed this concern by auditing the data of 850 women treated between 2000 and 2003. Women evaluated in this study were treated elsewhere and the surgical intervention was considered incomplete, they underwent revision surgery for the same. Of the 850 patients, 191 (45%) had received incomplete surgical intervention at other centers and 153 underwent completion revision surgery. Complete data were available for 148 patients, of which 123 patients had residual lymph nodes (LNs) in the axilla and 64 patients had metastatic LNs left behind. Similarly, Tewari *et al*.[18] addressed the concern of residual breast tissue in 37 patients of breast cancer undergoing an modified radical mastectomy. A biopsy from under the skin flap at the central point of the four quadrants (upper outer, upper inner, lower inner, and lower outer), 3 cm from the cut margin of the skin, was taken to examine for residual breast tissue. In 8 of the 37 (21.6%) cases, residual breast tissue and in 3 of these cases (37.5%), tumor tissue were found under the skin flap. The possible detrimental impact of inadequate surgical intervention in low-resource settings needs to be addressed.

Peri-operative interventions

Innovative studies addressing the peri-operative window of opportunity have been published based on the differential effect of surgery performed during the two phases of the menstrual cycle. The randomized controlled study published by Badwe *et al*.[19] randomized 976 women with operable breast cancer (OBC) to a single peri operative injection of hydroxy progesterone group versus no hydroxy progesterone.[19] The 5-year DFS and OS rates were not significant in the overall group; however, in 471 node-positive patients, the 5-year DFS and OS rates in the progesterone group versus control group were 65.3% versus 54.7% (hazard ratio [HR]: 0.72; 95% confidence interval [95% CI]: 0.54–0.97; $P = 0.02$) and 75.7% versus 66.8% (HR: 0.70; 95% CI: 0.49–0.99; $P = 0.04$), respectively.

Oncoplasty and whole breast reconstruction

The success of breast conservation is based on the removal of the primary tumor with adequate clear margins and in doing so maintaining the shape and contour of the breast. Achieving both goals together may be limited by the amount of tissue removed relative to the breast size. Oncoplastic surgery (OPS) allows for wide excision for BCS without compromising the natural shape of the breast and is based on the integration of plastic surgery techniques for immediate breast reshaping after wide excision for breast cancer. As the survival for breast cancer patients continues to improve, the future of surgery for breast cancer lies in integrating the principles of OPS into our practice as the focus of care shifts to improving QOL. Several Indian authors[20-22] have reported case series on the safety and esthetic outcome of oncoplastic procedures. The risk factors reported for poor cosmetic outcome were age, volume of breast tissue excised, and estimated percentage of breast volume excised ($P < 0.05$).

Breast-conserving surgery postneoadjuvant chemotherapy

The current level one evidence in support of BCT postneoadjuvant chemotherapy (NACT) is available for OBC only. Almost 30–40% of women in India present with locally advanced breast cancer (LABC). The largest cohort addressing BCT in LABC was published by Parmar *et al*.[23] Of the 664 women analyzed, 71% (469/664) of the women responded to NACT (22% clinical complete response [cCR] and 49% partial response [PR]) and 28.3% (188/664) underwent BCT. At a median follow-up of 30 months, local relapse rate was 8% after BCT and 10.7% after mastectomy. The DFS was superior after BCT, 72% versus 52% ($P < 0.001$) at 3 years and 62% versus 37% ($P < 0.001$) at 5 years, respectively. On multivariate analysis, the presence of lymphatic vascular emboli (LVE) was the major significant predictor of local recurrence ($P < 0.001$, HR: 2.52, 95% CI: 1.52–4.18).

Axillary surgery

Nadkarni *et al*.[24] described a stepwise technique of axillary surgery, using the medial pectoral pedicle as a landmark. This was a systematic approach which allowed us to train beginners more efficiently. Axillary dissection is still the standard treatment in cases of node-positive breast cancer, and it is associated with the morbidity of seroma, pain paresthesias, and lymphedema. Independent predictors for seroma formation are body mass index and extent of axillary dissection. Several Indian institutes have studied various methods to reduce the quantity of seroma,[25-27] ranging from novel techniques of suture flap fixation, use of compression dressing, adjusting the timing of drain removal, type of drain (suction or corrugated), and use of electrocautery or scissor for dissection. Consensus is still lacking among studies as there is conflicting evidence from the different groups.

As in the case of the primary tumor, surgery for the axilla has seen a shift toward more conservative approaches. A study[28] from the TMH reported the concept of low axillary sampling (LAS) compared to sentinel LN biopsy (SLNB) in breast cancer patients with clinically node-negative axilla. Axillary nodal metastases were found in 34.1% of the patients. The false-negative rate of sentinel node biopsy (SNB) (12.7%, 95% CI: 8.1–19.4) and LAS (10.5%, 95% CI: 6.6–16.2) was not significantly different ($P = 0.56$). LAS was found to be as accurate as SNB in predicting axillary LN status in women with clinically node-negative OBC.

Chintamani *et al*.[29] reported a post-NACT SNB validation study in a cohort of thirty women. Post 3 cycles of cyclophosphamide, adriamycin, and 5-flourouracil (CAF), the patients underwent SLNB (using methylene blue dye) followed by complete axillary LN dissection (levels I-III). The SLN identification rate in the present study was 100%. The sensitivity of SLNB was 86.6% while the accuracy was 93.3%. However, the randomized evidence on the same has reported high false-negative rate for SNB postchemotherapy.

Role of surgery in metastatic breast cancer

The role of locoregional treatment (LRT) in women with metastatic breast cancer (MBC) at diagnosis has been a matter of debate for years. The only published randomized controlled trial addressing the issue was done by Badwe *et al*.[30] from the Tata Memorial Centre, Mumbai, Maharashtra, India. Patients with MBC were randomly assigned to receive LRT directed at their primary breast tumor and axillary LNs or no LRT. Median OS was 19.2 months (95% CI: 15.98–22.46) in the LRT group and 20.5 months (16.96–23.98) in the no-LRT group (HR: 1.04, 95% CI: 0.81–1.34; $P = 0.79$), and the corresponding 2-year OS was 41.9% (95% CI: 33.9–49.7) in the LRT group and 43.0% (35.2–50.8) in the no-LRT group. The study concluded that there was no difference in OS. Surgery for the primary in cases of MBC should be reserved for palliating patients with bleeding or fungating tumors.

Indian Data on Radiotherapy

Accelerated partial breast irradiation

The pioneer institute in accelerated partial breast irradiation (APBI) in India is the TMH where APBI using interstitial brachytherapy is routinely offered over the past decade or so (even before the American Society for Radiation Oncology recommendations were published) in highly favorable group of early breast cancer, i.e., tumor size up to 3 cm and absence of adverse radiologic or pathologic features (negative margins, no LVE or EIC, and negative nodes). The first publication in this regard was related to the quality assurance of the procedure. Simulator X-rays, computed tomography (CT) scans, and dosimetric studies were repeated on alternate days in 14 consecutive patients treated with radical intraoperative two- or three-plane nylon catheter of high-dose rate (HDR) implant (34 Gy in 10 fractions within 5 days). A significant variation was found in catheter length, but no major change was noted in implant geometry, homogeneity, or in-homogeneity indexes. Hence, the authors concluded that the catheter fixation and exit catheter length should be measured daily, and if the implant is *in situ* for more than a few days, orthogonal X-rays and if indicated, dosimetry should be repeated at least once.[31] This was followed by a study of dosimetric comparison of conventional radiograph and three-dimensional CT (3DCT)-based planning using dose volume indices, which was done in 18 patients. The study demonstrated the superiority of the 3DCT over the conventional two-dimensional radiograph-based planning in terms of a reduction in normal breast irradiated with the prescription dose and improvement in conformity.[32] The clinical outcome of patients treated with

APBI was compared with patients treated with conventional whole breast radiation using match pair analysis. The median follow-up in the two groups was 43 months and 51 months, respectively. No difference was observed in two groups with respect to OS, DFS, or late sequelae. However, the APBI group had significantly better cosmetic outcome.[33] Similar match pair analysis with respect to QOL studied using EORTC QLQ-C30 and BR23 questionnaire suggested better body image perception and lesser financial difficulties in the APBI group.[34] This was followed by the report on the incidence of fat necrosis in breast cancer patients treated with APBI. At a median follow-up of 48 months, the 5-year actuarial incidence of fat necrosis was 18% with median time of development being 24 months. In this report, the volume of excision was highly correlated with the incidence of fat necrosis.[35] The recent most publication on APBI reports the clinical outcomes of prospectively treated 140 women with 3DCT-based brachytherapy at a median follow-up of 60 months.[36] The median tumor size was 2 cm with Grade III tumors in 82% of the patients. The 5- and 7-year local control rates (LC) were 97% and 92%, respectively. HER2 positivity was the only prognostic factor which had an adverse impact on LC (P = 0.01). The 5- and 7- year DFS and OS were 93%, 84%, 97.5%, and 89%, respectively. Good-to-excellent cosmetic outcomes at last follow-up were seen in 87 (77%) women. Thus, the clinical data on APBI, though nonrandomized, are mature and encouraging both with respect to oncological safety as well as late sequelae and QOL.

Hypofractionated radiotherapy

The mature results of the Manchester shorter fractionation schedule (35 Gy to chest wall [CW] and 40 Gy to axilla and supraclavicular region) were reported at a median follow-up of 67 months in 688 patients (608 received postmastectomy radiation therapy [RT] and 80 did not) treated during 1995–2000 at the Postgraduate Institute of Medical Education and Research, Chandigarh, India. The frequency of LRR with or without distant metastases was 8.5% and distant metastases were seen in 18.7% of the patients. The OS and LC rates were 81% and 94.4%, respectively, at 5 years.[37] The subsequent report evaluated the benefit of postmastectomy RT beyond CW in 293 patients with N1 nodal stage breast cancer treated during 2004–2007.[38] At a median follow-up of 55 months, 260 patients received RT; 212 to CW + supraclavicular field (SCF), 48 to the CW only; and 33 patients did not receive radiotherapy. There was no difference in the DFS (62% vs. 54%) or LRR (5% vs. 8%) between the two groups. However, OS at 5 years was significantly better in the CW + SCF group (88% vs. 76%).

Preliminary report of START-B type of fractionation in 135 patients (both postbreast conservation as well as mastectomy) of all stages (except metastatic) treated during 2011–2012 at the Tata Medical Centre in Eastern India is also encouraging. The acute and late radiotherapy sequelae (skin toxicity, lymphedema, and cosmesis) were clinically acceptable with no incidence of Grade IV toxicity or treatment interruption. Authors conclude that shorter treatment regimens should be encouraged in Indian setting to increase machine output time.[39]

Boost radiotherapy

Tumor bed following whole breast radiation (sequential) which is given in the majority of patients following breast conservation is given commonly with en face electrons, 3D conformal RT (3DCRT), or brachytherapy boost. Interstitial brachytherapy boost as a boost modality was very popular in 1980–1990s due to nonavailability of linear accelerator. The oldest series of 289 patients in early breast cancer from the TMH reported that dose per fraction >2.5 Gy with teletherapy, higher boost dose >20 Gy, and dose rate >100 cGy/h with low dose rate adversely affected cosmesis and contributed to the late complications.[40,41] With the availability of electrons and HDR brachytherapy, the comparison of the boost technique at the TMH reported that the type of tumor bed boost did not have a significant effect on the worsening of cosmetic outcome. However, there were significantly more late breast sequelae in women treated with single fraction HDR implants.[42] The concomitant boost technique, i.e., boost delivered on Saturday (12.5 Gy/5 fractions, n = 30) during the course of conventional whole breast radiotherapy was reported to be safer with respect to toxicity and cosmesis as compared to the cohort treated with sequential boost (15 Gy/6 fractions, n = 32).[43]

A pilot study of 10 patients reported from the JIPMER delivered peri-operative tumor bed boost (during the time of breast conservation surgery) to a dose of 15 Gy in 6 fractions over 3 days which was followed by whole breast RT after 1 week to a dose of 46 Gy in 23 fractions. At a median follow-up of 4.3 years, there was no local recurrence or mortality reported with overall satisfactory cosmetic outcome.[44] A similar small study from PGI of 15 patients reported quality assessment of interstitial implants and concluded that dose nonuniformity ratio and uniformity index best correlate late skin and subcutaneous tissue toxicity.[45]

A randomized trial of 40 patients compared electron boost (8–12 MeV, 15 Gy in 6 fractions) to brachytherapy boost (15 Gy in 3 fractions, 6 h apart) and reported inferior cosmetic outcome with brachytherapy (80% vs. 50%, P = 0.025). Similarly, a recent randomized trial of fifty patients from PGI compared 3DCRT with electrons for delivery of tumor bed boost to a dose of 16 Gy in 8 fractions following 40 Gy in 16 fractions to the whole breast, with respect to dosimetry, acute toxicity, and late sequelae. The authors concluded that 3DCRT boost is a better option than electrons dosimetrically, but results in slightly increased acute skin toxicity leading to treatment interruption. However, in centers where electron beam therapy is not available, 3DCRT photon can be used effectively for tumor bed boost.[46]

Indian Data: Chemotherapy in Breast Cancer

Chemotherapy in breast cancer has evolved rapidly in the last three decades, and Indian experience in this area is well documented. Some of the recent trials and reported series are outlined below. The incidence of LABC seems to be higher in the subcontinent, and most published literature on chemotherapy deals with this clinically relevant subgroup in Indian practice. This is perhaps reflected in the publications from Indian centers with most chemotherapy trials addressing women with LABC. The largest retrospective data have been published by Gupta *et al*. from All India Institute of Medical Sciences,

New Delhi, from a database of 3000 women, of whom 91 were eligible for survival outcomes.[47] Anthracycline-based regimes were used in 54 patients and docetaxel in 37 patients. Most (90%) were T4 tumors and 70% were Stage IIIB. Median numbers of preoperative cycles were six in anthracycline group and three in the docetaxel group. Overall clinical response rates for breast primary were 74.3% and 53.7% (CR: 28.6% vs. 16.7%, $P = 0.58$) while for axilla, overall response rate (ORR) was 75.7% versus 54.8% (CR: 51.4% vs. 40.4%, $P = 0.77$), respectively, for docetaxel and anthracycline groups. Corresponding pathological CR (pCR) rates were 19% versus 13%, respectively. There was no significant difference in DFS (3-year 56.84% vs. 61.16%, $P = 0.80$) and OS (3-year 70% vs. 78.5%, $P = 0.86$) between the two groups in spite of higher pCR. Several other small studies have also reported outcomes of NACT in women with LABC. The response rate in LABC to a single agent weekly paclitaxel regimen was evaluated in a prospective Phase II trial reported by Gupta *et al*. from the TMH.[48] This trial included women with large primaries median T size of 7 cm (2.5–15 cm)/N2-3 disease. The authors reported a pCR of 11.5%, with 23% women becoming eligible for breast conservation surgery after NACT in this group of women with large tumors/extensive nodal burden. The toxicity of the single agent weekly paclitaxel reported has been low, with no incidence of febrile neutropenia and 4% incidence of Grade III/IV peripheral neuropathy. The clinical and pathological response to chemotherapy after 2–6 cycles of anthracycline-based regimens (5-fluorouracil, adriamycin, and cyclophosphamide/5- fluorouracil-epirubicin- cyclophosphamide [FAC/FEC]) in LABC has been reported by Mukherjee *et al*. in a prospective study.[49] cCR was seen in 10% cases (4/40), 30% patients had (12/40) PR and 60% (24/40) had stable disease after NACT. pCR with no evidence of viable tumor was observed in 20% of the patients (8/40). Fifteen patients (37.5%) showed PR and 42.5% patients (17/40) had a stable disease. This study also has detailed descriptions on the histopathological changes after NACT. Both these studies also show significant disparity between clinical and pathological responses to NACT. A larger study evaluating clinical, radiological, and pathological responses published by Mukherjee *et al*. showed higher sensitivity for response evaluation by clinical examination compared to radiological evaluation. The study included 52 evaluable patients with nearly equal use of anthracycline- and taxane-based NACT. Of the 52 patients who completed the evaluation, 26.9% had cCR and 19.2% had pCR. Clinical evaluation had a sensitivity and specificity of 73.5% and 88.5%, respectively, compared to 14.2% and 100%, respectively, for radiological assessment.[49] Another large retrospective study by Raina *et al*. evaluating 128 patients with LABC who were treated with 6 cycles of neo-adjuvant FEC regimen showed that ORR (CR + PR) was 84.4%, cCR was 13.3%, and pCR was 7.8%. Median DFS and OS were 33 and 101 months, respectively. The DFS and OS at 5 years were 41% and 58%, respectively.[50] The impact of addition of taxanes in the adjuvant setting has been an area of research globally, and randomized prospective Phase II trial comparing sequential anthracycline cyclophosphamide (AC) and regimen to anthracycline alone has been reported by Roy *et al*.[51] The authors reported that adding paclitaxel to the AC led to a significant increase in DFS, with HR of 0.295 (95% CI: 0.104–0.835) $P = 0.021$ (<0.05). OS was also significantly improved, with HR of 0.308 (95% CI ratio: 0.103–0.917) $P = 0.034$ (<0.05). A seminal randomized large Phase III publication by Badwe *et al*. has evaluated the impact of "neo-adjuvant" progesterone on breast cancer survival. One thousand patients with OBC were randomly assigned to receive surgery or an intramuscular injection of depot hydroxyprogesterone 500 mg 5–14 days before surgery. Primary and secondary end points were DFS and OS, respectively. At a median follow-up of 65 months among 976 eligible patients, 273 recurrences and 202 deaths were recorded. In the progesterone group versus control group, 5-year DFS and OS rates were 73.9% versus 70.2% (HR: 0.87; 95% CI: 0.68–1.09; $P = 0.23$) and 80.2% versus 78.4% (HR: 0.92; 95% CI: 0.69–1.21; $P = 0.53$), respectively. In 471 node-positive patients, the 5-year DFS and OS rates in the progesterone group versus control group were 65.3% versus 54.7% (HR: 0.72; 95% CI: 0.54–0.97; $P = 0.02$) and 75.7% versus 66.8% (HR: 0.70; 95% CI: 0.49–0.99; $P = 0.04$), respectively. In multivariate analysis, DFS was significantly improved with progesterone in node-positive patients (adjusted HR: 0.71; 95% CI: 0.53–0.95; $P = 0.02$), whereas there was no significant effect in node-negative patients. Although there was no OS improvement for the women randomized to depot progesterone group, the subset of women with LN positive tumors had improvement in DFS and OS.

There has been a considerable concern regarding the toxicity of chemotherapy in Indian women and this has been addressed in many trials. Most trials evaluating NACT have reported no excessive/unexpected toxicities in Indian patients. The rate of cardiac toxicity is reported to be <2%. In the trials that evaluated taxanes, the incidence of hypersensitivity reactions to paclitaxel is approximately 5%. The incidence of paclitaxel-induced neuropathy (all grades) is approximately 10–12% with <2% patients developing Grade III/IV neuropathy. There has been no reported incidence of treatment-related mortality. The tolerance for breast cancer chemotherapy in India does not vary significantly from published results internationally.[47,51] The issue of toxicity has also been specifically addressed in a prospective observational study by Palappallil *et al*., comparing the toxicities of anthracycline alone against a sequential anthracycline and taxane regimen. The patients on the anthracycline regimen (FAC) had significantly higher incidence of anemia and skin/mucosal toxicity including hyperpigmentation/stomatitis ($P < 0.005$). The patients on the sequential chemotherapy regimen (AC followed by paclitaxel) had significantly higher rates of leucopenia, myalgia, arthralgia, and peripheral neuropathy ($P < 0.005$). Although both the regimens had different toxicity profiles, the QOL was better for patients on the AC-P regimen.[52]

Miscellaneous Topics

1. Neo-adjuvant chemo-radiation: A large series of 1117 consecutive cases of LABC treated with concurrent neoadjuvant chemo-radiotherapy protocol at the Cancer Institute (WIA) from South India, between 1990 and 1999 and followed through 2004, has been published.[53] Cyclophosphamide, methotrexate and 5-flourouracil (CMF), or anthracycline-based regimens were randomly used. RT to the CW or breast and ipsilateral supraclavicular region and axilla was delivered to a dose of 40 Gy in 20 fractions. Postoperatively, internal mammary RT was

delivered. Primary tumor downstaging was observed in 45% and nodal downstaging in 57.5%. The DFS rate of nodal downstaged patients at 5, 10, and 15 years was 75%, 65%, and 58%, respectively. The corresponding rates for pre- and post-operative node-negative patients were 70%, 60%, and 59%. The best survival was seen among those who were tumor- and node-negative postoperatively. Nodal downstaging halved the risk of disease recurrence and death compared with node-positivity, irrespective of tumor sterility

2. Influence of double-strand break repair on radiotherapy-induced acute skin reactions: In this study, DNA double-strand breaks and repair were analyzed by microscopic Y-H2AX foci analysis in peripheral lymphocytes from 38 healthy donors and 80 breast cancer patients before RT, a 2 Gy challenge dose of X-ray was exposed *in vitro*. The results suggest that the measurement of percentage residual damage by performing g-H2AX foci analysis has the potential to be developed into a clinically useful predictive assay[54]
3. RT with implanted cardiac pacemaker devices: A clinical and dosimetric analysis of patients and proposed precautions. In this case series of eight patients (three breast cancer) with *in situ* cardiac pacemakers, it was shown that though RT can be safely delivered, it mandates a cautious approach in planning and treatment delivery to ensure the least possible dose to the pacemaker and a close liaison with the cardiologist as well as pacemaker clinic[55]
4. Effectiveness of pranayama on cancer-related fatigue in breast cancer patients undergoing RT: In this trial, patients were randomized to perform pranayama along with RT (n = 80) or only RT with routine care (n = 80). There was a significant benefit of pranayama in reducing the fatigue scores and the authors concluded that pranayama may be utilized as an adjunct in the management of breast cancer patients[56]
5. The use of ayurvedic/Indian native medicine is widely prevalent. The role of ayurvedic compound Maharishi Amrit Kalash (MAK), an ayurvedic compound containing many herbs rich in antioxidants in the reduction of chemotherapy toxicity among women with breast cancer, was reported by Saxena *et al*. The randomized trial evaluated 214 patients with breast carcinoma receiving CMF or CAF, adjuvant or NACT. All patients received the same antiemetic therapy with ondansetron and dexamethasone. MAK demonstrated a significant reduction in chemotherapy-induced nausea and vomiting with improvement in generalized well-being. The treatment did not have a significant detriment in response to chemotherapy.

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Conflicts of interest

There are no conflicts of interest.

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