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Special Report

Consensus on contentious issues relevant for breast cancer management for the Indian scenario: Statements following a multicentre expert group meeting

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Management of breast cancer is multidisciplinary requiring critical analysis of emerging evidence especially with its appropriateness to local practice. A high level expert committee meeting was held to arrive at a consensus on controversial practical breast cancer management policies for Indian patients. Indian experts (n=39) from government and private centres who were part of the breast cancer multidisciplinary group, participated in the consensus meeting. A set of controversial yet practical questions were circulated among the experts at least two weeks in advance of the consensus meeting. International experts from the UK (n=6) also participated in the scientific discussions to add further light on the topics. The experts voted on the practical acceptable management policy for India. Consensus was defined as overwhelming (90-100% concurrence in voting), moderate (70-89% concurrence), low (50-70% concurrence) and non-consensus (<50% concurrence). Fifty eight questions based on pragmatic management strategies were framed and circulated to 39 participants. An overwhelming consensus was received in 51 of the 58 questions. The group considered the available evidence with a view for its practical applicability in Indian patients. This consensus document may aid in shaping breast cancer care for the breast oncology practitioners as well as the policymakers in the country.

Key words Breast cancer - chemotherapy - consensus - controversies - radiotherapy- surgery- targeted therapy

Optimal breast cancer management requires appropriate diagnosis and staging using clinical, imaging and pathological methods. The management plan depends on the extent of tumour burden and biology of the disease. Breast cancer treatment centres globally have standard policies based on available evidence. However, there are various practical challenges in implementing what is considered as gold standard depending on what is perceived as most appropriate by the medical team depending on the clinical, social, economic, geographical and other associated factors which affect access to therapy[1,2]. Standardization and quality assurance (QA) of therapy are the other issues that need to be taken into account. Emerging data, therefore, need to be analysed on a regular basis, to determine applicability for the local population, and important decisions on the cost-benefit ratio need to be taken before a recommendation is made. In addition,

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the mechanisms for basic QA and checks need to be in place within the multidisciplinary teams to ensure safe management policies. An expert team was constituted to discuss and generate consensus on the controversial issues faced in the management of breast cancer. A group of experts from the UK which participated in the development of the UK Consensus Guidelines for Breast Cancer Care, was also available as resource persons.

Consensus statements on breast cancer management included those released internationally by the American Society of Clinical Oncology (ASCO)[3], St. Gallen International Consensus[4], and National Comprehensive Cancer Network (NCCN)[5]. However, regional variations require a national consensus guideline, a good example of which is the document released by the UK team[6]. Indian consensus guidelines have also been developed[7] and recent efforts from the National Cancer Grid[8] have focussed on further enhancement and refinement in the protocol. With evolving evidence, some specific controversial issues emerge and a regional consensus needs to be agreed upon to ensure protocol adherent management. The objective of the present exercise was to achieve a consensus on some of these controversial issues among Indian experts.

Invitations were sent to academic, non-academic, private and public centres in India, where a multidisciplinary team-based breast cancer management approach was followed for breast cancer patients, and pathologists, surgeons, medical oncologists, radiation and clinical oncologists were invited. Controversial topics were summarized and specific areas with uncertainty were highlighted by the organising team at Tata Medical Center, Kolkata. These documents with these details were mailed to all invited experts at least two weeks before the consensus meeting which was planned in August 2019.

Consensus was defined as overwhelming with 90-100 per cent concurrence, 70-89 per cent concurrence was recorded as consensus/moderate consensus, 50-70 per cent as low concurrence and <50 per cent agreement on voting was recorded as non-consensus. The current document summarizes the results of the consensus meeting.

There were 14 experts from the public sector and 25 from the private sector. Six experts from the UK consisting of one surgical oncologist, one pathologist, two medical oncologists and two clinical oncologists acted as external resource experts.

Pathology consensus

The team discussed the need for following appropriate internal and external QA processes to ensure accurate histopathological and immunohistochemistry (IHC) reporting and how appropriate QA among other issues has improved the biological classification of breast cancer. The breast cancer oestrogen receptor (ER) and progesterone

Table I. Controversial areas discussed for breast pathology testing

Statements	Votes for (n=17) (%)	Consensus
Fixation time should be standardized and documented along with the type of IHC-Ab in reports. Specimens should be fixed within 1 h and should be fixed in at least 10 times the volume of 10% neutral-buffered formalin	100	Overwhelming
Biomarker testing should be done on core biopsy specimens - hence core biopsy should be performed as a part of recommended workup for all patients	100	Overwhelming
ER/PR on core need not be repeated unless the core is suboptimal or the tumour morphology is discordant or there are multiple tumours	100	Overwhelming
Reporting of percentage positive staining (>1% is cut-off) and some semi-quantitative method which gives proportion and intensity should be the standard for India	100	Overwhelming
If Ki-67 expression is reported then the laboratory should be encouraged to set up a standardized process for Ki-67 reporting*	100	Overwhelming

*The experts could not reach a consensus on the appropriate cut-off for Indian population. ER, estrogen receptor; PR, progesterone receptor; IHC, immunohistochemistry

receptor (PR) positivity rates reported from India are similar to that reported in Western countries[9]. However, some reports have suggested that triple-negative breast cancers may occur in about 15-20 per cent of the Indian women. These cancers are associated with a younger age at presentation, advanced stage and a higher risk of visceral metastases[10]. Further research is needed to improve the outcomes in this population. The following (Table I) specific areas were discussed and votes were taken to ascertain compliance on the issues.

While consensus was reached on the IHC processes to be followed for ER and PR positivity, a similar consensus was not reached for Ki-67 reporting. This stemmed from the need to implement automatic analysis of Ki-67 staining in IHC as manual methods are associated with significant inter-observer variation. Initial reports suggest that deep-learning techniques may be useful in this area, but these techniques need to be evaluated prospectively[11,12].

Surgical consensus

The surgical discussions focussed on reaching consensus on topics ranging from basic issues like surgical margin requirements to others related to the practical and safe implementation of advanced procedures such as breast oncoplasty, sentinel lymph node biopsy (SLNB) and techniques of marking the tumour bed, especially after oncoplastic breast procedures. The experts appreciated that in the absence of a screening programme, breast cancers in Indian women are more advanced at presentation; hence, the options of treatment for advanced disease like neo-adjuvant chemotherapy (NACT) and mastectomy were discussed. Table II highlights the consensus reached on surgical issues.

The experts acknowledged that the advanced stage at presentation for patients of breast cancer did not necessarily rule out aesthetic and functional considerations when planning surgery. However, caution is indicated in Indian patients before practising de-escalation of surgical treatment as reflected in the lack of consensus on the applicability of SLNB after NACT in patients with clinically node positive disease at presentation. The meta-analysis by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) suggesting poorer locoregional control following NACT was extensively discussed[13]. However, the experts felt outcomes of patients receiving NACT in centres which followed a protocol-based management approach was sufficiently good to mandate continuing the practice[14,15].

While not directly discussed in the meeting, practical concerns regarding adherence to treatment protocol are paramount when selecting patients with locally advanced breast cancer (LABC) for breast conservation[16]. All members agreed that such patients should be offered breast conservation only under a well-defined breast cancer multidisciplinary service (Table II). Furthermore, low axillary sampling may be an alternative to SLNB in resource-constrained settings[17].

Radiation oncology consensus

Several radiation oncology-specific controversial topics were discussed focusing on tailoring radiotherapy as per the risk profile of the disease as well

Table II. Controversial areas discussed for surgical consensus

Statement	Votes for (n=18) (%)	Consensus
In pre-NACT clinically and radiologically node negative patients it is safe and appropriate to do SLNB post chemotherapy	94	Overwhelming
Post-NACT SLNB should only be offered in centres with adequate expertise for upfront SLNB	100	Overwhelming
In patients with cN1 (1-3 nodes) who become cN0 on imaging after NACT, SLNB is not recommended	78	Consensus
Dual technique should be used post-NACT to identify SLNB	100	Overwhelming
Following NACT, three or more nodes should be sampled for SLNB to be considered adequate	100	Overwhelming
Mastectomy is a reasonable option for operable LABC. NACT could also be offered	79	Consensus
If reconstruction is to be done after mastectomy, primary reconstruction is considered as a safe and effective option	100	Overwhelming
Marking the tumour pre-NACT is strongly recommended using clips placed in the centre of the tumour	100	Overwhelming
T3 disease can be offered breast conservation post NACT	100	Overwhelming
cT4 disease BCS post NACT should be offered only under a well-defined multi-disciplinary breast cancer service	100	Overwhelming

NACT, neo-adjuvant chemotherapy; SLNB, sentinel lymph node biopsy; AND, axillary nodal dissection; LABC, locally advanced breast cancer; BCS, breast conservation surgery

as ensuring safer, less morbid radiotherapy treatments. The main topics of discussion were related to tumour bed boost after breast conservation, management of internal mammary nodal (IMN) disease, partial breast irradiation and avoidance of radiotherapy for the selected patients after breast conservation. The results of the discussion are summarized in Table III.

The experts concurred with the available evidence on the necessity of tumour bed boost[18,19] but emphasized that after complex breast surgery, boost cavity delineation was a challenging issue. The use of advanced techniques such as SIB (simultaneous integrated boost) was endorsed by the group members[20]. In contrast, there was a relative lack of consensus on elective irradiation of IMN. The UK team pointed out the evidence from Danish Breast Cancer Cooperative Group (DBCG) studies which was being increasingly used to guide IMN radiation in the UK[21]. The Indian team pointed out the uncertain benefit from the single randomized trial which evaluated IMN radiotherapy[22] as well as the complexity of obtaining quality radiation plans with IMN radiation[23]. Most of the panel members agreed that personalizing radiation therapy as per the risk factors can be done in appropriately selected patients[24,25]. There was a significant emphasis on the need for benchmarking and QA before routine implementation of partial breast irradiation.

Anti-HER2-targeted therapy

The use of HER2-targeted therapy was discussed extensively as significant advances have been made in combining agents and research has been focussed on evaluating resistance mechanisms (Table IV).

Increasing numbers of trastuzumab biosimilars[26,27] and availability of charitable funding have improved access to anti-HER2 therapy[28]. Thus, the experts felt that in the Indian context, one year of adjuvant trastuzumab should remain the standard of care. At the same time, it was acknowledged that abbreviated schedules might be considered on a case by case basis given the emerging evidence[29-32]. For patients who receive abbreviated trastuzumab regimens, it was not felt appropriate to simultaneously de-escalate chemotherapy using non-anthracycline regimens[29].

With the advent of combination neoadjuvant HER2 blockade with pertuzumab and trastuzumab, improved pathological response rates have been reported[33,34]. However, the evidence that this translates into meaningful clinical outcomes is weaker. It was perceived that increased pathological response rates with combination HER2 blockade were a reasonable surrogate for improved long-term disease outcomes.

Given the economic considerations of combination HER2 therapy and limited clinical data on long-term results, patient selection is the key. Patients

Table III. Summary of the consensus on radiation oncology topics

Statement	Votes for (n=10) (%)	Consensus
Tumor bed clip placement should be the standard of care (at least 5 clips-base and radial parenchymal margins) in patients undergoing BCS	100	Overwhelming
It is strongly recommended that the radiation oncologists and the surgical team should agree on the type of oncoplasty and if needed, should communicate between themselves to ensure appropriate coverage of tumour bed	100	Overwhelming
Simultaneous integrated boost is an option for selected cases of early breast cancer	100	Overwhelming
Routine using of staging workup CECT/PET for the detection of IMN was recommended in locally advanced cancer	100	Overwhelming
Prophylactic radiation of IMN in 4 or more positive axillary nodes (N2 disease) is not required	57	Low
Prophylactic radiation of IMN in 1-3 positive axillary nodes (N1 disease), T1/2 tumour is not required	100	Overwhelming
Prophylactic radiation of IMN high-risk node negative (T1/2) disease (LVI +, Grade III, inner quadrant, TNBC) is not required	83	Consensus
Advanced strategies for reducing cardiac doses when treating IMN (DIBH/ABC) should be considered	100	Overwhelming
Partially wide tangents is an acceptable technique for IMN radiation	100	Overwhelming
Initially positive IMN picked up on CT/PET disappearing post systemic therapy, the IMN should be treated	100	Overwhelming
A boost to the IMN should be considered if found positive/radiologically involved	100	Overwhelming
Radiotherapy should be recommended for all patients with invasive breast cancers post-BCS with limited exceptions	100	Overwhelming
There is a subset of elderly patients with low risk, Stage I, favourable biology (ER positive and HER2 negative) who are reliable for follow up who can safely avoid adjuvant RT alone after breast conservation (margin negative) after careful multidisciplinary consensus	100	Overwhelming
Multi-gene profiling is not recommended to determine the omission of adjuvant RT after breast conservation	100	Overwhelming
PBI can be offered outside of a prospective clinical trial	100	Overwhelming
Commissioning PBI should be done only after stringent QA protocol prior to implementation. Stringent dosimetric criteria are needed for safety	100	Overwhelming
Techniques for PBI should be dependent on available expertise and QA processes	100	Overwhelming
10-12 cases annually should be available for the institute where PBI is implemented	100	Overwhelming

BCS, breast conservation surgery; IMN, internal mammary node, DIBH, deep inspiration breath hold, ABC, active breath controller; LVI, lymphovascular invasion; PBI, partial breast irradiation; QA, quality assurance; ER, estrogen receptor, RT, radiotherapy; CECT, contrast-enhanced computed tomography, TNBC, triple negative breast cancer

with LABC, poor clinical response to NACT are the examples of situations where dual HER2 blockade may be offered after discussion of costs and potential benefits with the patient. On the other hand, there is robust evidence[35] of a significant clinical benefit for a switch to TDM-1 in the adjuvant setting for patients with less than pathological complete response after NACT and HER2 therapy: TDM-1 should be offered to all eligible patients in this setting.

Ovarian suppression

Updated results from the SOFT (Suppression of Ovarian Function Trial) and TEXT (Tamoxifen and Exemestane Trial) as well as the Korean study[3,36] suggest a significant and clinically meaningful overall survival advantage with ovarian suppression with tamoxifen. The experts discussed issues like method of ovarian suppression, as well as finer practice points related to follow up of these patients (Table V). Literature suggests that the majority of such patients derive a significant benefit with the addition of limited duration ovarian suppression to tamoxifen regardless of receipt of chemotherapy[37]. However, in the Indian context, the experts felt that surgical oophorectomy was an option given the economic status and lack of robust follow up mechanisms in most centres[28]. Switch to aromatase

Table IV. Summary of consensus statements on anti-HER2 therapy

Statement	Votes for (n=10) (%)	Consensus
One year of (neo)-adjuvant trastuzumab should be a preferred option for eligible patients for HER2-targeted therapy	100	Overwhelming
Six months of adjuvant trastuzumab is a reasonable alternative in some selected patients who experience, or are at a risk of, cardiac toxicity or have low risk disease like ER positive and/or node negative disease	100	Overwhelming
In patients who are planned for 6 months of trastuzumab, anthracycline should be strongly considered as a component of the chemotherapy regimen	100	Overwhelming
All patients eligible for (neo) adjuvant HER2-targeted therapy should at least be offered shorter duration regimens of trastuzumab, which are likely to result in better outcomes compared with no HER2-targeted therapy	100	Overwhelming
Trastuzumab biosimilars can be used in the neoadjuvant and/or adjuvant setting	100	Overwhelming
Dual HER2 blockade is currently not cost-effective in the Indian setting for breast cancer patients undergoing NACT	100	Overwhelming
Dual HER2 blockade is currently not cost-effective in the Indian setting in patients receiving adjuvant chemotherapy	100	Overwhelming
Switch to TDM-1 may be considered in patients who have not undergone pathological CR after chemotherapy with trastuzumab in neoadjuvant setting	100	Overwhelming

ER, estrogen receptor; NACT, neo-adjuvant chemotherapy; CR, complete response; TDM-1, trastuzumab emtansine

Table V. Summary of consensus statements on ovarian suppression

Statement	Votes for (n=11) (%)	Consensus
Ovarian suppression should be offered to most high risk premenopausal patients with ER-positive breast cancer who remain premenopausal	100	Overwhelming
Estradiol and FSH levels should be measured at regular intervals for premenopausal patients who are receiving ovarian suppression using a GnRH analogue when treatment with an aromatase inhibitor is contemplated	100	Overwhelming
All three methods of ovarian suppression are acceptable after discussion of the pros and cons with each patient	100	Overwhelming
Tumours with weak ER and/or PR positive staining (allred 3-5) are less likely to benefit from the addition of ovarian suppression	80	Consensus
Surgical oophorectomy is a safe and cost-effective method of ovarian suppression in Indian women	100	Overwhelming

ER, estrogen receptor, FSH, follicle-stimulating hormone; PR, progesterone receptor; GnRH, gonadotropin-releasing hormone

inhibitors when chemical castration is employed should be done carefully with serial hormonal assays.

Dose dense chemotherapy

Dose intensity is an important modifiable factor impacting control of micrometastatic disease in the curative setting and is largely determined by the selection of chemotherapy regimen. In the interest of maintaining dose intensity, there was a consensus that all planned NACT should be delivered prior to surgery (Table VI). Close monitoring of all such patients during chemotherapy was discussed and agreed upon. While the experts diverged in the kind of evaluation that should be done during monitoring, regular clinical evaluation was stressed upon. Members were in agreement that a mammogram can be considered as a part of response evaluation especially when breast conservation is considered. Members also agreed for early surgery in patients who were non-responders. The panel arrived at a consensus on the choice of chemotherapy regimen in the form of sequential anthracyclines and taxanes which have been shown to be better tolerated[38]. The panel agreed that dose dense chemotherapy regimens with compressed chemotherapy intervals and growth factor supported improve outcomes regardless of biological tumour subtype[39].

Table VI. Summary of consensus statements on the use of dose dense chemotherapy

Statement	Votes for (n=17)	Consensus
Dose dense chemotherapy is a preferred option in patients requiring adjuvant anthracycline-taxane chemotherapy	100	Overwhelming
If neoadjuvant chemotherapy is planned, all planned chemotherapy should preferably be delivered prior to surgery	95	Overwhelming
If neoadjuvant chemotherapy is planned, it is preferable to deliver it in a dose dense schedule	100	Overwhelming
Sequential anthracyclines and taxanes are the preferred regimen	100	Overwhelming
AC or EC for up to 4 cycles given every 14 days with growth factor support is an appropriate component of dose dense regimens	100	Overwhelming
Paclitaxel (175 mg/m^2 every 14 days or 80 mg/m^2 every week) should be considered as appropriate dose dense chemotherapy	100	Overwhelming
Use of appropriate supportive drugs and care is essential for safe administration of dose dense chemotherapy	100	Overwhelming
Dose dense chemotherapy should not be restricted to patients with TNBC	75	Consensus
Toxicity of dose dense chemotherapy versus standard frequency is a significant issue in the Indian scenario	100	Overwhelming
Docetaxel is not suitable for dose escalation or weekly administration	100	Overwhelming
Capecitabine should be considered after dose dense chemotherapy in patients with TNBC who have residual disease in the surgical specimen after NACT	53	Low
There is currently insufficient evidence to routinely include platinum drugs as a component of neoadjuvant chemotherapy in patients with TNBC	93	Overwhelming

TNBC, triple-negative breast cancer; NACT, neo-adjuvant chemotherapy; AC, adriamycin cyclophosphamide; EC, epirubicin cyclophosphamide

Limitations

This expert meeting was a consensus meeting and was not aimed at guidelines development. As a consensus development meeting resource stratification was not considered, though it was a part of the debates. The lack of consensus on several topics considered to be standard of care in the West is reflective of this. Due to time constraints in the meeting many contentious issues like use of positron emission tomography computed tomography (PET-CT) in staging of breast cancer as well management of oligometastatic cancers were not discussed in detail. As this meeting took place in 2019, several recent advances such as use of CDK-4 inhibitors in metastatic and adjuvant settings have not been discussed.

Conclusion

The one and half day meeting was well received by all experts who agreed on the importance of such consensus development meetings and the need for regional consensus. It is believed that this consensus document will serve as a stepping stone for improving quality of service and patient care across centres.

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