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Comparison Of NCCN And ESMO Guidelines In Locally Advanced Breast Cancer And Implications In A Resource-Constrained Healthcare Setting

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IMPORTANCE Locally advanced breast cancer has been associated with poor outcomes in developing countries because of the interplay of multiple factors. The management protocols of this disease are ever evolving. This article aims to compare NCCN and ESMO guidelines regarding the management of locally advanced breast cancer. The articles for comparative review have been taken from PubMed. The article reviews both protocols in domains of diagnosis, primary systemic therapy, surgery, radiotherapy, adjuvant therapy, and surveillance. Moreover, recommendations in special situations of pregnancy, male population, recurrence, and Covid 19 are mentioned. In addition, the applicability of these guidelines in a healthcare setting with limited tools has been analyzed.

KEYWORDS Locally advanced breast cancer. Primary systemic therapy, Neoadjuvant therapy, survival, Management, Epidemiology,

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Review Article

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Locally advanced breast cancer is an entity with evolving knowledge and management protocols. Breast cancer is the most common cancer diagnosed in females and accounts for the second-highest rate of cancer-related mortality in females[1]. Locally advanced breast cancer (LABC) contributes to 20% of cases of breast malignancy. In developing countries, the figures can be as alarming as 75%[2]. It has a five-year survival rate of less than 50%[3]. The rationale of this article was to compare current American and European algorithms for the management of locally advanced breast cancer. As Locally advanced breast cancer cases are on the rise in our region, this analysis would help us in devising management protocols for such patients in our region within the spectrum of available resources.

Locally advanced breast cancer encompasses the malignant tumors located within the breast tissue with locoregional spread. The sub-categories involve non-inflammatory and inflammatory breast cancer. According to AJCC-TNM (American Joint Committee on Cancer Tumor Node Metastasis), locally advanced breast cancer includes stage IIB(T3N0M0), and III. Thus, the spectrum includes:

- Tumors more than 5 cm in size with or without regional lymphadenopathy (N1–3)
- Tumors of any size with direct extension to the chest wall or skin, or both (including ulcer or satellite nodules), regardless of regional lymphadenopathy
- Presence of regional lymphadenopathy (clinically fixed or matted axillary lymph nodes, or any of infraclavicular, supraclavicular, or internal mammary lymphadenopathy) regardless of tumor stage
- Inflammatory breast cancer[4]

AJCC IIB and IIIA are considered operable and IIIB, IIIC are considered inoperable because of decreased chances of achieving Ro resection[5]. The clinical treatment of locally advanced breast cancer is complex and should be individualized[6]. The locally advanced breast cancer remains potentially curable with surgery, radiotherapy, and systemic therapy[7]. There has been an increasing trend towards utilizing primary systemic therapy in non-metastatic breast cancer to achieve control over occult systemic disease, obtain pathological complete response locally and decrease the extent of surgical tumor resection[8].

In the present article, we are reviewing recommendations in the NCCN and ESMO guidelines regarding operable and inoperable locally advanced breast cancer. In addition, we have rationalized the application of these protocols in our setup.

METHODOLOGY

After obtaining prior consent from the Institutional review board, we searched the updated NCCN guidelines version 4.2021 on breast cancer and ABC 5(Advanced Breast Cancer) guidelines from the 5th ESO-ESMO International consensus. In addition, we searched ESMO Clinical practice guidelines for Early breast cancer, locally recurrent and metastatic cancer, cancer, pregnancy and fertility, and 2nd ESO-ESMO International consensus guidelines to look for management options for operable locally advanced breast cancer . We

checked articles relating to the management of locally advanced breast cancer globally and in our region on PubMed to apply recommendations in constrained working situations like ours.

DISCUSSION

NCCN guidelines use categories 1, 2A,2B, and 3. Whereas, ESMO utilizes 5 levels of evidence and I to V and 5 grades of recommendation A to E.

The diagnostic algorithms in both guidelines revolve around the classic triple assessment regime. Genetic counseling is emphasized because 5% of breast cancers have BRCA mutations[9]. The lifetime risk of developing breast cancer in BRCA 1 mutation is 65 to 90%[10]. Both guidelines recommend the AJCC TNM system for clinical and pathological staging. ESMO guidelines include IIB and IIIA inoperable locally advanced breast cancer. NCCN guidelines, despite incorporating the dynamics of IIB, emphasize stage III to be referred to as locally advanced variety with IIIB and IIIC being inoperable ones.

Category	NCCN	ESMO
	History and Physical Exam, Diagnostic Bilateral mammogram, breast, and axillary ultrasound if necessary, with Core biopsy of tumor or lymph node. Pathology review of biopsy tissue with ER, PR, and HER 2 neu status and proliferation/grade. CT Chest, Abdomen +/-pelvis, and Bone scan CBC and a comprehensive metabolic panel including LFTS because of the need for neoadjuvant systemic therapy PET-CT is utilized if there is doubt in the findings of other imaging regimes. Cardiac imaging if chemotherapy is planned	Same recommendations. Emphasis on the categorization of Ki 67 status for luminal type cancers.
Genetic Risk assessment	Recommended in high risk, high probabilities, and family history categories	Endorses NCCN guidelines
Fertility and Sexual Health	Fertility and sexual health counseling mandatory	Same recommendation
Distress management	Required	Special emphasis on psychosocial support
Pregnancy Testing	Mandatory workup in premenopausal women	No clear statement

Table 1: Diagnostic and pretreatment workup

Regarding the pregnant population, both guidelines emphasize going for mammograms with shielding and ultrasound of the breast and axilla. FNA of the lesion is an acceptable option to the standard core biopsy. Ultrasound of abdomen, X-ray chest and CBC with differential and Liver function is undertaken. MRI thoracolumbar spine can be considered in cases of symptoms or equivocal imaging.

Category	NCCN	ESMO
Inoperable locally advanced breast cancer	T4 tumors	III B and IIIC
	N3 nodal disease	
	Bulky or matted N2 Axillary nodes	
	IBC	
Operable Locally Advanced Ca Breast	Large primary tumor relative to breast size in a patient wishing breast conservation	IIB and IIIA
	HER 2 +ve tumors and TNBC, if T>2 or N >1	
	Patients in whom definitive surgery may be delayed	
Monitoring of patient during therapy	Clinical and imaging if indicated	Same recommendation
Progression of disease during therapy	Alternate drug regime or Surgery	Same recommendation
Therapy not recommended in	i) Patients with ill-defined extent invasive carcinoma	No clear statement
	ii) Patients with the poorly delineated extent of tumor	
	iii) Non-palpable or clinically assessable tumors.	

Table 2: Indications of Primary systemic Therapy in LABC

Treatment protocols

Both guidelines endorse primary systemic therapy where possible in locally advanced breast cancer because it has been able to achieve a pathological complete response. This has been associated with extremely favorable disease-free and overall survival in locally advanced breast cancer patients11. In addition, it provides time for genetic testing and planning breast reconstruction. The primary systemic therapy also opens new avenues of research and development of refined management strategies for cancer breast. The chemotherapeutic regimes are similar with anthracyclines and taxanes being the recommended first-

line drugs. The neoadjuvant systemic therapy is the cornerstone in the management of inoperable variety. For the operable variety in which upfront surgery has the highest chances of achieving negative resection margins, decisions to give neoadjuvant systemic therapy should be balanced in terms of achieving breast conservation therapy versus ending up in mastectomy and tumor biology.

Primary Systemic therapy protocols for locally advanced breast cancer: Both guidelines endorse a multi-disciplinary approach for treatment decisions with stringent reviews regarding benefits and risks of a treatment option, patient preference, menopausal and performance status, and assessment of comorbidities. In addition, previous therapies with toxicity profile, disease-free interval, tumor burden, biologic age, socio-economic, psychosocial factors, and available therapies in the patient's country all must be taken into consideration for individualizing treatment protocols. There has been increased stress in both guidelines to deploy aggressive treatment, if permissible, involving radiotherapy and chemotherapy, in high-risk individuals including the young, age < 50, increased tumor burden, T>5 cm and >1 to 3 positive lymph node. lymphovascular invasion, atypical and high-grade histology and with a history of hereditary breast cancer.

These guidelines recommend the placement of detectable clips or markers on the tumor bed and suspicious axillary nodes before starting systemic therapy for cancer. This facilitates localization for future surgery, radiotherapy, and pathology review. Both guidelines endorse sequential chemotherapy with anthracyclines and taxanes and recommend combination therapies for patients with rapid clinical progression, life-threatening visceral metastasis, or the need for rapid symptom/disease control. Luminal B-like with triple-negative HER 2 +ve warrant chemotherapy. Luminal A-type ER+ve has a good overall prognosis and hormonal therapy alone can be given in such cases in absence of high-risk features in selected populations considering co-morbidities. For instance, a 70 to 80-year-old woman with Luminal A variety of locally advanced breast cancer can be given hormonal therapy alone if she cannot tolerate chemotherapy. As most patients are in the advanced stage or high-risk category in both guidelines, chemotherapy is administered to almost all of ER+ve locally advanced breast cancers. Ovarian ablation/ suppression strategies include surgical oophorectomy, ovarian irradiation, and LHRH agonists in both guidelines.

Categories	NCCN	ESMO
HR Positive LABC	Chemotherapy +/- Endocrine therapy. Endocrine therapy may be considered for strong ER-positive disease (at least >10% +ve on IHC) based on comorbidities or low-risk luminal biology based on clinical characteristics and genomic signatures. Endocrine therapy for premenopausal women includes an Aromatase inhibitor with ovarian suppression or Tamoxifen. Aromatase Inhibitor is a preferred option for post-menopausal women.	Chemotherapy with anthracycline- and taxane or endocrine therapy. The choice of Chemotherapy versus endocrine therapy depends on the tumor (grade, biomarker expression) and patient (menopausal status, performance status, com morbidities, preference) considerations. Emphasis is on illustration of Luminal A and B types including Ki 67 status. One of the options is to give endocrine therapy with CDK4/6 inhibitors
Triple-negative LABC	Taxanes (paclitaxel), anthracyclines (doxorubicin and liposomal doxorubicin), anti-metabolites (capecitabine and gemcitabine), microtubule inhibitors (eribulin and vinorelbine), platinum agents are preferred single agents for systemic chemotherapy. Combination chemotherapy regimens containing a platinum agent or a taxane are efficacious in patients with metastatic triple-negative breast cancer but remain controversial. Albumin-bound paclitaxel/carboplatin regimen is the preferred combination.	Chemotherapy with anthracycline- and a taxane. Platinum can be added with taxanes.
HER 2 Positive LABC	Patients with HER2-positive LABC should receive an initial chemotherapy program that incorporates preoperative trastuzumab and pertuzumab	Same recommendation In case of progression on anti-HER2 therapy, a combination of lapatinib with trastuzumab or the addition of TDM-1 is preferred.
Inflammatory LABC	Preoperative systemic chemotherapy with anthracycline and taxane is preferred. HER2-positive tumors can be treated by HER2-targeted therapy. The addition of trastuzumab for up to 1-year duration in systemic chemotherapy may improve the prognosis of HER-2 positive IBC cases. HER-2 positive IBC is more common than HR-positive IBC.	Systemic therapy with anthracycline and taxane with anti-HER2 therapy

Table 3: Primary systemic therapy regimens:

Category	NCCN	ESMO
Surgical options following systemic therapy	Mastectomy + Axillary staging+/- reconstruction Lumpectomy +/-surgical staging axillary staging in case of an initially operable tumor with positive lymph node	Same recommendation
Surgical margins	1mm and no tumor at the inked margin. For DCIS near resection margin, ideally, a 2mm margin is warranted, but the decision should be individualized.	same
After no response to pre-operative therapy	Individualize treatment	Palliative mastectomy not to be done unless surgery will result in an overall improvement in the quality of life of the patient
Axillary dissection	Axillary dissection to level II is recommended, up to level III is only carried out in case of grossly positive level II lymph nodes.	No clear statement

Table 4: Surgical Treatment in Locally Advanced Breast Cancer

Response to therapy is checked after every 2-4 cycles of chemotherapy and 2-4 months of endocrine therapy. This is done by detailed history, examination, and targeted imaging keeping in view the before therapy conducted test.

Recommendations for Surgery: Patients who respond to primary systemic therapy preferably complete therapy and then are planned for breast conservation versus mastectomy with axillary staging + /- reconstruction for non-inflammatory variety. NCCN recommends harvesting at least 10 lymph nodes for accurately staging axilla. Post-mastectomy radiotherapy is recommended in high-risk cases including the ones with involved lymph nodes, >4 positive axillary nodes, T3, T4 tumors. In an inoperable variety, all patients receive whole-breast/chest wall radiotherapy +/- the boost to tumor bed and radiotherapy to supraclavicular, infraclavicular, internal mammary, and axillary nodes at risk. Whereas in operable variety, the ones with positive lymph nodes on pathological TNM necessitate complete radiation protocol. In case of no response to therapy, additional systemic therapy can be considered before individualizing treatment. In the case of Inflammatory breast cancer, mastectomy with level II axillary dissection is a must if a patient responds to neoadjuvant therapy, as is radiotherapy. If the patient does not respond, additional systemic therapy or preoperative radiotherapy is considered. SLNB and breast reconstruction are generally not recommended in IBC patients.

ADJUVANT THERAPY PROTOCOLS

In both guidelines, if a preoperative chemotherapy course is given and not complete, it is administered first. Chemotherapy regimens are given generally before radiotherapy. NCCN recommends 21 gene RT -PCR assay to assess prognosis if a patient is a candidate for chemotherapy by tumor >0.5 cm and 1-3 positive nodes, to assess for prognosis.

Even the patients with favorable histologies end up receiving chemotherapy. Endocrine and chemotherapy are always given sequentially with endocrine therapy following chemotherapy. Endocrine and anti-HER2 medication can be given concurrently with radiation. The decisions are balanced in terms of progress-free survival and overall survival data. The addition of anti-HER2 therapy takes the pathologic complete response rate to 65 %12.

Category	NCCN	ESMO
HR +ve/HER2 -ve	Endocrine therapy. For Premenopausal: Tamoxifen for 5 y+/-ovarian suppression/ablation or an Aromatase inhibitor for 5 year+ ovarian suppression or ablation. If a patient becomes post-menopausal, an additional 5 years of Aromatase inhibitor or Tamoxifen can be given For Post-menopausal: Can be administered Aromatase inhibitor and Tamoxifen for 2-6 years with different regimes and then again to complete 5 or 10 years of endocrine therapy	Endocrine therapy with and without CDK4/6 inhibitors. Everolimus is an option as well in combination Could be AI, Tamoxifen with and without ovarian suppression/ablation, and fulvestrant.
HR-ve/HER2 +ve	Ado-trastuzumab alone for 14 cycles. Administer trastuzumab+/-pertuzumab for one year if toxicity develops to ado.	Continue anti-HER 2 for one year
HR+ve/HER2+ve	Endocrine therapy+ complete one year of trastuzumab+/-pertuzumab	Endocrine therapy + anti-HER2 therapy as maintenance or first-line therapy
HR-ve/HER2-ve	Consider 6-8 cycles of capecitabine	Carboplatin can be added to the regime.

Table 5: Adjuvant Therapy Recommendations

NCCN guidelines give a detailed elaboration of surveillance protocols whereas ESMO guidelines emphasize the important points.

Category	NCCN	ESMO
	History and physical exam 1-4 times per year as clinically appropriate for 5 years, then annually	Medical visits every 3 to 4 months for 2 years, every 6-8 months for the next 3-5 years, then annually
	Periodic screening for family history changes and genetic testing indications	
	Educate, monitor, and refer for lymphedema	
	Mammography every 12 months	Mammography recommended annually
	Routine imaging of reconstructed breast not required	Same recommendation
	Serial echocardiography for patients on anthracyclines-and Anti HER2 neu therapy	
	Screening for metastasis in presence of signs and symptoms	same
	Assess and encourage adherence to adjuvant endocrine therapy	same
	Annual gynecologic assessment of patients on Tamoxifen	
	Patients on an Aromatase inhibitor or who experience ovarian failure secondary to treatment need monitoring of bone health with bone mineral density determination periodically	Bone health monitoring recommended
	Active Lifestyle, healthy diet, limited alcohol intake, and maintaining ideal body weight 20-25 BMI recommended	Same
	Survivorship programs	
	Engagement of patients	
		HRT should not be used

Table 6: Surveillance Recommendations

LABC in Males: Male breast cancer constitute 1% of the disease burden[13]. The recommendations for men with breast cancer have mostly been derived from clinical trials from women. The management protocols are overall similar to the ones for women with breast cancer in both guidelines. Anthracyclines are recommended chemotherapeutic guidelines. Special emphasis has been put forth on adjuvant endocrine therapy as most of these cancers are ER +ve, especially in a recurrent setting where primary systemic therapy is of paramount importance. Surveillance patterns are similar whereby annual ipsilateral mammograms for lumpectomy and contralateral mammograms for mastectomy may be deployed. Fertility counseling, sexual and psychosocial health are dealt with in the same way as women.

	NCCN	ESMO
	The increased emphasis now on breast conservation as compared to traditional mastectomy. Ongoing Research domain	
	Indications for SLNB, ALND, radiotherapy, chemotherapy remain the same	
	21 gene assay score for prognostic information	
	Tamoxifen for 5 -10 years. If it is contraindicated, Aromatase inhibitor with a GnRH analog. Single-agent Aromatase inhibitor not recommended	Tamoxifen preferred option. For AI administration, GnRH analog or orchidectomy is preferred. Single-agent Aromatase inhibitor may be considered with close monitoring of response
	Bone density assessment at baseline and every 2 years for men on GnRH analogs	
	Fulvestrant alone can be used	
	CDK4/6 inhibitors, in combination with AI or Fulvestrant, mTOR inhibitors, and PIK3CA inhibitors may be used as an option as can be PARP inhibitors and immunotherapy	

Table 7: Management of LABC Male Breast Cancer

LABC in pregnancy: Most breast tumors during pregnancy are diagnosed at a locally advanced stage and are ER, PR-ve and around 30% are HER2 +ve14. The decision of terminating or continuing pregnancy should be made after detailed discussions with the patient. SLNB is individualized, should be done without blue dye, and according to NCCN, not recommended for the population under 30 weeks gestation.

Category	NCCN	ESMO
Primary systemic therapy	Chemotherapy not in the first trimester, after 35 weeks gestation, and within 3 weeks of planned delivery. Anthracycline and alkylating agent therapy.	Same recommendation except stopping chemotherapy after 33 weeks of gestation
	Endocrine therapy and radiotherapy contraindicated	same
	Anti-HER2 therapy in the postpartum period	same
Surgery	Recommended in all trimesters	Recommended in all trimesters, slightly increased fetal risk in the first trimester

Table 8: LABC during Pregnancy

Recurrent LABC: Workup for recurrent disease is the same as of locally advanced disease itself with a specification of biopsy of first recurrence and evaluation of ER/PR and HER2 status to differentiate recurrence from new primary. Both guidelines endorse comprehensive germline and somatic profiling, including BRCA, PIK3CA in HR-positive, and PDL-1 in TNBC to identify candidates for additional targeted therapies including PARP inhibitors and Tyrosine kinase inhibitors.

Local regional recurrence after a disease-free interval of 24 months and a complete excision predicts long-term survival. Systemic therapy including chemotherapy and Tamoxifen is recommended after complete excision. Approximately 30% of node-negative and 70% of node-positive breast cancers relapse[15].

Category	NCCN	ESMO
After Lumpectomy	Same recommendation	Mastectomy
After Mastectomy without radiotherapy	Same recommendation	Complete excision+ locoregional radiotherapy
After Mastectomy+ radiotherapy	Surgical resection. The decision of radiotherapy to be balanced between any prior radiation to the area and risk of late normal toxicity from radiation	Complete excision+ re-irradiation to limited areas
Inoperable tumor	Same recommendation	Primary systemic therapy first and the rest follow.

Table 8: Recurrent LABC

NCCN guidelines recommend surgical resection and radiotherapy for axillary recurrence and radiotherapy for supraclavicular and internal mammary recurrence. ESMO guidelines further recommend carefully decided pseudo adjuvant/secondary endocrine, chemo, and anti-HER2 therapy after surgery in selected patients due to the availability of low-quality data. Primary systemic therapy in such patients, with alternate regimes being ineffective or disease progression, will be with endocrine therapy (up to 3 cycles), anti HER 2 therapy as required with chemotherapy preferably for extensive visceral involvement. NCCN recommends similar protocols to previous treatment with emphasis on taxane-based regimes if not used previously, biosimilars for anti-HER2 therapy. Both guidelines encourage the use of other modalities including capecitabine, vinorelbine, and margetuximab

Sequential therapy is recommended but combination regimes can be used in case of high tumor burden, rapidly progressing disease, and visceral crisis. Patients with BRCA mutations are recommended for PARP inhibitors in triple-negative variety in both guidelines. In the case of previously treated disease, platinum-based therapy is recommended in BRCA. Both guidelines advise Alpelisib and fulvestrant in previously treated HR+ve/HER2 -ve lesions. PD L1 entities are treated with Atezolizumab. ESMO recommends against the use of NTRK fusion and MSI-H/d MMR treatment whereas NCCN endorses them when no alternate satisfactory treatment is available. The addition of targeted therapy to chemotherapy increases rates of pathologic complete response which is a predictor of disease-free and overall survival[16].

LABC AND COVID 19

ESMO guidelines endorse locally advanced breast cancer on a high priority list and emphasis is on neoadjuvant therapy with special emphasis on planned lesser hospital visits and oral therapy whenever possible. NCCN has the statement that Cancer won't wait and neither should you, resume screening and treatment of cancer.

Locally Advanced Breast cancer in a resource-limited set up: There are three important aspects to be taken into account regarding managing locally advanced breast cancer in a resource-limited setting

- Therapeutic modalities available
- Financial costs implicated
- Patient preferences

As regards to diagnostic challenges, there must be a fine balance between imaging modalities to pick the lesions and spread of cancer. In addition, PET-CT is not a realistic option in our setup in most situations in the public sector.

The modality of breast conservation therapy and SLNB, although a wonderful tool for many years now, remains a

challenge in our setup, based on the costs involved and detailed follow-up required in a high-volume overwhelmed healthcare setup. In our private sector, it is an excellent option. On the contrary, in the public sector, combined decision-making by patients and doctors to opt for mastectomy rather than breast conservation therapy is a sensible option. This is strengthened by the fact that poor survival outcomes have been reported in locally advanced breast cancer in our region[17].

Systemic chemotherapy, both before and after surgery, has not been able to show significant differences in long-term outcomes[18]. It has improved surgical outcomes when given preoperatively[19]. So in a limited setting like ours, clinical decision making with the experts in locally advanced breast cancers, in achieving upfront negative surgical margins, followed by adjuvant therapy can have a huge impact on the dynamics of the burdened healthcare system. In addition, patients with inflammatory breast cancer; contributing 7-10% of breast cancer-related mortality, can deservingly get primary systemic therapy[20]. This again emphasizes the dire need of making national guidelines for managing these patients within the resource framework.

Advanced breast cancer has reported median overall survival of 2-3 years. What to speak of survival rates in a population with a prevalence of around over 60 %[21]. The probable reason for more cases presenting in a locally advanced stage is multiple including ignorance of disease and screening pathways, the social stigma of being caught by cancer, and hesitancy of getting a checkup from a male-driven health care system. In addition, the use of unconventional therapies is quite common[22]. The situation has worsened because of Covid 19. It is the need of the hour to run empowered national-level education programs involving social, electronic, and print media aimed at developing preventing protocols and diagnosing breast cancer earlier to decrease morbidity and mortality in this patient group.

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