National Guidelines for the Management of Early and Locally Advanced Breast Cancer in Sri Lanka

National Cancer Control Programme
Ministry of Health
Sri Lanka

NATIONAL GUIDELINES FOR THE MANAGEMENT OF EARLY AND LOCALLY ADVANCED BREAST CANCER IN SRI LANKA

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Ministry of Health

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Message from the Director General of Health Services

Breast cancer is the commonest cancer among women, in Sri Lanka as well as worldwide. The incidence of Breast cancer increases yearly, making it a public health burden. Early detection and early treatment is important in breast cancer, as it has good survival rates. Therefore, it is important to initiate the national strategies in early detection of breast cancer and also establish proper treatment pathways for the diagnosed breast cancer patients.

The National Cancer Control Programme, as the focal point of the national response on prevention and control of cancer, has initiated and developed the "National Guidelines for the Management of Early and Locally Advanced Breast Cancer in Sri Lanka". This guideline would provide evidence based recommendations in treatment and would improve the quality of care received by the breast cancer patients. The enhancement of early detection and diagnosis of breast cancer by the Ministry of Health, through the establishment of breast clinics at tertiary care institutions island-wide would be further boosted by this guideline, improving the survival of the breast cancer patients.

It is my utmost pleasure to wish the National Cancer Control Programme for initiating the development and publishing this worthy guideline. Finally, I would like to thank the Director and the team of National Cancer Control Programme for their strong commitment to initiating, developing and publishing this guideline, the Sri Lanka College of Oncologist and international reviewers for their technical support, the World Health Organization for their invaluable partnership and all other stakeholders who contributed for the successful completion of this worthy cause. I would also like to acknowledge the Sri Lanka College of Oncologists for their technical contribution, the World Health Organization for their partnership and all other stakeholders who contributed to the successful completion of this important activity.

I would like to thank the Director and the team at National Cancer Control Programme for their strong commitment to initiating, developing and publishing this guideline.

Dr. Asela Gunawardena
Director General of Health Services
Ministry of Health

Message from the Deputy Director General, Non-Communicable Diseases

The goal of the National Strategic Plan (2020-2024) of the National Cancer Control Programme (NCCP) is to reduce the incidence of preventable cancers, to detect early detectable cancers at an early stage and to provide a continuum of cancer care to all cancer patients in the country in an equitable manner. The diagnosis and treatment of cancer is considered as one of the key components in the National Strategic Plan.

Breast cancer is the most common cancer among women in Sri Lanka. According to the estimates, 24% of all newly diagnosed cancers among women, are breast cancers. If detected early and treated properly and promptly Breast cancer has a good survival rate. Therefore, it is important to have a proper treatment pathway, to go hand in hand with the screening and early detection. By developing the "National Guidelines for the Management of Early and Locally Advanced Breast Cancer in Sri Lanka" the National Cancer Control Programme aims to fulfill the above gap, which would improve the quality of care as well as the survival of the breast cancer patients.

I am happy to see that the NCCP has taken necessary steps in spearheading strategies to prevent and control breast cancer in Sri Lanka and to achieve the national targets. I would like to thank the Director and the Diagnosis and Treatment Unit of the National Cancer Control Programme, the Sri Lanka College of Oncologists, international reviewers, the World Health Organization and all other stakeholders for their contribution in developing this guideline.

Dr Champika Wickramasinghe
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Deputy Director General, Non-Communicable Diseases
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Message from the Director

The National Strategic Plan on Prevention and Control of Cancer in Sri Lanka (2020-2024) identified the development of management guidelines of common cancers as a strategic priority. It is with great pleasure that National Cancer Control Programme presents the "National Guidelines for the Management of Early and Locally Advanced Breast Cancer in Sri Lanka". This national guideline is developed with the aim of guiding decisions and criteria regarding diagnosis, management, and treatment of breast cancer to help achieve maximum clinical effectiveness, cost-effectiveness and to reduce unwarranted variation and maintain the quality of care provided.

The National Strategic Plan on Prevention and Control of Cancer in Sri Lanka (2020-2024) identified the development of management guidelines of common cancers as a strategic priority. This will achieve to obtain maximum clinical effectiveness and cost-effectiveness. I hope this guideline will serve during the delivering appropriate care and reducing unwarranted variation and maintain the quality of care.

This guideline has been developed by a multi-disciplinary team of technical experts to provide best possible options for the Sri Lankan patients, to improve their survival and quality of life. The National Cancer Control Programme appreciate the experts of the Guideline Development Technical Committee including the international reviewers, Professor Charloette E. Coles, Professor of Clinical Oncology, University of Cambridge, UK. Dr. Udaiveer Panwar, Consultant Clinical Oncologist, University Hospitals Plymouth NHS Trust, UK, for their continuous and enthusiastic efforts to make this guideline a reality. The National Cancer Control programme sincerely thank the College of Oncologists, Association of Onco-Surgeons, College of Surgeons, College of Radiologists, College of Pathologists for their technical contribution. I would also like to thank the World Health Organization for their partnership in completing this endeavor.

Finally, I would like to thank the Diagnosis and Treatment Unit of the National Cancer Control Programme for coordinating this activity and I hope this guideline will serve to optimize diagnosis, management and treatment of cancer in Sri Lanka.

Dr. Janaki Vidanapathirana
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Director
National Cancer Control Programme

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- Sri Lanka College of Oncologists
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- Association of Onco-surgeons
- College of Surgeons of Sri Lanka
- College of Pathologists of Sri Lanka
- World Health Organization

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CHAPTER 1

INTRODUCTION

The incidence of breast cancer in Sri Lanka is rising with nearly 3000 women being diagnosed each year[1]. A large retrospective analysis revealed that nearly 14% of patients had de novo metastases at presentation while another 18% had locally advanced disease[2]. While the reported five-year disease-free survival of 71.6% in patients with localised disease was satisfactory breast conservation surgery rates stood at a dismal 4%, even though nearly 24% of patients had stage I disease[2]. These data highlight the urgent need for better patient education, more effective early detection and screening initiatives as well as streamlining patient care pathways.

The objective of this guideline is to provide evidenced based, pragmatic recommendations that would improve the quality of care delivered to women with early and locally advanced breast cancer in Sri Lanka.

CHAPTER 2

DIAGNOSTIC WORK-UP AND STAGING

The triple assessment of clinical examination, imaging and histopathology remains the cornerstone of the diagnostic work-up in patients suspected to have breast cancer.

2.1 Clinical Evaluation

A full description of the clinical evaluation of patients suspected to have breast cancer is beyond the scope of this guideline, and we will focus on some salient aspects:

A full history should be obtained noting in particular: breast and axillary lumps, nipple discharge, symptoms suggestive of metastatic disease, family history, menstrual history and comorbidities such as cardiac, hepatic and renal dysfunction.

A complete general examination and an examination of the breasts, axillae and supraclavicular fossae should be performed and the tumour should be staged according to American Joint Committee on Cancer staging Tumour (T) Node (N) Metastases (M) system 8th edition[3].

Key Recommendations

The triple assessment of clinical examination, imaging and histopathology remains the cornerstone of the diagnostic work-up in patients suspected to have breast cancer.

A full history should be obtained, and a complete general examination and an examination of the breasts, axillae and supraclavicular fossae should be performed and the tumour should be staged according to the American Joint Committee on Cancer staging system.

2.2 Imaging

All patients with suspected breast cancer should undergo bilateral mammography and ultrasonography before pathological evaluation. Ultrasonography is widely available in almost all hospitals where surgery for breast cancer is performed. Mammography provides important information by further characterizing the extent of clinically evident breast lesions and by detection of clinically occult breast lesions both in the ipsilateral and contralateral breasts.

Due to resource limitations, currently there are practical difficulties in obtaining timely access to mammography prior to pathological confirmation and definitive surgery. However, it is of pivotal importance that mammographic and ultrasound imaging be performed prior to biopsy.

As a practical measure to overcome these delays, we recommend performing an ultrasound scan of bilateral breasts as the initial imaging investigation. We further recommend that referral pathways be established in hospitals without mammography units to the nearest hospitals with such facilities.

Radiology departments should prioritise patients with suspicious clinical and/or ultrasonographic evidence of malignancy when scheduling mammographic appointments to enable this investigation to be completed before biopsy. It is incumbent on the Ministry of Health to take urgent steps to expand diagnostic mammography facilities in the country.

If obtaining access to mammography within 2 weeks is not practicable, it is acceptable to proceed with ultrasound guided core biopsy. However, mammography should be performed before definitive surgery.

European guidelines recommend placement of surgical clips during biopsy in patients with a high suspicion of cancer and we would encourage this practice in our setting as well[3]. In patients in whom neoadjuvant chemotherapy with a view to facilitating breast conservation surgery is being offered, placement of surgical clips under ultrasound guidance is strongly recommended[3].

Magnetic resonance imaging of the breast is recommended in patients with lobular carcinoma, inconclusive findings on ultrasound and mammography, and in patients planned for treatment with neoadjuvant chemotherapy with a view to facilitating breast conservation surgery[3].

However, we recognise that access to magnetic resonance imaging of the breast is very limited and confined to few tertiary care hospitals in the country. We therefore would limit its use to patients with inconclusive findings on ultrasound and mammography, especially in patients less than 40 years of age.

Key Recommendations

All patients with suspected breast cancer should undergo bilateral mammography and ultrasonography before pathological evaluation.

As a practical measure to overcome delays, we recommend performing an ultrasound scan of bilateral breasts as the initial imaging investigation. Patients with a clinical and radiological suspicion of malignancy should be referred to the nearest radiology unit with facilities to perform a mammogram.

Magnetic resonance imaging of the breast is recommended in patients with inconclusive findings on ultrasound and mammography.

2.3 Pathology

Pathological confirmation of malignancy can be achieved with either fine needle aspiration cytology or core needle biopsy.

For the primary breast tumour, we recommend that a core needle biopsy be performed for histological confirmation of the primary breast tumour since it enables confirmation of invasive disease and provides tissue for assessment of immunohistochemical biomarkers[4]. Either fine needle aspiration biopsy or core needle biopsy could be performed in the clinically or radiologically suspicious lymph nodes.

We strongly discourage performing excision biopsy unless at least two attempts at guided core needle biopsy failed to yield a confirmatory diagnosis. At least 2 cores should be obtained and in patients with suspected multifocal disease all lesions should be biopsied as far as possible.

While it is good practice to perform core needle biopsy of breast lesions and fine needle cytology of axillary lymph nodes under ultrasound guidance, it is certainly appropriate to perform these tests without image guidance in patients with clinically palpable masses.

With increasing use of neoadjuvant chemotherapy, immunohistochemistry provides vital information which is pivotal to deciding subsequent management decisions. Therefore, apart from confirming malignancy and assessment of histological type and grade, immunohistochemistry (IHC) for Oestrogen Receptor (ER), Progesterone Receptor (PR), Her2/Neu overexpression (Her2) and the proliferation marker Ki67 should be performed in all core biopsy samples with invasive cancer.

Currently, for assessment of IHC for ER and PR the Allred score is used in Sri Lanka, with a score of 3 or more defined as positive. However, the American Society of Clinical Oncology (ASCO) / College of American Pathologists (CAP) updated guidelines of 2019 defines positivity as immunoreactivity of 1% or more tumour cells, with samples staining 1-10% being reported as “low positive” [5]. We recommend mentioning the Allred score in the histopathology report, but in line with the ASCO/CAP guidelines we recommend reporting ER/PR status as follows:

- Immunoreactivity in less than 1 % of tumour cells: Negative
- Immunoreactivity 1%-10% of tumour cells : Low positive
- Immunoreactivity in 10% or more tumours cells: Positive

For testing and scoring of Her2 overexpression by IHC, we recommend following the ASCO/CAP updated guidelines published in 2018 as summarized below[6]:

- IHC 3+ (Positive): Circumferential stating that is complete, intense and in more than 10% of tumour cells
- IHC 2+ (Equivocal): Weak to moderate complete staining that is observed in more than 10% of tumour cells
- IHC 1+ (Negative): Incomplete membrane stating that is weak or faint and observed in more than 10% of tumour cells
- IHC 0 (Negative): No staining or Incomplete membrane stating that is weak or faint and observed in less than 10% of tumour cells

Testing for gene amplification using in-situ hybridization (ISH) techniques for detection of HER2 gene amplification is recommended for patients with equivocal Her2 overexpression on IHC. A positive result is indicated by a HER2/Chromosome 17 Centromere (CEP17) ratio of equal or more than 2 and average HER2 signal per cell of 4 or more. For patients with equivocal results on ISH we recommend performing additional work up as suggested by the ASCO/CAP guidelines[6].

ISH testing is currently not available in the state sector and this investigation can only be performed elsewhere if patients can afford its cost. Until ISH testing is available in the state sector, we recommend that a mechanism be established for this investigation to be performed outside of the state sector at free cost to the patient.

For Ki67 we suggest considering <10% as low risk, 10-20% as intermediate risk and >20% as high risk as recommended by the European guidelines[6].

Based on the IHC profile, which is a surrogate marker for intrinsic tumour types, patients should be categorized as follows:

- Luminal A: ER+ PR+ Her2- Ki67 Low
- Luminal B Her 2 Negative: ER+ PR- Her2- or ER+ PR+ Her2- and High Ki67
- Luminal B Her 2 Positive: ER+ Her2+ Any PR Any Ki67
- Her2 Positive (non-luminal): ER- PR- Her2+ Any Ki67
- Triple Negative: ER- PR- Her2- Any Ki67

Since there is some evidence of benefit with adjuvant endocrine therapy in patients with ductal carcinoma-insitu (DCIS) we recommend performing IHC for ER and PR, in addition to other IHC markers needed for confirmation of DCIS3. IHC for Her2/neu overexpression in DCIS is not recommended, as there is no role for Her2 directed therapy in this setting.

Key Recommendations

Core needle biopsy of suspicious breast lesions and either fine needle cytology or core needle biopsy of suspicious axillary lymph nodes should be performed preferably under image guidance. At least 2 cores should be obtained and in patients with suspected multifocal disease all lesions should be biopsied as far as possible.

In patients in whom neoadjuvant chemotherapy with a view to facilitating breast conservation surgery is being offered, placement of surgical clips under ultrasound guidance is strongly recommended.

Performing excision biopsy is strongly discouraged unless at least two attempts at core needle biopsy failed to yield a confirmatory diagnosis.

Immunohistochemistry (IHC) for Oestrogen Receptor (ER), Progesterone Receptor (PR), Her2/Neu overexpression (Her2) and the proliferation marker Ki67 should be performed in all core biopsy samples with invasive cancer. IHC for ER, PR and Her2 should be reported according to the ASCO/CAP guidelines.

Testing for gene amplification using in-situ hybridization (ISH) techniques for detection of Her2 gene amplification is recommended for patients with equivocal Her2 overexpression on IHC.

ISH testing is currently not available in the state sector and this investigation can only be performed elsewhere if patients can afford its cost. Until ISH testing is available in the state sector, we recommend that a mechanism be established for this investigation to be performed outside of the state sector at free cost to the patient.

For Ki67 we suggest considering <10% as low risk, 10-20% as intermediate risk and >20% as high risk.

Patients should be categorized into Luminal A, Luminal B Her 2 Negative, Luminal B Her2 Positive, Her2 Positive (non-luminal) and Triple Negative based on the IHC profile.

Clinical pathways should strive to ensure that a complete diagnosis including immunohistochemistry profile is available within 6 weeks of the first consultation.

2.4 Staging

Routine staging is recommended only in patients with locally advanced disease (T3, T4 or N2 disease) and in those with symptoms suggestive of metastatic disease[3]. In patients for whom staging is deemed necessary we recommend a computed tomography scan of the chest and abdomen and bone scintigraphy.

Key Recommendations

Routine staging (computed tomography scan of the chest and abdomen and bone scintigraphy) is recommended in patients with locally advanced disease (T3, T4 or N2 disease) and in other patients with symptoms suggestive of metastatic disease.

2.5 Other Investigations

We recommend performing a complete blood count, liver and renal profile, serum calcium and alkaline phosphatase levels and an echocardiography. We do not recommend performing the tumour marker CA 15.3, as it has no proven value in early or locally advanced breast cancer.

2.6 Recommended timelines for diagnostic workup

The following timelines are recommended only as a guide to ensure timely diagnosis and initiation of treatment. However, we appreciate that for reasons beyond their control, clinicians may not be able to ensure compliance with these targets in some instances. It is incumbent upon the Ministry and the National Cancer Control Programme to provide necessary logistical support to ensure that these targets could be met in actual practice.

Clinical pathways should strive to ensure that a complete diagnosis including immunohistochemistry profile is available within 6 weeks of the first clinic visit.

Time to first Specialist Consultation	Next available clinic (within 1 week)
Imaging: Ultrasonography	2 weeks from date of request (in patients of high clinical suspicion of malignancy)
Imaging: Mammography	2 weeks from date of request (in patients with high suspicion on clinical and ultrasonic evidence)
Imaging: Staging	2 weeks from date of request
Core needle Biopsy (CNB)	1 week after ultrasonography and mammography
Histopathology Reporting (initial)	2 weeks after CNB
Immunohistochemistry of CNB	3 weeks after CNB

CHAPTER 3

TREATMENT

The management of early breast cancer is ideally delivered by a multidisciplinary team of specialists with support from medical and nursing staff. Surgical treatment of breast cancer is performed in secondary and tertiary care hospitals throughout the country. Clinical Oncologists have now been appointed to 25 centres covering almost every district in the country. Multi-disciplinary team meetings are now functional in most of these centres and should be encouraged

We recommend discussing every new diagnosis of breast cancer in a multidisciplinary meeting comprising surgeons, clinical oncologists, radiologists, and pathologists. We further recommend that such meetings be held every week to ensure timely decision making.

For patients undergoing breast cancer surgery in hospitals without an oncology unit, we recommend discussing these cases at the MDT meeting in the closest hospital with an oncology unit.

At the MDT meeting the following decisions need to be made in relation to local and systemic treatment.

- Upfront surgery or neoadjuvant chemotherapy (NAC) followed by surgery
- Type of breast surgery (Mastectomy or Breast Conservation Surgery [BCS])
- Treatment of the Axilla (Sentinel Lymph Node biopsy or Limited Axillary Sampling or Axillary Clearance)
- Adjuvant Radiotherapy and Systemic Therapy

Key Recommendations

We recommend discussing every new diagnosis of breast cancer in a multidisciplinary meeting comprising surgeons, clinical oncologists, radiologists, and pathologists.

3.2 Upfront Surgery vs Neoadjuvant Chemotherapy (NAC) followed by surgery

The decision of upfront surgery or NAC followed by surgery needs to be individualized to each patient based on a consideration of the following factors:

- Stage of the tumour
- Tumour biology
- Intended Primary treatment (wide local excision or mastectomy)
- Intended treatment of the axilla (sentinel node biopsy or axillary clearance)

Neoadjuvant chemotherapy is indicated in patients presenting with either T4 disease (including inflammatory breast cancer) or N2 or more nodal disease regardless of tumour biology. In these patients, breast conservation surgery or mastectomy along with standard axillary clearance is recommended depending on the response to NAC.

In patients with T1-3 N0-1 tumours, the benefit of NAC lies in downstaging the primary tumour to facilitate breast conservation surgery in addition to the ascertaining prognosis by pathological response. HER2 Positive and some triple negative tumours have an excellent response to NAC. In addition, escalation strategies in both these tumour groups (T-DM1 and Neratinib in HER2 positive tumours and capecitabine in triple negative tumours) have shown improvements in survival of patients with residual tumour following NAC.

Therefore, many international guidelines recommend considering NAC in most patients with HER2 positive and triple negative tumours[3]. However, despite a strong biology rationale, there is no robust evidence to suggest that NAC results in a superior survival in comparison to adjuvant chemotherapy in early breast cancer.

For patients with T1 N0 disease, we recommend upfront surgery regardless of tumour biology as these tumours are often eminently resectable with breast conservation surgery. Given their excellent prognosis it is unlikely that any strategy of escalation even in patients with residual tumour following NAC would be of tangible benefit in these patients.

We recommend proceeding with upfront surgery (either breast conservation or mastectomy) in patients with ER+ Her2- T1-T2 N1 and T3 N0-1 tumours as the response to NAC is poor in these tumours.

For patients with T1-T2 N1 and T3 N0-1 tumours which are HER2 positive or triple negative we recommend considering NAC as a strategy of facilitating breast conservation surgery. The surgical management of these patients should be wide local excision followed by standard axillary clearance after completing NAC. Due to lack of evidence and experience we recommend against performing sentinel node biopsy in patients who become clinically and radiologically node negative after NAC.

For patients with T2 N0 tumours which are HER2 positive or triple negative, we recommend considering the merits of NAC and its impact on the treatment of the axilla on an individual basis. Sentinel node biopsy (see under treatment of axilla) after NAC in patients with clinically and radiologically node negative tumours is another bone of contention, with some studies showing higher rates of false negativity. An alternative approach in these patients is to perform sentinel node biopsy prior to NAC.

While international guidelines recommend performing sentinel node biopsy after completion of NAC in cN0 patients, there is both a lack of experience as well as a dearth of robust evidence to support this in our setting. As such we recommend either performing sentinel lymph node biopsy before chemotherapy in patients with cT2N0 tumours receiving NAC or axillary clearance after completion of NAC. Post NAC sentinel node biopsy for these patients should be undertaken with caution.

If mastectomy is decided as the surgical treatment in patients with T1-T3 N0-N1 tumours, the benefit of NAC is limited to the prognostic value of its pathological response and subsequent treatment escalation if residual tumour is present.

As mentioned previously placement of surgical clips under ultrasound guidance is mandatory prior to neoadjuvant chemotherapy if it is undertaken with a view to downstaging the tumour for breast conservation surgery.

Key Recommendations

Neoadjuvant chemotherapy (NAC) is indicated in patients presenting with either T4 disease (including inflammatory breast cancer) or N2 or more nodal disease regardless of tumour biology. In these patients, breast conservation surgery or mastectomy along with standard axillary clearance is recommended depending on the response to NAC.

For patients with T1 N0 disease, we recommend upfront surgery regardless of tumour biology as these tumours are often eminently resectable with breast conservation surgery.

For patients with T1-T2 N1 and T3 N0-1 tumours which are HER2 positive or triple negative we recommend considering NAC as a strategy of facilitating breast conservation surgery. The surgical management of these patients should be wide local excision followed by standard axillary clearance after completing NAC.

For patients with T2 N0 tumours which are HER2 positive or triple negative, we recommend considering the merits of NAC and its impact on the treatment of the axilla on an individual basis. If these patients are treated with NAC, we recommend performing a sentinel node biopsy prior to NAC or a standard axillary clearance after NAC. Post NAC sentinel node biopsy should be undertaken with caution.

Patients with ER+ Her2- T1-T2 N1 and T3 N0-1 tumours should proceed with upfront surgery since response to NAC is poor.

Placement of surgical clips under ultrasound guidance is mandatory prior to NAC if it is undertaken with a view to facilitating breast conservation surgery.

3.3. Mastectomy versus Breast Conservation Surgery

Surgery is the primary treatment of early breast cancer and the two alternatives are either mastectomy or breast conservation with wide local excision followed by adjuvant whole breast radiotherapy. Various mammo-plastic procedures are becoming increasingly popular and has enabled performing breast conservation surgery with good cosmetic effects.

There is robust data, both from large randomized clinical trials with over 20 years follow-up and from population-based registry studies that BCS is in clinical equipoise with Mastectomy in terms of Breast Cancer Specific Survival (BCSS) and Overall Survival (OS)[7,8]. Indeed, there is a substantial volume of evidence from large registry data that both BCSS and OS might be inferior in patients treated with mastectomy in comparison to patients treated with a breast conservation approach[9,10]. European guidelines recommend cautioning patients who opt for mastectomy instead of breast conservation that both OS and BCSS may be inferior, and we endorse this recommendation in our setting[3].

Unfortunately, breast conservation rates remain low in Sri Lanka and a retrospective audit of more than 200 patients treated with mastectomy revealed that as much as 70% of cases may have been suitable for breast conservation[2,11].

Contraindications for breast conservation is the presence of multicentric disease, inflammatory breast cancer or large tumour size relative to breast volume and factors that preclude adjuvant radiotherapy such as previous radiotherapy to the chest. We recommend that breast conservation surgery with wide local excision be offered as the preferred surgical treatment option to most patients with early breast cancer in the absence of these contra-indications.

Although whole breast radiotherapy is mandated after conservative surgery, it can now be delivered with a treatment regimen as short as one week. Clinicians should be mindful of overstating its adverse effects as it is well-tolerated with minimal side effects such as skin erythema and mild fatigue.

We recommend that the following information be given to patients who are suitable for breast conservation surgery.

- Breast Conservation Surgery is at least as equal to mastectomy in terms of OS and BCSS
- OS and BCSS of patients treated with mastectomy may be inferior to BCS
- Patients treated with BCS have a better long-term quality of life and functional outcome.

In patients undergoing breast conservation surgery for invasive cancer, absence of tumour (invasive cancer and DCIS) at the inked margin is sufficient. In patients with a positive inked

margin, we recommend performing re-excision. For patients with DCIS and no invasive cancer a wider margin of 2mm is required and we recommend re-excision in cases where the tumour is within 2mm of the inked margin. In patients with DCIS and/or invasive cancer with inadequate margins after two attempts at excision, we recommend offering mastectomy.

All patients treated with mastectomy should be offered breast reconstruction which could be either immediate or delayed. There is an increasing trend to offer immediate reconstruction as this has a better psychological impact on the patient. A full discussion on reconstructive surgery is beyond the scope of these guidelines but essentially reconstruction can be performed using autologous tissue (lattismus dorsi muscle or trasversus abdominus muscle among others) or implants. If post mastectomy radiotherapy is likely to be indicated, autologous tissue-based reconstruction has a superior outcome and can be performed at the time of mastectomy.

Key Recommendations

The primary treatment of non-metastatic breast cancer is surgery with either breast conservation surgery (BCS) or mastectomy.

Contraindications to BCS are multicentric disease, T4 primary tumour (including inflammatory breast cancer), large tumour relative to breast volume and contraindications for adjuvant whole breast radiotherapy.

We recommend BCS as the treatment of choice for all early breast cancer patients without contraindications to it.

We recommend that the following information be given to patients who are suitable for breast conservation surgery:

- BCS has equal or possibly superior survival to mastectomy
- Patients treated with BCS have a better long-term quality of life and functional outcome.

In patients undergoing BCS invasive cancer, absence of tumour (invasive cancer and DCIS) at the inked margin is sufficient. In patients with a positive inked margin, we recommend performing re-excision. If margins are still positive after two attempts at excision we recommend offering mastectomy.

All patients treated with mastectomy should be offered breast reconstruction

3.4 Treatment of the Axilla

All patients with invasive cancer need an assessment of the axillary lymph node status as spread to axillary lymph nodes is one of the most important prognostic factors in early breast cancer. However, the therapeutic value of axillary nodal dissection is questionable especially in patients with micrometastases or limited macrometastases[12,13,14,15].

Nearly 15% of patients undergoing axillary clearance may develop lymphoedema which has a significant detrimental impact on the quality of life. Sentinel lymph node biopsy allows determination of axillary lymph node spread with substantially lower rates of lymphoeodema (<10%).

3.4.1 Sentinel lymph node biopsy

Following the landmark trial by Veronesi et al sentinel lymph node biopsy replaced axillary clearance in patients with early breast cancer and negative lymph nodes after triple assessment[12]. In this trial patients with negative sentinel lymph nodes did not undergo further axillary surgery while patients with positive lymph nodes underwent axillary nodal clearance.

Subsequently the International Breast Cancer Study Group Trial 23–01 demonstrated that patients with micrometastastic (<2 mm) deposits in the sentinel nodes can be safely spared an axillary nodal clearance with no difference in survival[13]. The American College of Surgeons Oncology Group Z0011 trial showed that axillary dissection can also be omitted in patients T1-T2 invasive and with less than three 3 macrometastases on sentinel node biopsy[14]. In this trial all patients were treated with breast conservation surgery and received adjuvant radiotherapy. Interestingly, upon review of the radiotherapy fields it was observed that about half of patients in both arms received high tangential fields, where the superior border reached within 2cm of the humeral head[15]. Most patients in this trial were more than 50 years of age with predominantly T1 primary tumours that were grade 1-2, ER+ and Her2-. Therefore, UK guidelines recommend not proceeding with axillary clearance in patients with 1-2 macrometastases only if all of the above criteria are fulfilled[16].

Sentinel lymph nodes can be identified using methylene blue dye, radiopharmaceutical tracer or a combination of the two[17]. While the combined technique facilitates quicker identification of sentinel lymph node, the dye technique alone can be used successfully in centres without nuclear medicine facilities[17].

For patients with tumours less than 5cm and clinically and radiologically negative axillary nodes we recommend performing a sentinel lymph node biopsy using either methylene blue dye, radiopharmaceutical tracer or a combination of the two. We recommend intraoperative assessment of sentinel lymph nodes using either imprint cytology, cytology smears or frozen section. However if intraoperative assessment is not feasible it is acceptable to proceed with conventional histological assessment as an axillary clearance would only be indicated in patients with three or more macrometastases.

We recommend against performing sentinel lymph node biopsy in patients with cytologically or pathologically confirmed axillary lymph nodes and in patients with negative lymph nodes but with tumours which are more than 5cm in size. These patients should undergo a standard axillary nodal clearance.

While Sentinel lymph node biopsy can generally be omitted in patients with DCIS treated with breast conservation surgery. It is indicated in patients with DCIS undergoing mastectomy as well as in patients treated with lumpectomy for upper outer quadrant tumours as these procedures will change the original draining patterns, and a subsequent sentinel node biopsy cannot be performed if histopathology indicates invasive cancer.

In patients in whom a sentinel lymph node biopsy is performed, axillary clearance should be performed if there are:

- Three or more macrometastases (>2mm)
- Macrometastases with extra-nodal extension
- One or more macrometastases if one of the following criteria are met:
    - Age is less than 50 years
    - The primary tumour is treated with mastectomy
    - ER negative or HER2 positive tumour
    - Grade III tumour
    - tumour size is more than 2cm

We recommend not proceeding with axillary dissection in patients with negative lymph nodes, isolated tumour cells (<0.2mm) or micrometastases (<2mm) only. In patients with macrometastases (2mm or more), axillary clearance can be avoided in patients being treated with breast conservation and adjuvant radiotherapy if the number of involved nodes is less than three with no extra-nodal extension.

3.4.2 Axillary Nodal Sampling

If sentinel node biopsy is not feasible another alternative is axillary nodal sampling where the surgeon removes a small number of nodes (typically four) that can be felt. A Cochrane review of axillary nodal sampling versus axillary nodal clearance revealed that there was no difference in overall survival and locoregional recurrence[18].

In centres without facilities for sentinel node biopsy we recommend axillary nodal sampling in patients with clinically and radiologically negative axillary lymph nodes.

3.4.3 Axillary Lymph node clearance

We recommend performing a level I and II axillary lymph node clearance for patients with tumours more than 5cm in size, locally advanced disease, previous breast or axillary surgery or clinically and radiologically positive lymph nodes and for patients with three or more macrometastases or extranodal extension on sentinel lymph node biopsy. Axillary dissection should harvest a minimum of ten lymph nodes.

Key Recommendations

For patients with cT1-2 N0 tumours, we recommend performing a sentinel lymph node biopsy (SLNB) using either methylene blue dye, radiopharmaceutical tracer or a combination of the two. We recommend Intra-operative assessment of sentinel lymph nodes using either imprint cytology, cytology smears or frozen section. SLNB should be performed with caution in patients treated with neoadjuvant chemotherapy as experience is limited in our setting.

In patients in whom SLNB is performed, axillary clearance should be performed if there are three or more macrometastases (>2mm) and any macrometastases with extra-nodal extension. In patients with 1-2 macrometastases, axillary clearance would need to be performed if any of the following criteria are met: the treatment of the primary tumour is mastectomy, grade III tumour, tumour size is more than 2cm, ER negative or Her2 positive on IHC.

If performing SLNB is not feasible we recommend performing axillary nodal sampling as an alternative in patients cT1-2 N0 tumours.

Axillary clearance is recommended in all patients with cT3 or higher primary tumours as well as those with cN1 or higher axillary nodal stage. Standard axillary clearance includes dissection of levels I and II and should harvest a minimum of 10 lymph nodes.

3.5 Adjuvant Radiotherapy

3.5.1 Adjuvant radiotherapy after breast conservation

Adjuvant whole breast radiotherapy is indicated in all patients treated with breast conservation surgery. A meta-analysis of ten trials showed that the addition of adjuvant radiotherapy reduces the risk of local recurrence by nearly 70% and breast cancer specific survival by 16% in patients treated with breast conservation surgery[19].

The PRIME II trial in the United Kingdom investigated whether radiotherapy could be safely omitted in patients with low-risk early breast cancer[20]. Patients over 65 years of age and low risk tumours (ER+ Grades 1-2, Size <3 cm) were randomized to adjuvant whole breast radiotherapy versus no radiotherapy following lumpectomy. In this trial while the addition of radiotherapy significantly reduced the risk of local recurrence, the absolute difference was only 2.8% (4.1% vs 1.3%) and there was no difference in overall survival (93.9% in both groups)[20]. Based on these results United Kingdom National Institute for Health and Care Excellence (NICE) guidelines on breast cancer recommends clinicians to consider omitting whole breast radiotherapy in this group of patients.

We recommend offering whole breast radiotherapy to all patients with invasive cancer or DCIS treated with breast conservation surgery. Clinicians could consider not offering whole breast radiotherapy in patients above 65 years who meet the following criteria after full explanation of risks and benefits: DCIS, T1 or T2 tumours less than 3cm, node negative and ER+ PR+ Her2-, grade 1-2, and are willing to take endocrine treatment for 5 years.

Key Recommendations

We recommend offering whole breast radiotherapy to all patients with invasive cancer or DCIS treated with breast conservation surgery. Clinicians could consider not offering whole breast radiotherapy in patients above 65 years who meet the following criteria after full explanation of risks and benefits: DCIS, T1 or T2 tumours less than 3cm, node negative and ER+ PR+ Her2, Grade 1-2 and are willing to take endocrine treatment for 5 years.

3.5.2 Post-mastectomy adjuvant radiotherapy

Adjuvant post-mastectomy radiotherapy (PMRT) reduces the risk of local recurrence and breast cancer specific mortality in patients with node positive disease and in patients with node-negative T3 or T4 invasive cancer[19,21.]

The 2014 meta-analysis by the Early Breast Cancer Trialists' Collaborative Group showed that this benefit persists in patients with 1-3 positive lymph nodes[22]. However, with the advent of sentinel lymph node biopsy, the benefit of PMRT in patients with T1-2 tumours with 1-3 lymph nodes particularly those with micrometastases is uncertain[23]. The SUPREMO trial will reveal the benefit of PMRT in patients intermediate risk factors for local recurrence (1-3 involved axillary lymph nodes, T2 invasive cancer with lymphovascular invasion or Grade III tumours)[24].

We recommend adjuvant PMRT in patients with T3 or T4 invasive cancer or 4 or more involved axillary lymph nodes and in patients with 1-3 involved lymph nodes with macrometastases. PMRT is also recommended in patients with positive margins.

We recommend weighing the risks and benefit and offering PMRT in patients with 1-3 involved lymph nodes with micrometastases. In the absence of proven efficacy, we recommend not offering PMRT for patients with T1 or T2 N0 invasive cancer.

Key Recommendations

Adjuvant Post mastectomy radiotherapy (PMRT) is recommended in patients with T3 or T4 invasive cancer or 4 or more involved axillary lymph nodes and in patients with 1-3 involved lymph nodes with macrometastases. PMRT is also recommended in patients with positive margins. PMRT could be considered in patients with 1-3 involved lymph nodes with micrometastases. PMRT should not be offered for patients with pT1-2 N0 invasive cancer.

3.5.3 Dose of radiotherapy

There is robust evidence to support non-inferiority for moderately hypofractionated radiotherapy regimens of adjuvant whole breast radiotherapy and PMRT. Following the START B trial 40 Gy in 15 fractions over 3 weeks became standard of care in many countries[25].

The Recently published results of the FAST FORWARD trial conducted in the UK showed equivalence with a one week regimen of 26 Gy in 5 fractions with 40 Gy in 15 both in terms of tumour control and toxicity[26]. In this trial most patients were node negative although patients with N1 disease were included. Boost to tumour bed was permitted for patients receiving whole breast radiotherapy following breast conservation, but patients offered supraclavicular or axillary nodal radiotherapy were excluded. Following the results of this trial, 26 Gy in 5 fractions has replaced 40 Gy in 15 fractions for patients receiving adjuvant whole breast and PMRT without nodal irradiation[27,28].

A substudy of this trial opened for patients with T1-T3 N1-N3a tumours treated with adjuvant whole breast radiotherapy or PMRT along with supraclavicular and/or axillary radiotherapy. The primary end-point will be normal tissue toxicity (arm swelling). Patients offered internal mammary node radiotherapy were excluded. With only five functional linear accelerators in the country, the one-week fractionation regimen permits thrice the number of patients to be treated in comparison with a three week regimen.

We recommend 26 Gy in 5 fractions for patients treated with adjuvant whole breast radiotherapy and PMRT in whom nodal irradiation is not considered. For patients requiring nodal irradiation we recommend treating to a dose of 40 Gy in 15 fraction over three weeks.

Key Recommendations

26 Gy in Five fractions over one week is recommended for patients offered adjuvant whole breast radiotherapy or post-mastectomy radiotherapy in whom nodal irradiation is not considered. 40 Gy in 15 fractions over three weeks is recommended for patients receiving nodal radiotherapy.

3.5.4 Treatment Volume

3.5.4.1 Partial Breast Irradiation versus Whole Breast Irradiation in patients treated with breast conservation surgery

The IMPORT LOW trial in the United Kingdom, investigated partial breast irradiation in comparison to conventional whole breast irradiation in patients above 50 years with T1-T2 (less than 3cm) N0-N1 tumours who underwent lumpectomy (with margins >2mm)[29]. In the partial breast irradiation group, the clinical target volume comprised the tumour bed plus a 1.5 cm margin with an additional 1cm margin for the Planning Target Volume[29]. Both groups were treated to a dose of 40 Gy in 15 fractions over three weeks using forward planned intensity modulated radiotherapy with medial and lateral tangential fields[29]. There was no difference in local, regional or distant relapse between the whole breast and partial breast irradiation groups with superior breast appearance and fibrosis in the partial breast irradiation group[29].

Since locoregional control and cancer specific and overall survival is equal to whole breast radiotherapy we recommend considering offering partial breast irradiation for patients meeting the inclusion criteria of the IMPORT LOW trial[29]. This technique is easily deliverable in centres with linear accelerators in our country. Although the IMPORT LOW trial used the three week 40 Gy in 15 fraction regimen, following the results of the FAST FORWARD trial we consider it appropriate to use the 26Gy in 5 fractions for partial breast irradiation as supported by international guidelines[27,28].

Patients with lobular cancer were excluded from the IMPORT LOW trial and a subsequent protocol amendment also excluded patients with grade 3 tumours and those with pN1 nodal stage[29]. In addition, more than 90% of patients did not have lymphovascular invasion while nodal radiotherapy and tumour bed boost were not permitted in this trial[29]. We therefore recommend considering partial breast irradiation in all patients treated with BCS and are above 50 years of age who fulfill the following criteria: Treatment is delivered in a linear accelerator, invasive ducatal carcinoma, stage is pT1-2 N0, tumour size is less than 3cm, margins are more than 1mm, grade 1-2, lymphovascular invasion is absent, tumour bed boost and nodal radiotherapy is not offered.

Key Recommendations

Partial breast irradiation should be considered in all patients treated with BCS and are above 50 years of age who fulfill the following criteria: treatment is delivered in a linear accelerator, invasive ductal carcinoma, tumour stage is pT1-2 N0, tumour size is less than 3cm, margins are more than 1mm, grade 1-2, lymphovascular invasion is absent, tumour bed boost and nodal radiotherapy is not offered. We recommend a dose of 26 Gy in 5 five fractions over one week in this setting.

3.5.4.2 Tumour bed boost in patients treated with breast conservation surgery

The results of the European Organisation for Research 33and Treatment in Cancer (EORTC) boost trial confirmed a reduction in local relapse with no difference in survival in patients stage I and II early breast cancer treated with adjuvant whole breast radiotherapy and a tumour bed boost following breast conservation surgery. The effect was greatest in patients younger than 50 years of age and high grade tumours (20 year local relapse rate 9% versus 38%)[30,31].

We recommend delivering tumour bed boost of either 12 Gy in 4 fractions (2 Gy equivalent dose of 16 Gy) following adjuvant whole breast radiotherapy for patients treated with BCS and are aged 50 or less or having a grade III tumour. A simultaneous integrated tumour bed boost of 48 Gy in 15 fractions can also be considered in patients being offered adjuvant radiotherapy to a dose of 40 Gy in 15 fractions to the whole breast (example: patients requiring nodal radiotherapy).

Key Recommendations

Tumour bed boost of 12 Gy in 4 fractions (2 Gy equivalent dose of 16 Gy) following adjuvant whole breast radiotherapy should be considered in patients treated with breast conservation surgery and are aged 50 or less or with a grade III tumour. A simultaneous integrated tumour bed boost of 48 Gy in 15 fractions can also be considered in patients being offered adjuvant radiotherapy to a dose of 40 Gy in 15 fractions to the whole breast

3.5.4.3 Regional Nodal radiotherapy

Trials of PMRT included chest wall, supraclavicular and internal mammary lymph nodes in the treatment volume[22]. Two large randomised trials investigated the benefit of regional nodal irradiation (supraclavicular and internal mammary nodes) in early breast cancer - the Canadian MA.20 trial of patients treated with breast conservation surgery and the EORTC trial which included patients treated with both breast conservation and mastectomy[32,33]. In both these trials nodal radiotherapy resulted in an improvement in disease free survival with no improvement in overall survival over chest wall or whole breast radiotherapy.

The benefit of internal mammary node (IMN) irradiation was shown in the Danish Breast Cancer Group cohort study where IMN radiotherapy improved overall survival and breast cancer specific mortality[34]. In this study the effect was mainly seen in patients with T3 tumours and more than 4 lymph involved lymph nodes.

We recommend supraclavicular nodal radiotherapy in patients with pT4 or pN2 or higher nodal stage and for all patients with N1 disease receiving adjuvant radiotherapy.

We recommend considering IMN radiotherapy for patients with pT4 tumours or pN2 or higher nodal stage and for patients with medial tumours and pN1 nodal stage in patients being treated in the linear accelerator. For patients with left sided tumours implementation of cardiac sparing techniques is mandatory with IMN radiotherapy.

Key Recommendations

Offer Supraclavicular nodal radiotherapy to all patients with pT4 or pN2 or higher nodal stage. Consider Supraclavicular nodal radiotherapy in patients with pT1-3 tumours and pN1 nodal stage receiving adjuvant radiotherapy.

Consider Internal mammary radiotherapy for all patients with pT4 tumours or pN2 or higher nodal stage and for patients with medial tumours and pN1 nodal stage, if treated in a linear accelerator.

3.5.4.4 Cardiac Sparing

Ischaemic heart disease is a recognised complication of adjuvant radiotherapy to the breast, particularly in left sided tumours and a large population-based study showed a linear relationship (with no threshold dose) between mean heart dose and risk of late cardiac events[35]. While it is still unclear which cardiac substructures are most sensitive to the effects of radiotherapy, the left anterior descending artery has been identified as a particularly susceptible target[36]. Cardiac sparing assumes great importance in patients with left sided tumours in which the internal mammary lymph nodes are also included in the treatment volume.

In left-sided tumours which are in the upper quadrants, conformal shielding of the heart can be safely undertaken without compromising dose to the tumour bed. In patients with tumours in the lower half several techniques that move the heart away from the radiotherapy field have been described such as prone irradiation and deep inspiration breath hold with active breathing coordinator. However, these techniques require additional equipment to implement[36].

A novel technique, known as "voluntary deep inspiratory breath-hold", which requires no additional equipment was investigated in the HEARTSPARE study conducted in the United Kingdom[36]. This study showed dosimetric equivalence with the more expensive deep-inspiratory breath-hold with the active breathing coordinator. This technique can be implemented in our radiotherapy departments with linear accelerators.

Key Recommendations

We recommend implementing cardiac sparing techniques in patients with left sided cancers receiving treatment in the linear accelerator. For patients with upper half tumours conformal shielding of the heart is recommended while for patients with lower half tumours we recommend cardiac sparing using the voluntary deep inspiratory breath hold technique.

3.6 Systemic Treatment

3.6.1 Risk stratification

Invasive breast cancer is considered a systemic disease from its very outset as shown by the NSABP B04 trial which predated adjuvant systemic treatment[37]. This study compared radical mastectomy with total mastectomy and radiotherapy. No systemic treatment was delivered to patients in this trial. Nearly 30-40% of patients developed distant metastasis[37]. Apart from preventing distant metastasis, there is good evidence that systemic treatment will also improve local control[38]. The decision on adjuvant systemic treatment should be made on a consideration of the patient's absolute risk of disease recurrence, benefit of treatment and risk of toxicitiy in each individual patient. We recommend using the NHS "Predict" (https://breast.predict.nhs.uk/tool) tool as an aid to determining the benefit of adjuvant systemic treatment. A number of other such tools are available for this purpose.

Key Recommendations

The decision on adjuvant systemic treatment should be made on a consideration of the patient's absolute risk of disease recurrence, benefit of treatment and risk of toxicitiy in each individual patient. We recommend using the NHS "Predict" (https://breast.predict.nhs.uk/tool) tool as an aid to determining the benefit of adjuvant systemic treatment.

3.6.2 Adjuvant Chemotherapy

3.6.2.1 Benefit of Adjuvant Chemotherapy

Chemotherapy is generally indicated and should be considered in all patients with ER negative tumours and HER2 positive tumours who are fit enough to receive it, except in patients with node negative disease and a tumour size of less than 5mm (AJCC staging T1a N0 M0)[3]. It is also beneficial in patients with T3 or higher tumours and those with N2 disease or higher regardless of tumour biology[3].

Patients with T1-2N0-N1 luminal A tumours can be safely treated with endocrine therapy alone[39,40,41,42]. This is supported by results of the TAILORx study which showed a less than 2% risk of distant metastases in patients with a low recurrence score and no benefit with adjuvant chemotherapy in patients with intermediate risk recurrence scores using a 21 gene expression assay[41,42]. Even in premenopausal patients there is robust data to suggest that these patients do not derive any benefit from adjuvant chemotherapy[43].

There is evidence to support some benefit from adjuvant chemotherapy in patients with node positive HER2 negative luminal B tumours and we recommend offering adjuvant chemotherapy to these patients[44]. In patients with node negative disease (T1-2 N0) HER 2 negative luminal B tumours we recommend weighing the risk and benefit on an individual basis.

Key Recommendations

Adjuvant chemotherapy should be offered to all patients in the following categories who are fit enough to receive it:

- Patients with triple negative or HER2 positive tumours which are of T1b N0 or higher stage
- Patients with luminal A tumours which are pT3 N0 or pN2 or higher nodal stage
- Patients with luminal B HER 2 negative tumours which are pT3 N0 or pN1 or higher nodal stage

We recommend weighing the risk and benefit in patients with pT1-2 N0 Luminal B Her2 negative patients on an individual basis.

3.6.2.2 Adjuvant Chemotherapy Regimen

The meta-analysis from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) showed that anthracycline based regimen are superior to non-anthracycline polychemotherapy regimens and the addition of taxanes to anthracyclines resulted in further benefit leading to an overall reduction in the risk of breast cancer mortality by about a third[45]. It was further shown that dose intensified chemotherapy will lead to a further reduction in the risk of breast cancer mortality by 10-15% leading to an overall reduction of 40% with the use of adjuvant chemotherapy[46].

In general, regimens used in the adjuvant setting can be used in the neoadjuvant setting[3]. It has been shown that the addition of carboplatin to anthracycline and taxane based regimens in TNBC results in a superior pathological complete response[47]. However, there is no impact on survival and no robust evidence of benefit in the adjuvant setting [3,47].

Another study showed that adjuvant capecitabine in patients not achieving a complete pathological response after 6-8 cycles of anthracycline and taxane based neoadjuvant chemotherapy results in superior OS and DFS[48]. The effect was more pronounced in patients with triple negative tumours, but platinum was not used in the neoadjuvant regimens[48].

Although the recent European guidelines discourage the use of 5-fluorouracil based regimens based on a study showing superior efficacy when it was replaced with sequential docetaxel, these regimens are used widely in many centres in Sri Lanka and in the United Kingdom and we are therefore unable to make any recommendation against its use[3,49].

Table 1 lists the commonly used conventional and dose intensified chemotherapy regimens used in the adjuvant and neoadjuvant setting.

In summary, we recommend:

- Offer dose-intensified anthracycline and taxane based regimens for use in both adjuvant and neoadjuvant settings for patients who are fit enough to receive it.
- In patients unsuitable for dose-intensified schedules were recommend conventional regimens.
- In patients with triple negative tumours receiving neoadjuvant treatment we suggest addition of carboplatin.
- For triple negative tumours treated with neoadjuvant chemotherapy without platinum agents, we suggest considering adjuvant capecitabine in patients not achieving a complete pathological response.

Key Recommendations

Offer dose-intensified anthracycline and taxane based regimens for use in both adjuvant and neoadjuvant settings for patients who are fit enough to receive it.

Consider carboplatin based chemotherapy regimens in patients with triple negative tumours receiving neoadjuvant treatment

Consider adjuvant capecitabine in patients with triple negative tumours not achieving a complete pathological response after treatment with neoadjuvant chemotherapy if the regimens did not contain a platinum agent

3.6.3 Anti-HER2 therapy

3.6.3.1 Trastuzumab

Trastuzumab reduces the risk of breast cancer mortality by 50% in HER2 positive tumours and is indicated in all patients with tumours >5mm (T1b or higher)[50,51,52]. Trastuzumab was delivered sequentially after adjuvant chemotherapy in the HERA trial while it was delivered concurrently with taxane chemotherapy in the NSABP B-31 trial[50,51]. The Breast Cancer International Research Group 006 trial additionally tested the carboplatin docetaxel and trastuzumab schedule[52]. The NCCTG trial N9831 also compared trastuzumab delivered sequentially and concurrently with taxanes and showed a non-significant trend towards superior DFS with an absolute gain of 4% and a 23% risk reduction[53]. A phase II trial of patients with low risk early disease (T1-T2 < 3cm N0) showed that single agent adjuvant paclitaxel delivered concurrently with trastuzumab achieves excellent outcomes[54].

In patients treated with neoadjuvant and adjuvant chemotherapy we recommend combining trastuzumab with the taxane component of chemotherapy. In patients with node negative disease with tumours less than 3cm we recommend considering treating with single agent weekly paclitaxel in combination with trastuzumab.

Key Recommendations

Offer adjuvant trastuzumab in addition to chemotherapy to all patients with HER2+ tumours which are of T1b N0 or higher stage and fit enough to receive it. In patients receiving taxane based adjuvant chemotherapy regimen adjuvant trastuzumab should be delivered concurrently with taxanes.

Consider weekly Paclitaxel in combination with trastuzumab for patients with T1-T2 (less than 3cm) N0 HER2+ tumours.

In patients with HER2+ tumours being offered neoadjuvant chemotherapy (see section 3.2), trastuzumab should be delivered in combination with a taxane.

3.6.3.2 Trastuzumab induced Cardiotoxicity

The main side effect of trastuzumab is cardiac toxicity which is reversible if detected early. Trastuzumab must not be administered concurrently with anthracyclines. The United Kingdom National Cancer Research Institute recommendations for monitoring cardiac health in patients treated with trastuzumab provide clear and pragmatic guidelines of management and we recommend following them for all patients treated with adjuvant or neoadjuvant trastuzumab as set out briefly below[55].

Trastuzumab could be safely initiated if the left ventricular ejection fraction (LVEF) is above the lower limit of normal (LLN) and there are no symptoms or signs of cardiac failure. If LVEF is below LLN or if the patient has symptoms or signs of cardiac failure, a cardiology referral is mandatory for optimisation of cardiac function and trastuzumab may be initiated after a careful assessment.

After initiation cardiac function needs to be monitored at 4 months and 8 months of treatment. Treatment can be continued if there are no clinical features of cardiac failure, the LVEF is above LLN and any trastuzumab induced LVEF decrease is less than 10%. Trastuzumab should be discontinued if LVEF is below 40% and/or with clinical evidence of cardiac failure. In patients without clinical features of cardiac failure and LVEF below LLN but above 40% or in patients with a trastuzumab induced LVEF decrease of 10% or more with LVEF above LLN, trastuzumab should be temporarily stopped and cardiology opinion sought with a view to optimising cardiac function. Trastuzumab could be resumed if LVEF improves and is above LLN and LVEF decline is less than 10%.

Key Recommendations

Trastuzumab could be safely initiated if the left ventricular ejection fraction (LVEF) is above the lower limit of normal (LLN) and there are no symptoms or signs of cardiac failure. If LVEF is below LLN or if the patient has symptoms or signs of cardiac failure, a cardiology referral is mandatory for optimisation of cardiac function and trastuzumab may be initiated after a careful assessment. After initiation cardiac function needs to be monitored at 4 months and 8 months of treatment.

3.6.3.3 Duration of Adjuvant Trastuzumab

The duration of adjuvant trastuzumab has been the subject of much controversy. The HERA trial established 1 year of trastuzumab as standard of care[50]. Two large phase III non-inferiority trials, PHARE and PERSEPHONE tested reducing this duration to 6 months with conflicting results[56,57]. While the hazard ratios (1.06-1.07) and absolute difference in 3 year DFS (0.4-0.8%) were similar in the two trials, due to pre-specified margins, the PHARE trial did not prove non-inferiority while the PERSEPHONE trial confirmed equivalence of 6 months adjuvant trastuzumab with 12 months of treatment. Further confounding the issue was the heterogeneity observed in the subgroup analysis of the PERSEPHONE trial, which showed that patients treated with concurrent trastuzumab and those with ER negative tumours trended towards a benefit with 12 months of treatment. No such difference was observed in the PHARE trial, which showed a consistent effect across all subgroups.

The discordant results of these trials mean that 12 months of adjuvant trastuzumab remains the standard of care. However, European guidelines recommend considering 6 months of trastuzumab in low risk patients, given the modest overall benefit with 12 months of adjuvant trastuzumab even though unequivocal equivalence could not be established.

Despite biosimilars, trastuzumab remains one of the most expensive anti-cancer treatments in Sri Lanka. Although, non-inferiority could not be established in strict statistical terms due to conflicting outcomes in the two trials, its results confirm that the benefit of 12 months of adjuvant trastuzumab is modest with an absolute gain of less than 1%. Six months of trastuzumab would substantially reduce costs and a cost-effectiveness analysis of six months versus twelve months of adjuvant trastuzumab in resource limited settings is urgently needed.

While twelve months of total adjuvant trastuzumab is standard of care in the adjuvant setting, we recommend strongly considering six months of treatment especially in low risk tumours such as hormone sensitive tumours, tumours with complete pathological response following neoadjuvant chemotherapy and tumours with negative lymph nodes, since the absolute benefit with prolonged trastuzumab is small.

Key Recommendations

Adjuvant trastuzumab should be delivered for at least 6-12 months (including neoadjuvant treatment). The benefit of trastuzumab beyond 6 months is uncertain and likely to be small especially in patients with tumours that are node negative disease, have ER+ tumours or achieved a complete pathological response following neoadjuvant treatment.

3.6.3.4 Pertuzumab, Trastuzumab emtansine and Neratinib

In the neoadjuvant setting pertuzumab when used in combination with trastuzumab and taxanes results in a significant improvement in pathological response rates[58]. The addition of pertuzumab to trastuzumab leads to modest gains in survival in the adjuvant setting especially in patients with node positive disease (absolute gain of 2.5%)[59]. In patients treated with neoadjuvant trastuzmab and not achieving a complete pathological response, replacing adjuvant trastuzumab with trastuzumab emtansine (T-DM1) reduces the risk of death or disease recurrence by 50% (absolute improvement 11%)[60]. The anti-HER2 tyrosine kinase inhibitor neratinib also improves DFS in patients with ER+ HER2+ tumours when delivered for 1 year, commencing after completing adjuvant trastuzumab[61]. However, significant diarrhoea was a major side effect. These drugs are not routinely in the government sector at present. As such we make no recommendations for its use in this background.

Key Recommendations

Since pertuzumab, trastuzumab emsantine nd neratinib are not consistently and routinely available in the government sector, no recommendations can be made on its use at this point in time.

3.6.4 Adjuvant Endocrine therapy

3.6.4.1 Premenopausal patients

Adjuvant tamoxifen for 5-10 years is standard of care adjuvant endocrine treatment in this setting[62,63]. Compared to 5 years of treatment, extending treatment to 10 years results in a modest reduction in mortality[63]. The results of SOFT and TEXT trials showed that ovarian suppression results in superior DFS in patients with premenopausal hormone sensitive tumours[64]. In addition, it was shown that exemestane and ovarian suppression led to further improvements in outcome compared to ovarian suppression and tamoxifen[64]. Ovarian suppression can be achieved with either oophorectomy, gonadotrophin releasing hormone agonists or irradiation[64].

Therefore, we recommend considering ovarian suppression and adjuvant exemestane in patients who are of sufficient risk to receive adjuvant chemotherapy, and where menstruation has returned within 2 years of completion of adjuvant chemotherapy[3,64]. Patients less than 40 years with hormone sensitive tumours are also at high risk of developing recurrence, and these patients should be considered for ovarian suppression even if chemotherapy is not indicated[3,64].

Key Recommendations

Offer ovarian suppression with (either surgery or GnRH analogues) for premenopausal patients with ER+ tumours if younger than 40 years of age or adjuvant chemotherapy is indicated based on tumour risk stratification.

Offer adjuvant tamoxifen for 5-10 years in patients with ER+ tumours not treated with ovarian suppression. Offer adjuvant treatment with an aromatase inhibitor as for post-menopausal patients in patients treated with ovarian suppression.

3.6.4.2 Post menopausal patients

Aromatase inhibitors improve DFS by 4% over tamoxifen in postmenopausal patients and OS is improved by 1-2%[65,66]. Aromatase inhibitor therapy can be either upfront or following 2 years or 5 years of tamoxifen. In patients not tolerating aromatase inhibitors, tamoxifen remains a safe alternative[3]. The optimal duration of aromatase inhibitor therapy is unknown but data suggest modest benefit beyond 5 years[3].

Patients treated with aromatase inhibitors who do not receive adjuvant bisphosphonate therapy for recurrence reduction (see section 3.6.5) should undergo an assessment of bone mineral density. Those with a T Score of less than -2 or those with risk factors for osteoporotic fractures should receive antiresorptive therapy[67].

Key Recommendations

Offer adjuvant treatment with an aromatase inhibitor (anastrozole, letrozole or exemestane) for post-menopausal patients with ER+ tumours for 5 years. Offer adjuvant treatment with tamoxifen for 5-10 year in patients not tolerating aromatase inhbitors.

3.6.4.3 Adjuvant Endocrine therapy in DCIS

Adjuvant tamoxifen reduces the risk of invasive breast cancer and DCIS in patients with ER+ DCIS treated with lumpectomy with or without radiotherapy with no effect on mortality[68]. Adjuvant aromatase inhibitors lead to a further reduction in breast cancer recurrence compared to tamoxifen alone with no significant effect on mortality[69,70].

Adjuvant tamoxifen or aromatase inhibitors may be offered to selected patients with ER+ DCIS as a strategy of reducing the risk of breast cancer recurrence after explaining the absence of any reduction in mortality.

Key Recommendations

Consider adjuvant endocrine therapy as a strategy of reducing risk of breast cancer recurrence in selected patients with ER+ DCIS after explaining the risks of treatment and that there is no reduction in mortality with such treatment.

3.6.5 Adjuvant Bisphosphonate Therapy

The meta-analysis by the EBCCTG showed a significant reduction in bone recurrence with use of adjuvant bisphosphonate therapy with no reduction in overall or breast cancer specific mortality[71]. However, it was shown that in post-menopausal patients, adjuvant bisphosphonate therapy resulted in a significant reduction of breast cancer mortality by 18%[71]. The benefit was seen in all subgroups of postmenopausal patients regardless of hormone sensitivity, tumour grade or nodal status[71].

We therefore recommend offering adjuvant intravenous zoledronic acid 4mg every six months for five years for all post-menopausal breast cancer patients including patients with chemotherapy induced menopause and those treated with ovarian suppression.

Key Recommendations

Offer adjuvant intravenous zoledronic acid 4mg every six months for five years for all post-menopausal breast cancer patients including patients with chemotherapy induced menopause and those treated with ovarian suppression

CHAPTER 4

FOLLOW-UP

The objectives of follow-up are to detect salvageable disease recurrence and manage treatment related complications.

We recommend clinical review which includes clinical breast examination every 3 months for the first two years, every six months for the next three years and annually thereafter.

An annual mammogram for 5 years following completion of treatment is recommended for all patients.

Bone mineral density should be assessed annually in all patients treated with ovarian suppression and/or treated with aromatase inhibitors and not treated with bone resorptive agents.

There is no evidence that routine blood investigations, chest radiograph or ultrasound scans during follow-up improves outcomes and we strongly recommend against performing these investigations.

Key Recommendations

Follow-up of patients after completion of adjuvant treatment should comprise clinical review every 3 months for first 2 years, every 6 months for next 3 years and annually thereafter for the next 5 years. An annual mammogram should be performed for 5 years.

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Table 1

Chemotherapy schedules: Early and locally advanced breast cancer

Her-2 negative breast cancer

1.	Dose dense AC → 2weekly paclitaxel	IV Doxorubicin 60mg/m2-D1 IV Cyclophosphamide 600mg/m2-D1 ↘ IV Paclitaxel 175mg/m2 D1 3h	Cycled every 14 days for 4 cycles Cycled every 14 days for 4 cycles
2.	Dose dense AC → weekly paclitaxel	IV Doxorubicin 60mg/m2-D1 IV Cyclophosphamide 600mg/m2-D1 ↘ IV Paclitaxel 80mg/m2 D1 1h	Cycled every 14 days for 4 cycles Weekly for 12 weeks
3.	AC → weekly paclitaxel	IV Doxorubicin 60mg/m2-D1 IV Cyclophosphamide 600mg/m2-D1 ↘ IV Paclitaxel 80mg/m2 D1 1h	Cycled every 21 days for 4 cycles Weekly for 12 weeks
4.	AC → Docetaxel	IV Doxorubicin 60mg/m2-D1 IV Cyclophosphamide 600mg/m2-D1 ↘ IV Docetaxel 100mg/m2 D1	Cycled every 21 days for 4 cycles Cycled every 21 days for 4 cycles
5.	FEC 75	IV Epirubicin 75mg/m2-D1 IV Cyclophosphamide 600mg/m2-D1 IV 5FU 600mg/m2-D1	Cycled every 21 days for 4-6 cycles
6.	FEC 100	IV Epirubicin 100mg/m2-D1 IV Cyclophosphamide 500mg/m2-D1 IV 5FU 500mg/m2-D1	Cycled every 21 days for 4-6 cycles
7.	FEC-T	IV Epirubicin 100mg/m2-D1 IV Cyclophosphamide 500mg/m2-D1 IV 5FU 500mg/m2-D1 ↘ IV Docetaxel 100mg/m2 D1	Cycled every 21 days for 3 cycles Cycled every 21 days for 3 cycles
8.	TC	IV Docetaxel 75mg/m2-D1 IV Cyclophosphamide 600mg/m2-D1	Cycled every 21 days for 4-6 cycles
9.	AC	IV Doxorubicin 60mg/m2-D1 IV Cyclophosphamide 600mg/m2-D1	Cycled every 21 days for 4 cycles

10.	CMF	PO Cyclophosphamide 100mg/m2-D1-D14 IV Methotrexate 40mg/m2-D1 &D8 IV 5FU 600mg/m2- D1& D8 } Cycled every 28 days for 6 cycles
11	Modified CMF	IV Cyclophosphamide 600mg/m2-D1 IV Methotrexate 40mg/m2-D1 IV 5FU 600mg/m2- D1 } Cycled every 21 days for 6 cycles
12.	Weekly paclitaxel+ carboplatin	IV Paclitaxel 80mg/m2-D1, D8, D15 IV Carboplatin AUC 5/6 -D1 } Cycled every 21 days for 4 cycles
13.	Docetaxel+ Carbo-platin	IV Docetaxel 75mg/m2-D1 IV Carboplatin AUC 6 -D1 } Cycled every 21 days for 4-6 cycles
14.	EC	IV Epirubicin 75mg/m2-D1 IV Cyclophosphamide 600mg/m2-D1 } Cycled every 21 days for 4-6 cycles
15.	TAC	IV Docetaxel 75mg/m2-D1 IV Doxorubicin 50mg/m2-D1 IV Cyclophosphamide 500mg/m2-D1 } Cycled every 21 days for 6 cycles
16.	Weekly Paclitaxel	IV Paclitaxel 80mg/m2 weekly for 12 cycles
17.	Capecitabine	PO Capecitabine 1000-1250mg/m2 BD D1-D14 Cycled every 21 days for 6-8 cycles

Her-2 positive breast cancer

18.	AC → paclitaxel + Trastuzumab	IV Doxorubicin 60mg/m2-D1 IV Cyclophosphamide 600mg/m2-D1 } Cycled every 21 days for 4 cycles ↘ IV Paclitaxel 80mg/m2 weekly -12weeks IV Trastuzumab 4mg/kg with first dose of Paclitaxel, followed by IV Trastuzumab 2mg/kg weekly to complete 01year/6months of treatment* * Alternatively IV Trastuzumab 6mg/kg every 21 days may be used following the completion of Paclitaxel
19.	AC → Docetaxel + Trastuzumab	IV Doxorubicin 60mg/m2-D1 IV Cyclophosphamide 600mg/m2-D1 } Cycled every 21 days for 4 cycles ↘ IV Docetaxel 100mg/m2-D1 } Cycled every 21 days for 4 cycles **+ EITHER** IV Trastuzumab 4mg/kg with first dose of Docetaxel, followed by IV Trastuzumab 2mg/kg weekly to complete 01year/6months of treatment* * Alternatively IV Trastuzumab 6mg/kg every 21 days may be used following the completion of Docetaxel **OR** IV Trastuzumab 8mg/kg with first dose of Docetaxel, followed by IV Trastuzumab 6mg/kg 3 weekly to complete 01year/6months of treatment
20.	dose dense AC → paclitaxel + Trastuzumab	IV Doxorubicin 60mg/m2-D1 IV Cyclophosphamide 600mg/m2-D1 } Cycled every 14 days for 4 cycles ↘ IV Paclitaxel 175mg/m2 D1 3h - Cycled every 14 days for 4 cycles + IV Trastuzumab 4mg/kg with first dose of Paclitaxel, followed by IV Trastuzumab 2mg/kg weekly to complete 01year/6months of treatment* * Alternatively IV Trastuzumab 6mg/kg every 21 days may be used following the completion of Paclitaxel
21.	TCH	IV Docetaxel 75mg/m2-D1 IV Carboplatin AUC 6-D1 } Cycled every 21 days for 6 cycles **+** IV Trastuzumab 4mg/kg week 1, followed by IV Trastuzumab 2mg/kg weekly for 17 weeks, followed by IV Trastuzumab 6mg/kg every 3 weeks to complete 01year/6months of treatment

22.	Docetaxel/ Cyclophosphamide + Trastuzumab	IV Docetaxel 75mg/m2-D1 IV Cyclophosphamide 600mg/m2-D1 } Cycled every 21 days for 4 cycles **+ EITHER** IV Trastuzumab 4mg/kg week 1, followed by IV Trastuzumab 2mg/kg weekly for 11 weeks, followed by IV Trastuzumab 6mg/kg every 3 weeks to complete 01year/6months of treatment **OR** IV Trastuzumab 8mg/kg week 1, followed by IV Trastuzumab 6mg/kg 3 weekly to complete 01year/6months of treatment
23.	FEC → Docetaxel + Trastuzumab	IV Epirubicin 100mg/m2-D1 IV Cyclophosphamide 500mg/m2-D1 } Cycled every 21 days for 4-6 cycles IV 5FU 500mg/m2-D1 IV Docetaxel 75mg/m2-D1 IV Trastuzumab 8mg/kg with first dose of Docetaxel, followed by IV Trastuzumab 6mg/kg 3 weekly to complete 01year/6months of treatment

APPENDIX

Summary of Recommendations

Diagnosis

Triple Assessment

- The triple assessment of clinical examination, imaging and histopathology remains the cornerstone of the diagnostic work-up in patients suspected to have breast cancer.

Clinical Examination

- A full history should be obtained, and a complete general examination and an examination of the breasts, axillae and supraclavicular fossae should be performed and the tumour should be staged according to the American Joint Committee on Cancer staging system.

Imaging

- All patients with suspected breast cancer should undergo bilateral mammography and ultrasonography before pathological evaluation.

- As a practical measure to overcome delays, we recommend performing an ultrasound scan of bilateral breasts as the initial imaging investigation. Patients with a clinical and radiological suspicion of malignancy should be referred to the nearest radiology unit with facilities to perform a mammogram.

- Magnetic resonance imaging of the breast is recommended in patients with inconclusive findings on ultrasound and mammography.

Pathological Diagnosis

- Core needle biopsy of suspicious breast lesions and either fine needle cytology or core needle biopsy of suspicious axillary lymph nodes should be performed preferably under image guidance. At least 2 cores should be obtained and in patients with suspected multifocal disease all lesions should be biopsied as far as possible.

- In patients in whom neoadjuvant chemotherapy with a view to facilitating breast conservation surgery is being offered, placement of surgical clips under ultrasound guidance is strongly recommended.

- Performing excision biopsy is strongly discouraged unless at least two attempts at core needle biopsy failed to yield a confirmatory diagnosis.

Immunohistochemistry

- Immunohistochemistry (IHC) for Oestrogen Receptor (ER), Progesterone Receptor (PR), Her2/Neu overexpression (Her2) and the proliferation marker Ki67 should be performed in all core biopsy samples with invasive cancer. IHC for ER, PR and Her2 should be reported according to the ASCO/CAP guidelines.

- Testing for gene amplification using in-situ hybridization (ISH) techniques for detection of Her2 gene amplification is recommended for patients with equivocal Her2 overexpression on IHC.

- ISH testing is currently not available in the state sector and this investigation can only be performed elsewhere if patients can afford its cost. Until ISH testing is available in the state sector, we recommend that a mechanism be established for this investigation to be performed outside of the state sector at free cost to the patient.

- For Ki67 we suggest considering <10% as low risk, 10-20% as intermediate risk and >20% as high risk.

- Patients should be categorized into Luminal A, Luminal B Her 2 Negative, Luminal B Her2 Positive, Her2 Positive (non-luminal) and Triple Negative based on the IHC profile.

Time to complete diagnosis

- Clinical pathways should strive to ensure that a complete diagnosis including immunohistochemistry profile is available within 6 weeks of the first consultation.

Staging

- Routine staging (computed tomography scan of the chest and abdomen and bone scintigraphy) is recommended in patients with locally advanced disease (T3, T4 or N2 disease) and in other patients with symptoms suggestive of metastatic disease.

Treatment

Multidisciplinary discussion

- We recommend discussing every new diagnosis of breast cancer in a multidisciplinary meeting comprising surgeons, clinical oncologists, radiologists, and pathologists.

Neoadjuvant chemotherapy

- Neoadjuvant chemotherapy (NAC) is indicated in patients presenting with either T4 disease (including inflammatory breast cancer) or N2 or more nodal disease regardless of tumour biology. In these patients, breast conservation surgery or mastectomy along with standard axillary clearance is recommended depending on the response to NAC.

- For patients with T1 N0 disease, we recommend upfront surgery regardless of tumour biology as these tumours are often eminently resectable with breast conservation surgery.

- For patients with T1-T2 N1 and T3 N0-1 tumours which are HER2 positive or triple negative we recommend considering NAC as a strategy of facilitating breast conservation surgery. The surgical management of these patients should be wide local excision followed by standard axillary clearance after completing NAC.

- For patients with T2 N0 tumours which are HER2 positive or triple negative, we recommend considering the merits of NAC and its impact on the treatment of the axilla on an individual basis. If these patients are treated with NAC, we recommend performing a sentinel node biopsy prior to NAC or a standard axillary clearance after NAC. Post NAC sentinel node biopsy should be undertaken with caution.

- Patients with ER+ Her2- T1-T2 N1 and T3 N0-1 tumours should proceed with upfront surgery since response to NAC is poor.

- Placement of surgical clips under ultrasound guidance is mandatory prior to NAC if it is undertaken with a view to facilitating breast conservation surgery.

Surgical treatment of the primary tumour

- The primary treatment of non-metastatic breast cancer is surgery with either breast conservation surgery (BCS) or mastectomy.

- Contraindications to BCS are multicentric disease, T4 primary tumour (including inflammatory breast cancer), large tumour relative to breast volume and contraindications for adjuvant whole breast radiotherapy.

- We recommend BCS as the treatment of choice for all early breast cancer patients without contraindications to it.

- We recommend that the following information be given to patients who are suitable for breast conservation surgery:

- o BCS has equal or possibly superior survival to mastectomy.
- o Patients treated with BCS have a better long-term quality of life and functional outcome.

- In patients undergoing BCS invasive cancer, absence of tumour (invasive cancer and DCIS) at the inked margin is sufficient. In patients with a positive inked margin, we recommend performing re-excision. If margins are still positive after two attempts at excision we recommend offering mastectomy.
- All patients treated with mastectomy should be offered breast reconstruction.

Surgical treatment of the axilla

- For patients with cT1-2 N0 tumours, we recommend performing a sentinel lymph node biopsy (SLNB) using either methylene blue dye, radiopharmaceutical tracer or a combination of the two. We recommend Intra-operative assessment of sentinel lymph nodes using either imprint cytology, cytology smears or frozen section. SLNB should be performed with caution in patients treated with neoadjuvant chemotherapy as experience is limited in our setting.
- In patients in whom SLNB is performed, axillary clearance should be performed if there are three or more macrometastases (>2mm) and any macrometastases with extra-nodal extension. In patients with 1-2 macrometastases, axillary clearance would need to be performed if any of the following criteria are met: the treatment of the primary tumour is mastectomy, grade III tumour, tumour size is more than 2cm, ER negative or Her2 positive on IHC.
- If performing SLNB is not feasible we recommend performing axillary nodal sampling as an alternative in patients cT1-2 N0 tumours.
- Axillary clearance is recommended in all patients with cT3 or higher primary tumours as well as those with cN1 or higher axillary nodal stage. Standard axillary clearance includes dissection of levels I and II and should harvest a minimum of 10 lymph nodes.

Adjuvant radiotherapy

- We recommend offering whole breast radiotherapy to all patients with invasive cancer or DCIS treated with breast conservation surgery. Clinicians could consider not offering whole breast radiotherapy in patients above 65 years who meet the following criteria after full explanation of risks and benefits: DCIS, T1 or T2 tumours less than 3cm, node negative and ER+ PR+ Her2-, grade 1-2, and are willing to take endocrine treatment for 5 years.
- Adjuvant Post mastectomy radiotherapy (PMRT) is recommended in patients with T3 or T4 invasive cancer or 4 or more involved axillary lymph nodes and in patients with 1-3 involved lymph nodes with macrometastases. PMRT is also recommended in patients with positive margins. PMRT could be considered in patients with 1-3 involved lymph nodes with micrometastases. PMRT should not be offered for patients with pT1-2 N0 invasive cancer.

- 26 Gy in Five fractions over one week is recommended for patients offered adjuvant whole breast radiotherapy or post-mastectomy radiotherapy in whom nodal irradiation is not considered. 40 Gy in 15 fractions over three weeks is recommended for patients receiving nodal radiotherapy.

- Partial breast irradiation should be considered in all patients treated with BCS and are above 50 years of age who fulfill the following criteria: Treatment is delivered in a linear accelerator, invasive ductal carcinoma, tumour stage is pT1-2 N0, tumour size is less than 3cm, grade 1-2, lymphovascular invasion is absent, margins are more than 1mm, tumour bed boost and nodal radiotherapy is not offered. We recommend a dose of 26 Gy in 5 five fractions over one week in this setting.

- We recommend delivering tumour bed boost of either 12 Gy in 4 fractions (2 Gy equivalent dose of 16 Gy) following adjuvant whole breast radiotherapy for patients treated with BCS and are aged 50 or less or having a grade III tumour. A simultaneous integrated tumour bed boost of 48 Gy in 15 fractions can also be considered in patients being offered adjuvant radiotherapy to a dose of 40 Gy in 15 fractions to the whole breast.

- Offer Supraclavicular nodal radiotherapy to all patients with pT4 or pN2 or higher nodal stage. Consider Supraclavicular nodal radiotherapy in patients with pT1-3 tumours and pN1 nodal stage receiving adjuvant radiotherapy.

- Consider Internal mammary radiotherapy for all patients with pT4 tumours or pN2 or higher nodal stage and for patients with medial tumours and pN1 nodal stage, if treated in a linear accelerator.

- We recommend implementing cardiac sparing techniques in patients with left sided cancers receiving treatment in the linear accelerator. For patients with upper half tumours conformal shielding of the heart is recommended while for patients with lower half tumours we recommend cardiac sparing using the voluntary deep inspiratory breath hold technique.

Adjuvant systemic therapy

- The decision on adjuvant systemic treatment should be made on a consideration of the patient's absolute risk of disease recurrence, benefit of treatment and risk of toxicitiy in each individual patient. We recommend using the NHS "Predict" (https://breast.predict.nhs.uk/tool) tool as an aid to determining the benefit of adjuvant systemic treatment.

Adjuvant chemotherapy

Adjuvant chemotherapy should be offered to all patients in the following categories who are fit enough to receive it.

- Patients with triple negative or HER2 positive tumours which are of T1b N0 or higher stage.
- Patients with luminal A tumours which are pT3 N0 or pN2 or higher nodal stage.
- Patients with luminal B HER 2 negative tumours which are pT3 N0 or pN1 or higher nodal stage.
- We recommend weighing the risk and benefit in patients with pT1-2 N0 Luminal B Her2 negative patients on an individual basis.
- Offer dose-intensified anthracycline and taxane based regimens for use in both adjuvant and neoadjuvant settings for patients who are fit enough to receive it.
- Consider carboplatin based chemotherapy regimens in patients with triple negative tumours receiving neoadjuvant treatment.
- Consider adjuvant capecitabine in patients with triple negative tumours not achieving a complete pathological response after treatment with neoadjuvant chemotherapy if the regimens did not contain a platinum agent.

Adjuvant trastuzumab

- Offer adjuvant trastuzumab in addition to chemotherapy to all patients with HER2+ tumours which are of T1b N0 or higher stage and fit enough to receive it. In patients receiving taxane based adjuvant chemotherapy regimen adjuvant trastuzumab should be delivered concurrently with taxanes.
- Consider weekly Paclitaxel in combination with trastuzumab for patients with T1-T2 (less than 3cm) N0 HER2+ tumours.
- In patients with HER2+ tumours being offered neoadjuvant chemotherapy (see section 3.2), trastuzumab should be delivered in combination with a taxane.
- Trastuzumab could be safely initiated if the left ventricular ejection fraction (LVEF) is above the lower limit of normal (LLN) and there are no symptoms or signs of cardiac failure. If LVEF is below LLN or if the patient has symptoms or signs of cardiac failure, a cardiology referral is mandatory for optimisation of cardiac function and trastuzumab may be initiated after a careful assessment. After initiation cardiac function needs to be monitored at 4 months and 8 months of treatment.

- Adjuvant trastuzumab should be delivered for at least 6-12 months (including neoadjuvant treatment). The benefit of trastuzumab beyond 6 months is uncertain and likely to be small especially in patients with tumours that are node negative disease, have ER+ tumours or achieved a complete pathological response following neoadjuvant treatment.

- Since pertuzumab, trastuzumab emsantine and neratinib are not consistently and routinely available in the government sector, no recommendations can be made on its use at this point in time.

Adjuvant Endocrine therapy in invasive carcinoma

- Offer ovarian suppression with (either surgery or GnRH analogues) for premenopausal patients with ER+ tumours if younger than 40 years of age or adjuvant chemotherapy is indicated based on tumour risk stratification.

- Offer adjuvant tamoxifen for 5-10 years in patients with ER+ tumours not treated with ovarian suppression. Offer adjuvant treatment with an aromatase inhibitor as for post-menopausal patients in patients treated with ovarian suppression.

- Offer adjuvant treatment with an aromatase inhibitor (anastrozole, letrozole or exemestane) for post-menopausal patients with ER+ tumours for 5 years. Offer adjuvant treatment with tamoxifen for 5-10 year in patients not tolerating aromatase inhbitors.

Adjuvant endocrine therapy in patients with ductal carcinoma in-situ (DCIS)

- Consider adjuvant endocrine therapy as a strategy of reducing risk of breast cancer recurrence in selected patients with ER+ DCIS after explaining the risks of treatment and that there is no reduction in mortality with such treatment.

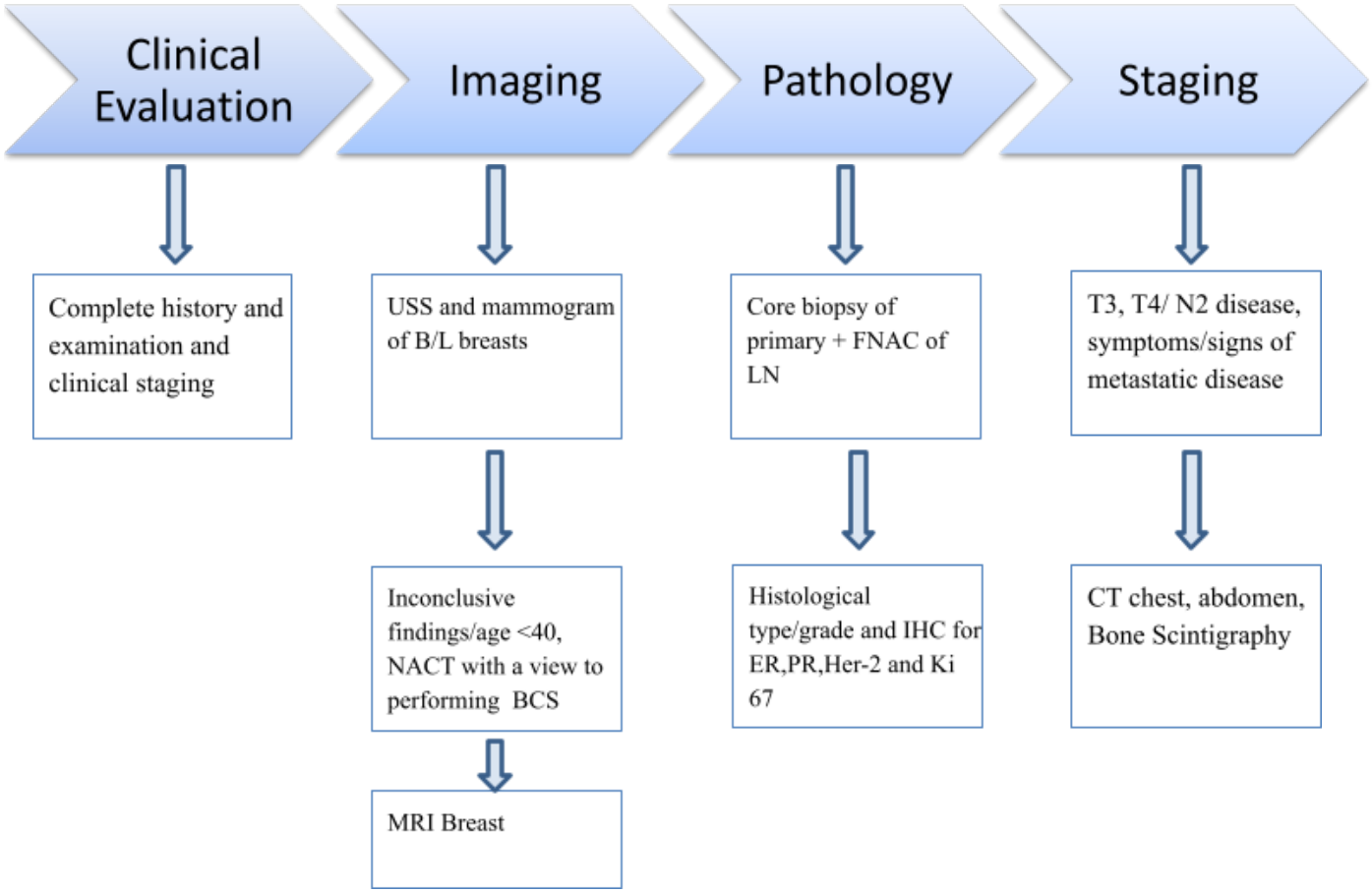
Adjuvant zoledronic acid

- Offer adjuvant intravenous zoledronic acid 4mg every six months for five years for all post-menopausal breast cancer patients including patients with chemotherapy induced menopause and those treated with ovarian suppression.

Follow-up

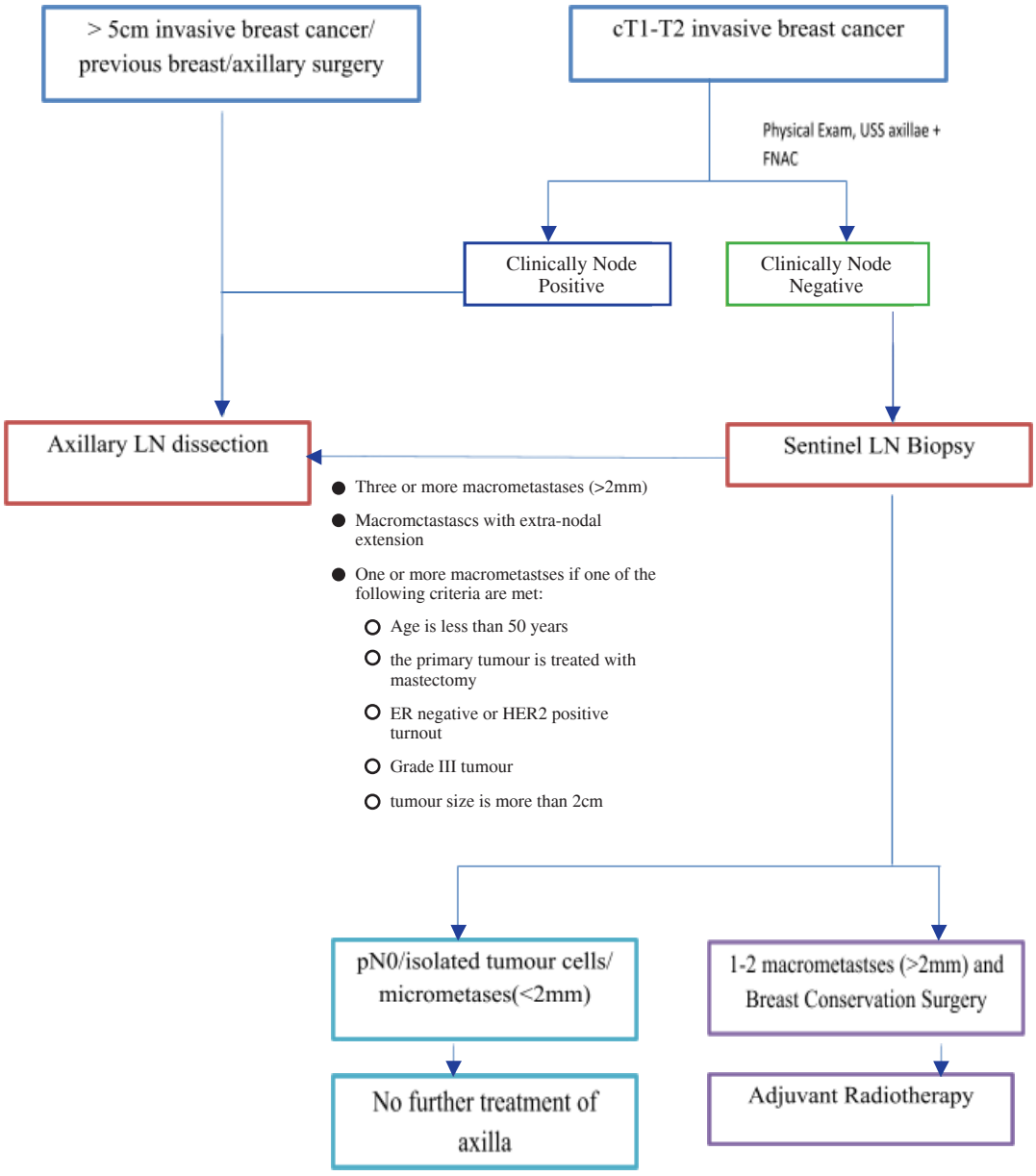
- Follow-up of patients after completion of adjuvant treatment should comprise clinical review every 3 months for first 2 years, every 6 months for next 3 years and annually thereafter for the next 5 years. An annual mammogram should be performed for 5 years.

Diagnostic Workup and Staging for Suspected Breast Cancer



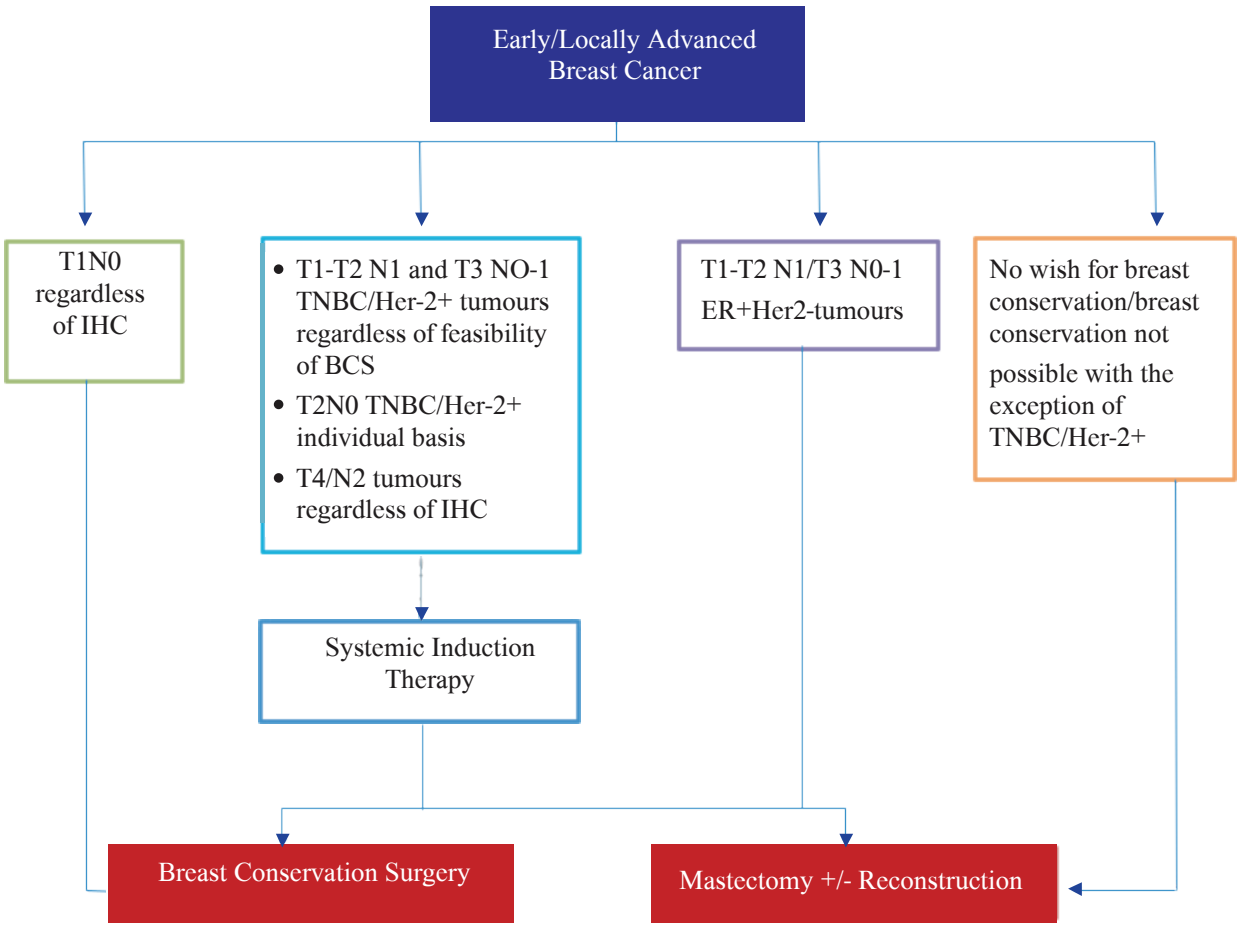
USS: Ultrasound Scan, B/L: Bilateral, FNAC: Fine Needle Aspiration Cytology, LN: lymph node/s, NACT: Neoadjuvant Chemotherapy, BCS: Breast Conservation Surgery, IHC: Immunohistochemistry

Treatment of the Axilla



USS: Ultrasound Scan, B/L: Bilateral, FNAC: Fine Needle Aspiration Cytology, LN: lymph node/s, , BCS: Breast Conservation Surgery, IHC: Immunohistochemistry

Upfront Surgery vs Neoadjuvant Chemotherapy (NAC) followed by surgery



TNBC: Triple Negative Breast Cancer, IHC: Immunohistochemistry

National Cancer Control Programme
Ministry of Health

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