AGBreastCare

AMADER GRAM BREAST CARE

(AMADER GRAM BREAST CARE EDUCATION, CLINICS AND CENTER PROGRAM-AGBCECCP)

CLINICAL PRACTICE GUIDELINES

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CONSIDERATIONS IN USE AND EXTENT OF THESE GUIDELINES

These guidelines are a consensus of the authors regarding currently accepted approaches to care of known or suspected breast cancer in the context of Bangladesh. Evidence from published scientific data and, in particular, uncertainty about efficacy, toxicities and cost efficacy of high-income country-based guidelines for Bangladeshi women, have been important in developing these statements (Love, 2008 a). Any clinician considering these guidelines is expected to use independent medical judgment in the context of specific medical circumstances to determine any individual patient's medical treatment.

These guidelines, in the current version, cover only the commonest clinical circumstances seen with women with uncertain breast problems or diagnosed with breast cancer in Bangladesh. There are many cases in which specific information to assist in guiding best diagnostic and treatment decisions is not presented here. When this is true, the reader is urged to consult the current American NCCN guidelines (nccn.org), and carefully consider application of these to the particular patient problem.

In the face of limited data about the specific risks and benefits to Bangladeshi women from treatments for breast cancer, the authors of these guidelines have taken conservative positions, and encourage efforts to develop rigorous data to inform decisions which can benefit more women. At present, in particular evaluating the risk and benefits of systemic adjuvant therapies in any patients, involves complex estimates in individual cases. The reader is encouraged to use www.adjuvantonline.com to develop possible upper and lower estimates of benefits of these therapies. Similarly the recommendations given for drug use for management of symptoms and pain must be considered to be suggestions and careful consideration of indications and contraindications for specific drugs in individual patients must occur, and these therapies must be monitored closely by professionals.

These guidelines will be updated periodically.

PROCESS METRIC GOALS FOR BREAST CANCER CARE

DIAGNOSIS
All patients with a breast mass of undefined nature will have pathologic investigation to establish a definitive tissue diagnosis.

All patients will have all elements of the guideline-defined medical history and physical examination staging evaluations recorded in their medical record on the day of their visit.

All patients who have tissue biopsy-proven cancer will have guideline-defined laboratory staging studies completed within two weeks of the date of cancer diagnosis.

There will be a quality control program for all surgical pathology laboratory studies (including for example participation in the UK NEQAS quality control program for hormonal receptor testing).

TREATMENT
Every patient with a pathologic-established diagnosis of cancer, will have a written, medical record-documented multidisciplinary group review-established plan for treatment.

Every patient with an established diagnosis of cancer will be begun on appropriate treatment of some type within three weeks of diagnosis.

There will be an annual audit by an international, external multi-disciplinary group of physicians of the records of a randomly selected sample of 15% of all patients seen during the previous year for evidence of adherence to the goals listed here, and treatment quality.

Discussion
Quality improvement should be an important routine for health care professionals. Measurement plays an important role in improvement of medical care quality.
Listed above here are specific quality indicators that are measurable, and that are suggested "starting" basic indicators for assessing quality of breast cancer care.

STAGING EVALUATION OF PATIENTS WITH DIAGNOSED, SUSPECTED, OR RECURRENT OR METASTATIC INVASIVE BREAST CANCER

*Medical history including: date of last menstrual period if pre- or peri-menopausal, occurrence of hot flashes, signs of supraclavicular or cervical lymph node enlargement; symptoms of pulmonary or pleural metastases---cough, shortness of breath, or chest discomfort; liver area discomfort; localized long bone or spine pain.

*Physical examination including: blood pressure; height; weight; (calculated BMI); breast volume estimation+ evaluation for supra-clavicular, infra-clavicular and cervical lymph node ; specific dimensions of any breast, axillary or other lymph node masses; cardiac and lung chest auscultation; liver palpation; gynecologic examination.

*Written documentation of each of these evaluations in each patient's medical record is expected to confirm that the evaluation has been carefully done.

+Breast volume/size: Estimate using standard bra sizes A,B,C, and D

LABORATORY STAGING STUDIES IN PATIENTS WITH CLINICAL STAGE I-III INVASIVE BREAST CANCER

(Anticipating that such patients will be candidates for surgical treatment)

*Chest X-ray, with specific interpretation of status of bones, pleurae, lung fields, hilar areas, and size of cardiac silhouette, with measured cardiac/thoracic ratio.

In usual circumstances a PA film only is indicated. If however, the presence of internal mammary lymph nodes would be of critical importance in staging, and metastatic involvement of these nodes is suspected, (as with a large or medial tumor), a lateral film should also be considered for evaluation of the anterior mediastinal space.

*Complete blood count, including a platelet count.
*Ultrasound image of the liver, with specific dimensions of any identified abnormality.
*Serum creatinine and alkaline phosphatase
*Random blood sugar
*Electrocardiogram (for patients>30 years old)
*Urinalysis
For hyperglycemia and infection (each of which pose risks for post-operative wound infections).

NOTES:
The use of the serological markers CEA, CA15-3, and CA27.29 as markers for diagnosis, staging, or to detect recurrence after primary breast cancer therapy, is NOT recommended because "the data are insufficient" to make such recommendations (ASCO Guidelines, 2000 and 2007).

Creation and submission of electronic reports is recommended.

Additional radiologic imaging studies should only be considered if there are specific indications and there is a solid case that the additional testing is very likely to provide significant value to the patient and decision-making process. (Puglisi, 2005; Iglehart, 2009):

*Bone scan: if the patient has localized bone symptoms and/or an elevated serum alkaline phosphatase level.
*Chest imaging with special chest X rays or CT scan: if the patient has pulmonary symptoms and a regular chest X ray provides inadequate information.

EVALUATION OF A BREAST MASS OF UNCERTAIN NATURE

EVALUATION

*Medical history: duration, size change, tenderness of any mass.

*Physical examination: specific location and dimensions; tenderness.

*Breast ultrasound examination noting: shape and size of mass; posterior acoustics; edge shadowing and vascularity.

MANAGEMENT

*If changes define a cyst, then observation.

*If changes define a very symptomatic cyst: → fine needle aspiration biopsy. Cytological examination of any fluid is NOT recommended.

*If changes define a classical fibroadenoma, then for patients under age 30, observation. For patients over age 30, management should be dictated by details of the individual case.

*If changes are consistent with an indeterminate solid lesion → core needle biopsy

EVALUATION OF SIGNS AND SYMPTOMS CONSISTENT WITH BENIGN BREAST CONDITIONS

EVALUATION for BREAST PAIN

*Medical history: Is discomfort truly mammary? Cyclical or non-cyclical; laterality; record worst and usual levels of discomfort using the following combined visual analogue scale:

*Is discomfort produced on examination? Is there definitive absence of serious abnormality and absence of breast masses?

*Breast ultrasound
Are cysts or ductal ectasia seen?

MANAGEMENT

→Reassurance grounded in negative physical examination and specific ultrasound findings. Restrict caffeine intake (in medicine for example). Assure good breast support.

→ Consider low dose oral contraceptive.

→In only extreme cases consider

Danocrine (Danazol) 100 mg daily.(A weak androgen). A trial for two months should be first considered.

Tamoxifen 10 or 20mg. (Antiestrogen)

EVALUATION AND MANAGEMENT OF NIPPLE DISCHARGE

EVALUATION

Medical history: Bloody (90% due to papilloma) versus non-bloody discharge; single duct versus multi-duct discharge; spontaneous versus appearance-only-on expression pressure

MANAGEMENT

Multi-duct discharge →Observation
Single duct discharge →. Duct excision

TISSUE SPECIMEN COLLECTION AND MANAGEMENT FOR HORMONE RECEPTOR AND HER-/NEU TESTING

Strong consideration should be given to doing hormonal receptor testing only on core biopsy tissues because the major quality control issues--particularly pre-analytic issues---ischemic time/fixation time and sampling--- can only be well controlled in this setting (Uy, 2007; Mann, 2005).

For core biopsy specimens the following pre-analytic tissue management issues are important (Golstein, 2007; Yasiji, 2009):

*Time to fixation ("cold" ischemic time): should always be less than one hour; time should be recorded. High temperatures before fixation (for example leaving the specimen sitting in sunlight) should be avoided.

*Core biopsy or 2 mm sections/slices (including normal breast tissue) should be placed immediately into 10% neutral, buffered, room temperature, formalin for >8 at a minimum to 72 hours. (1:20 volume of tissue:volume of formalin).

Total fixation time should be recorded.

*The formalin used should be changed daily, and the pH should be maintained at >7.0.

For mastectomy specimens, the tissue should immediately be transferred to a Pathology laboratory, making sure that the pathologist is there at the time of receipt of the sample. If this is not possible, then the entire tissue specimen should be placed immediately in 10% neutral buffered formalin (1:20 volume of tissue:volume of formalin). The requisition must include information on the time the specimen was removed from the patient and also time the specimen was placed into formalin. The specimen should then be sent to the Pathology laboratory in such a way, that the specimen is not exposed to direct sunlight. The specimen must be received in the Pathology laboratory within 48 hours of removal from the patient. A request to perform hormone receptor testing should accompany the specimen.

SYSTEMIC ADJUVANT TREATMENTS

STAGE II-IIIB *

The administration of these therapies and management of their toxicities are complex, and achieving best and safe outcomes for patients requires well-trained and experienced oncologic physicians, nurses and pharmacists. Tumor hormone receptor testing, accomplished following appropriate tissue management (see above guidelines, page 14), should be strongly considered whenever possible.

Pre-menopausal** women with estrogen receptor positive*** and/or progesterone receptor positive***tumors:

Surgical oophorectomy + tamoxifen 20 mg daily for 5 years (Love, 2008 b). While one study has suggested that oophorectomy in the luteal phase of the menstrual cycle may be more effective, further data are required to justify this as a guideline recommendation.

Pre-menopausal** women with estrogen receptor negative and progesterone receptor negative tumors:

Chemotherapy with CMF at 21 day intervals for 6 cycles**** or doxorubicin/cyclophosphamide at 21 day intervals for 4 cycles, if tumor can be determined to be Her-2/neu over-expressing by IHC (3+IHC score)***** (EBCTCG, 2005; Pritchard, 2006; Wolf, 2007)

Postmenopausal women with estrogen receptor positive and/or progesterone receptor positive tumors:

Tamoxifen 20 mg daily for 5 years (EBCTCG, 2005).

Postmenopausal women with estrogen receptor negative and progesterone receptor negative tumors: Chemotherapy with CMF at 21 day intervals for 4 cycles**** (EBCTCG, 2005)

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*Patients with Stage I disease (T1—tumor 2 cm or less in greatest dimension) should have individualized treatment. Patients with Stage IIIc disease (N3→10 axillary nodes with metastases or supraclavicular lymph node involvement), should have treatment based on the guidelines for LABC.
**Menopause is defined as permanent cessation of menses for 12 or more months. Thus a woman who has had a menstrual period in the preceding 12 months is considered to be pre-menopausal.

***Hormone receptor positive status is defined according to the presence of an Allred score of 3 or more (meaning that at least 1% of cells stain for receptor protein) (Harvey, 1999; ASCO/CAP Guidelines, 2009 to be published)

****Cyclophosphamide 600 mg/m2 iv day 1; methotrexate 40 mg/m2 iv day 1; 5-fluorouracil 600 mg/m2 iv day 1 (CMF). Doses should be calculated based on actual body weight (Budman, 1998). While scientific reports of the results of CMF treatments in patients of European genetic background suggest that the "Bonadonna" 28 day regimen (with 14 days of oral cyclophosphamide) is more effective than the intravenous CMF regimen, gastrointestinal toxicity-nausea and vomiting-with this regimen is frequent, and depending on availability and optimal use of anti-emetic therapies, compliance and efficacy can be low (Goldhirsch, 1998). This circumstance alters the risk-benefit ratio for Bangladeshi women. While there are not specific rigorous data on the issue of the optimal number of cycles of IV CMF, there are suggestive data that greater than four cycles are more effective.

The authors have therefore chosen 6 cycles for premenopausal women. For postmenopausal women, where the absolute benefits are smaller, and the risks often greater (particularly for less-than-optimally controlled emesis and intravascular volume depletion in individuals with vascular disease), 4 cycles are recommended.

The recommended safe, conservative, and effective approach is to calculate doses based on actual body weight, administer 75% of calculated doses for the first cycle, and then, critically, to escalate doses based on individual patient's toxicity experience (Budman, 1998). This strategy accommodates uncertainty

about limiting toxicity suspected to occur at higher rates in Asian populations, while attaining adequate doses which are believed to exceed critical threshold levels (Bonadonna, 1981; Budman, 1998).

*****Doxorubicin 60 mg/M2 IV day 1 and cyclophosphamide 600mg/M2 IV day every 21 days. The same approach to optimal dose calculation as is presented in the previous paragraph for CMF is advocated here for this regimen also. Testing for Her-2/neu over-expression beyond IHC is impractical, expensive and of marginal benefit in Bangladesh. With attention to pre-analytic tissue management procedures as outlined in these guidelines, the likelihood of a 3+ IHC test being a false positive is low. With any other IHC test result, the risks and benefits suggest that NOT using this Doxorubicin regimen is the safest approach.

MANAGEMENT OF PRIMARY AND RECURRENT LOCALLY ADVANCED BREAST CANCER (LABC)

In the local and systemic treatment guidelines here (Figures 1 and 2), sequential decision points for any primary or recurrent locally advanced breast tumor address:

1. Technical operability; 2. Availability of radiation therapy; and 3. Availability of tumor hormone receptor testing. Any technically operable tumor should first be treated with mastectomy and axillary node surgery. This recommendation is made because this is the one significant therapy that is always available and can be safely completed with a reasonable expectation of benefit. In patients with recurrent, essentially initially-inadequately-treated breast cancer, evolving concepts of the importance of adequate local therapy on survival , and data on revision surgery support an aggressive surgical approach, if the tumor is technically operable (Punglia, 2007; Thorat, 2008).

There are several studies suggesting that if a breast tumor is technically resectable, (i.e. safely with at least 1 cm surgical/pathological margins), there may be overall survival benefits, even if distant metastatic disease is present (Khan, 2002; Rapiti, 2006; Babiera, 2006; Blanchard, 2006; Gnerlich, 2007). Preliminary data from an Indian randomized trial confirm that impact on survival of this approach is very unlikely to be adverse (Badwe, 2008). Thus if a patient with stage IV metastatic breast cancer has a technically operable primary breast tumor, it is recommended that mastectomy and axillary dissection should be strongly considered.

Radiation therapy is a critical treatment in all cases of LABC treated with breast surgery. If there is no capacity for this treatment, management of patients with LABC should be transferred to a location where such capacity IS present and can be made available to all patients needing this treatment. The role of this treatment in improving local control and thus survival has been re-emphasized recently and specific data are clear in demonstrating benefits with even "optimal" systemic approaches (Punglia, 2007; McGuire, 2007). Adjuvant radiation therapy is cost effective (Love, 2003). Thus loco-regional radiation therapy after breast surgery is recommended.

Systemic therapies in operable LABC should be guided by results of carefully performed tumor hormonal receptor testing (Figure 2). In pre-menopausal women, adjuvant surgical oophorectomy and tamoxifen has been demonstrated to confer disease-free and overall survival benefits comparable to those achieved with anthracycline- based chemotherapy together with combined LHRH and tamoxifen therapy, and is remarkably cost-effective (Love, 2008 b; Davidson, 2005). If the patient is considered to be incurable because of systemic/distant metastatic disease, then the surgical oophorectomy/tamoxifen approach in premenopausal women with hormone receptor positive tumors, is supported by preliminary data from Torrisi, and strongly justified based on data in stage IV hormone receptor positive disease trials (Torrisi, 2004; Klijn, 2001).

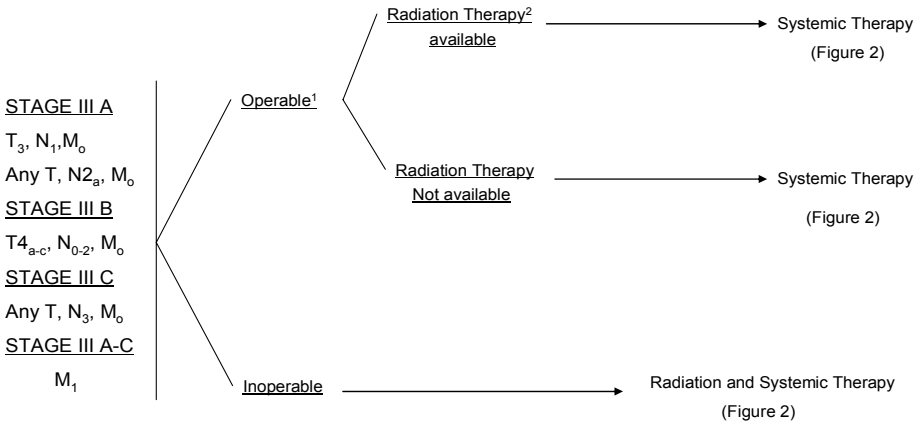
In hormone receptor negative cases, the selection of optimal chemotherapies is particularly difficult. Cyclophosphamide 600 mg/m2 iv day 1; methotrexate 40 mg/m2 iv day 1; 5-fluorouracil 600 mg/m2 iv day 1 (CMF) for 6 cycles is recommended on the basis of likely greater safety. The recommended safe, conservative and effective approach is to calculate doses based on actual body weight, administer 75% of calculated doses for the first cycle, and then, critically, to escalate doses based on individual patient's toxicity experience (Budman, 1998). This strategy accommodates uncertainty about limiting toxicity suspected to occur at higher rates in Asian populations, while attaining adequate doses which are believed to exceed critical threshold levels (Bonadonna, 1981; Budman, 1998).

Doxorubicin 60 mg/M2 IV day 1 and cyclophosphamide 600mg/M2 IV day every 21 days for four cycles is a second, but less favored option. Four cycles of this regimen might be considered better than 6 cycles of CMF in feasibility This anthracycline-based regimen is suggested to be more effective in Her-2/neu positive tumors, and is recommended in this subset of patients (Paik, 1998; Paik, 2000; Thor, 1998; Pritchard, 2006).

Inoperable patients, whose loco-regional disease might be anticipated to become operable with local radiation and systemic therapy, should have serious consideration given to use of radiation therapy as the primary local treatment. As the text at the far right of figure 2 notes, any patient whose local disease

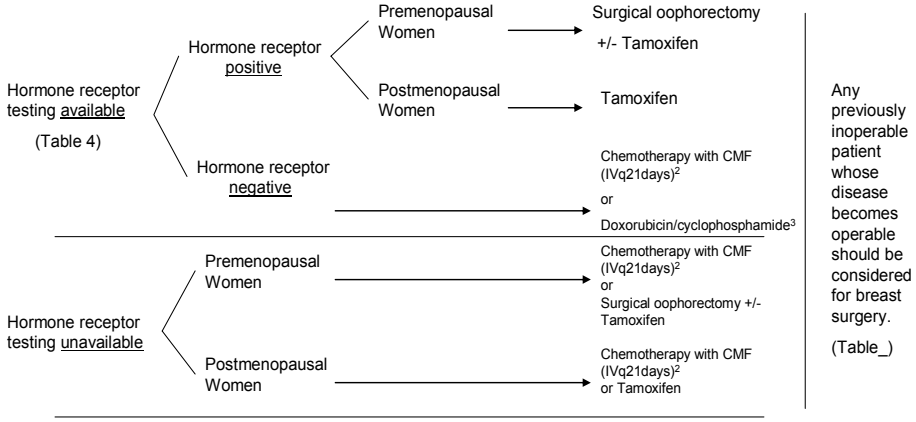
becomes technically operable after systemic and or radiation therapy should be considered for primary breast surgical treatment.

Figure 1
Recurrent or primary locally advanced breast cancer: local treatment.



1. If operable modified radical mastectomy with at minimum a level II axially node dissection. See criteria, Table 2.
2. If radiation therapy is available, regional node/supraclavicular and internal mammary, and chest wall radiation. See criteria Table 3.

Figure 2
Recurrent or primary locally advanced breast cancer: systemic therapies.



1. Therapies to be considered after local treatments are completed.
2. CMF (IVq21days) = Cyclophosphamide 600mg lm^2, metrorexade 40mg lm^2, 5 flurouracil 600mg lml all LV all day 1.
3. Doxorubicin cyclophosphamide = doxorubicin 60mg lm^2, and cyclophospmide 600 mg lm^2, both IV on day 1.

REPORTS OF SURGICAL PATHOLOGICAL EXAMINATIONS OF BREAST TISSUES

CORE NEEDLE, EXCISIONAL OR INCISIONAL BIOPSIES:

Diagnosis: Invasive or In-situ If invasive, give histologic sub-type, and assessment regarding presence or absence of lympho-vascular invasion

HORMONE RECEPTOR TEST RESULTS:

Adequacy of sample: Adequate, inadequate, limited-but interpretable.

Fixation times: Not known, known –indicate duration

Assay descriptors: Methods of assay including sources and antibody clones of reagents used.

Assay interpretation: >=1% staining positive is the accepted cutoff. % cells staining positive, and average intensity should both be reported to give an "Allred" score.

Caveats: Fixation issues Intrinsic controls: positive or negative

MASTECTOMY SPECIMENS:

Specimen type and description (right or left)
Gross specimen findings: dimensions of apparent tumor or tumors; distances from the surgical margins; location of tumor(s) in specimen; evidence of multi-centricity; dimensions of nodal masses

Microscopic

- Histologic cell type (Azzopardi, WHO Classification, 1982)
- Margins for invasive and non-invasive components
- Presence of in situ component
- Histologic grade (Nottingham Index; Todd, 1987)
- Evidence of lympho-vascular invasion
- Skin or nipple involvement
- Findings in non-tumorous tissues
- Total number of lymph nodes identified (minimum should be 8)
- Number of lymph nodes with evidence of metastases
- Evidence of extra-nodal extension of metastatic disease
- Size of largest nodal metastasis

BREAST SURGERY PROCEDURES

The use of an international surgical safety checklist, as follows, is strongly recommended (Haynes, 2009).

SURGICAL SAFETY CHECKLIST ELEMENTS*

Sign in

Before induction of anesthesia, members of the team (at least the nurse and an anesthesia professional) orally confirm that:

- The patient has verified his or her identity, the surgical site and procedure, and consent
- The surgical site is marked or site marking is not applicable
- The pulse oximeter is on the patient and functioning
- All members of the team are aware of whether the patient has a known allergy

- The patient's airway and risk of aspiration have been evaluated and appropriate equipment and assistance are available.
- If there is a risk of blood loss of at least 500 ml (or 7 ml/kg of body weight, in children), appropriate access and fluids are available

Time out

Before skin incision, the entire team (nurses, surgeons, anesthesia professionals, and any others participating in the care of the patient) orally:

- Confirms that all team members have been introduced by name and role
- Confirms the patient's identity, surgical site, and procedure
- Reviews the anticipated critical events
- Surgeon reviews critical and unexpected steps, operative duration, and anticipated blood loss
- Anesthesia staff review concerns specific to the patient
- Nursing staff review confirmation of sterility, equipment availability, and other concerns
- Confirms that prophylactic antibiotics have been administered ≤60 min before incision is made or that antibiotics are not indicated
- Confirms that all essential imaging results for the correct patient are displayed in the operating room

Sign out

- Before the patient leaves the operating room:
- Nurse reviews items aloud with the team
- Name of the procedure as recorded
- That the needle, sponge, and instrument counts are complete (or not applicable)
- That the specimen (if any) is correctly labeled, including with the patient's name
- Whether there are any issues with equipment to be addressed
- The surgeon, nurse, and anesthesia professional review aloud the key concerns for the recovery and care of the patient

*This checklist is based on the first edition of the WHO Guidelines for Safe Surgery.

Operability (Greene, 2002; Haagenson, 1943; Singletary, 2002);

Strong contraindications

- Extensive (1/3rd of breast) edema of the breast skin
- Inflammatory signs-erythema and skin edema (T4d)
- Satellite tumor nodules in the skin (T4b)
- Arm edema because of extensive axillary node disease
- Fixation of tumor to chest wall (T4a)
- Axillary lymph nodes fixed to skin or axillary tissues
- Intercostal or parasternal nodules
- High tumor-to-size-of-breast ratio.
- Unachievable tumor free margins of at least 1 cm.

Relative contraindications

- Skin ulceration (T4b)
- Axillary lymph nodes >=2.5 cm
- Supraclavicular lymphadenopathy (N3c)

PRIMARY BREAST SURGERY PROCEDURES and operative report

Clinical trial data are clear in indicating that there is no survival or local recurrence advantage with muscle removal (radical mastectomy) unless there is actual invasion of the tumor thru the fascia into the muscle- and even then , only appropriate 1-2 cm margins are required- not total pectoral muscle removal.

A clear description of:

- Left or right breast procedure
- Pre and post operative diagnoses
- ALL tumor parameters- exact sizes and locations (including the o'clock position and the anterior/posterior position in the breast)
- Clinical evidence of skin and/or nipple involvement Clinical examination of axilla with axilla "open"
- Description of any muscle and/or chest wall involvement with
- precise locations Exact anatomic description of extent of nodal involvement and
- resection Any complication such as intercostal brachial nerve preservation or removal; any injury to long thoracic or
- thoracodorsal nerves; injury to axillary vein /artery.
- Blood loss.

AXILLARY NODAL SURGERY PROCEDURES for

Anatomically defined level I and II apparent disease
With 8-10 nodes at minimum evaluated.

INDICATIONS FOR COMPLETE (TO LEVEL III) AXILLARY DISSECTION:

Level III is defined as medial to the superior border of the pectoralis—the terms subclavicular or apical are also used to describe lymph nodes in this area. Any evidence of metastatic involvement in interpectoral (Rotter's) or level I or II axillary lymph nodes is indication for a level III axillary dissection. (Thorat, 2008)

MANAGEMENT OF PATIENTS WITH DISTANT METASTATIC (STAGE IV) BREAST CANCER

HISTORY AND PHYSICAL EXAMINATION→ SEE STAGING EVALUATION GUIDELINE, PAGE **8**

LABORATORY EVALUATION STUDIES-

- Chest X-ray
- Complete blood count
- Ultrasound image of the liver
- Serum creatinine and alkaline phosphatase

If specifically indicated by localized bone symptoms, plain radiographs of specific symptomatic bones should be performed.

IF THE HORMONE RECEPTOR STATUS OF THE CANCER IS UNKNOWN, STRONGLY CONSIDER BIOPSY OF LIKELY METASTATIC TISSUE FOR DETERMINATION OF THIS PARAMETER.

LYTIC BONE METASTASES PRESENT-→
And expected survival >3months, creatinine < 2.0 mg/dl, and serious dental disease is absent (a risk factor for jaw osteonecrosis) → Consider oral bisphosphonate therapy with clodronate 1600 mg by mouth daily (Hillner, 2003).

HORMONE RECEPTOR POSITIVE (ER AND/OR PR POSITIVE) (see footnote page -------)

Premenopausal* → surgical oophorectomy + tamoxifen 20 mg daily

Postmenopausal* →tamoxifen 20 mg. daily

HORMONE RECEPTOR NEGATIVE OR NO RESPONSE TO HORMONAL THERAPY(IES):

→ Oral methotexate (2.5 mg twice daily two days per week) and oral cyclophosphamide (50 mg daily).**

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*Menopause is defined as permanent cessation of menses for 12 or more months. Thus a woman who has had a menstrual period in the preceding 12 months is considered to be pre-menopausal.

**This metronomic oral methrotrexate/cyclophosphamide regimen is selected because of significant levels of efficacy demonstrated in patients with metastatic cancer treated with this regimen, with low toxicity and low financial cost (Bottini, 2006; Colleoni, 2002)).

MANAGEMENT OF COMPLICATIONS OF SYSTEMIC CHEMOTHERAPIES

NAUSEA, VOMITING

If related to disease in which the mechanism is prokinetic:

- Metoclopramide (Metocol,Motilon 10mg tablets; suspension 5mg/5m; Injectable 10mg/2ml)
  Starting dose: 10mg every 8 hours or as needed for nausea not requiring continual therapy.

- Domperidon (Omidon 10 mg tablets)
  Starting Dose: 10mg -20mg every 8 hours or as required for and maximum of 3 to 5days

If **Chemotherapy** related:

5HT3 blocker.

- Ondansatrone 8mg (Onaseron 8mg tablets;,Injectable 4mg or 8mg/5ml)(Onsat, Osetron, Emisat 8mg tablets; 8mg/4ml injectable)
  Starting dose: 8 mg every 8 hours.

If **Morphine related**

Dopamine receptor blocker.

- Haloperidol (Halop 5mg tablets)
  Starting dose: 1.5 mg at night or 1.5 mg every 12 hours.

NEUTROPENIA:

Neutropenia is defined as an absolute neutrophil count <1500/ml.

If there is fever with neutropenia, look for a specific cause, and treat that cause with an appropriate antibiotic. If no specific infectious site or cause is identified, begin a broad spectrum antibiotic such as Ceftriaxone.

Neutropenia on day 1 of chemotherapy

- Delay of chemotherapy until neutropenia is resolved AND make a 25% dose reduction in each of the chemotherapy drugs for **ALL** future treatments.

DIARRHEA

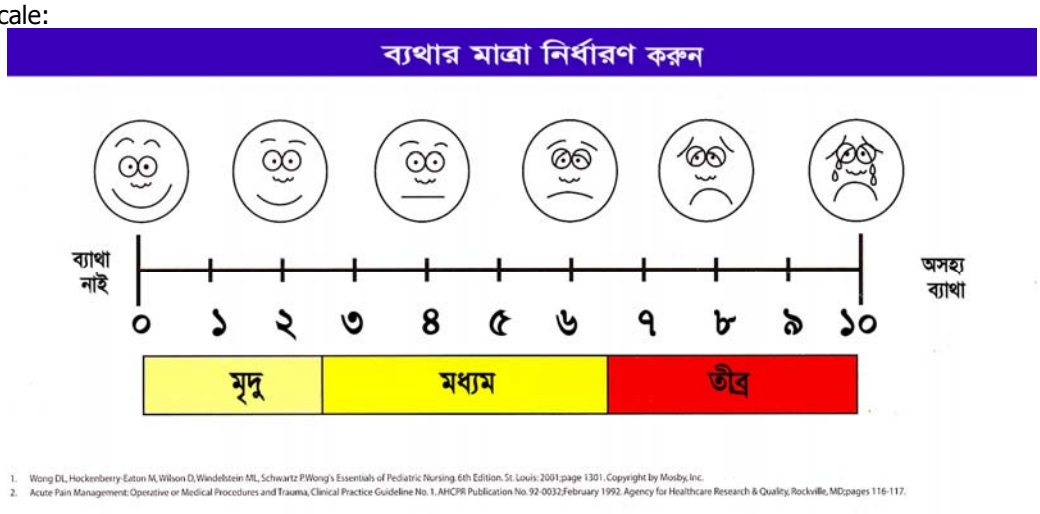
If the principle cause appears to be previously administered chemotherapy:

- Loperamide (Imotil,Lomosec 2mg)
  Starting dose: Two tablets immediately and then every 2-4 hours to a maximum of 6 tablets per 24 hours.

ASSESSMENT AND MANAGEMENT OF ADULT CANCER PAIN

Ask: Does the patient report having any pain?

- If yes: Score pain using the following combined visual analogue scale:



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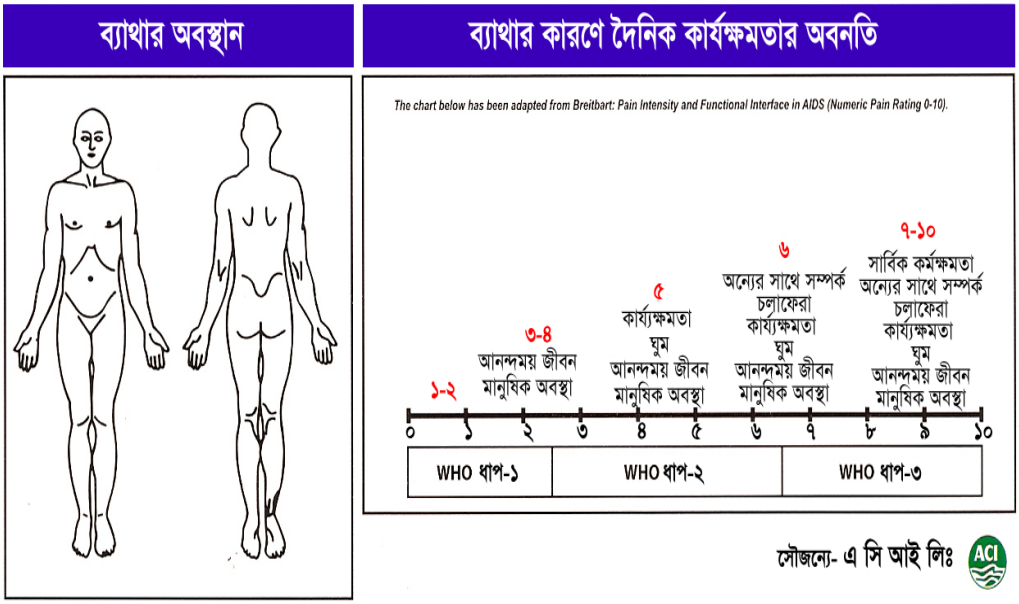
2. Acute Pain Management: Operative or Medical Procedures and Trauma, Clinical Practice Guideline No. 1. AHCPR Publication No. 92-0032;February 1992. Agency for Healthcare Research & Quality, Rockville, MD;pages 116-117.



VISUAL ANALOGUE SCALE

Definitions-

Mild pain : Score 1-3
Moderate pain : Score 4-6
Severe pain : Score 7-10

MANAGEMENT

The World Health Organization guideline step-ladder approach is recommended as follows (WHO, 2009):
↓

Mild Pain	Moderate Pain	Severe Pain
↓	↓	↓
Paracetamol	Weak Opioids	Morphine
±NSAIDS	±NSAIDS	± Non-opioid analgesic
± Adjuvants	± Adjuvants	± Adjuvants

NSAIDS: Non steroidal anti-inflammatory drugs

- Diclofenac (Mobifen,Voltaren) 50 mg
  Starting dose: 50 mg every 8 hours with food.

- Ketorolac Tromethamine (Minolac,Rolac 10mg) 10 mg every 8 hours
  If taken for more than several days round the clock, these drugs can cause stomach ulceration. If such treatment is used then consideration should be given to adding anti-ulcerant drugs also.

Nonopioid analgesic

- Paracetamol (Napa,Xcel) 500mg tablet; Suspension 125mg in 5 ml)
  Starting doses are 1 gm every 6 hours

Weak opioid

- Tramadol 50mg, 100mg tablets;100mg/1ml/injectable. (Anadol, Lucidol,Tendia,Winpain)
  Starting dose is 50 mg every 8 hours.

Strong Opioid

- Morphine is available in oral doses as sustained release tablets of 15mg and 30 mg and in injectable form with 15mg in a 1 ml vial.
  Starting dose: 15 mg every 12 hours.

  Whenever regular morphine administration is anticipated, it should be given together with a laxative drug such as Laxen, two tablets at bedtime, to prevent constipation.

Adjuvants commonly used along with opioids are:

Anxiolytic drugs such as-

- Lorazepam (a short acting benzodiazepine) 1mg tablets. (Lozicum)
  Starting dose: 1 mg once a day.
- Bromazepam 3mg tablets. (Lexotenil,Laxyl) may be preferred in patients with insomnia.
  Starting dose: Half a tablet at bedtime.

The goal should be to achieve and maintain freedom from pain. To reach this goal drugs should be given "by the clock", that is every 3-6 hours, rather than "on demand"
This WHO three-step approach emphasizes administering the right drug in the right dose at the right intervals.

Watson, 2004; Watson 2006.

American Joint Committee on Cancer (AJCC) TNM staging system for breast cancer

A revised version of this system will be available in the summer of 2009 and will be posted here at that time. . Until this time the reader is encouraged to access the current staging system at-

NCCN Clinical Practice Guidelines in Oncology. V.1.2009 Accessed on line at: http://nccn.org/professionals/physician_gls/PDF/breast.pdf.

Follow-up evaluations of patients without disease

The goals of follow-up evaluations are to-

1. Detect recurrent disease in potentially more manageable stages and lesser extents.
2. Identify complications of treatments.
3. Detect second primary malignancies in potentially curable stages. The commonest of these are second breast cancers, uterine and colon malignancies.

*Medical history including: date of last menstrual period if pre- or peri-menopausal, occurrence of hot flashes, signs of supraclavicular or cervical lymph node enlargement; symptoms of pulmonary or pleural metastases---cough, shortness of breath, or chest discomfort; liver area discomfort; localized long bone or spine pain.

*Physical examination including: blood pressure; height; weight; (calculated BMI); breast volume estimation; evaluation for supra-clavicular, infra-clavicular and cervical lymph node ; specific dimensions of any breast, axillary or other lymph node masses; cardiac and lung chest auscultation; liver palpation; gynecologic examination.

No "routine" laboratory or radiologic studies are recommended based on data from two randomized studies and one set of American recommendations (Roselli, 1994; GIVO investigators, 1994; Smith, 1998).

Similarly, the use of the serological markers CEA, CA15-3, and CA27.29 as markers for diagnosis, staging, or to detect recurrence after primary breast cancer therapy, is NOT recommended because "the data are insufficient" to make such recommendations (ASCO Guidelines, 2000 and 2007).

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