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Algorithm for the Management of Breast Cancer

1. Breast CA Suspect (A)
2. Open biopsy (B)
3. (+) Cancer? (C)
4. Stage (D)
5. Stage O? (Y)
6. LCIS? (E)
7. Observation
8. Refer
9. N
10. DCIS
11. Lumpectomy with nodal sampling or MRM
12. ER/PR +? (F)
13. Adjuvant Hormonal Treatment
14. N
15. Stage I or II? (Y)
16. Breast Conservation or MRM (G)

Figure A
Ax LN+? (H)

ER/PR+? (F)

Adjuvant chemotherapy + Hormonal treatment

(+) margin or (+) LN?

Adjuvant chemotherapy ± Hormonal treatment

(+/-) margin or (+/-) LN?

Observe

Adjuvant chemotherapy

Observe

Adjuvant Radio-therapy (I)

Pre-menopausal?

Menopausal

Tumor size <0.5 cm or 0.6-1.0 cm or with favorable prognostic factors?

Observe

Go to #10

Go to #2

Figure B
Stage III?

Operable?

MRM

ER/PR+?

Stage IV

(Palliative Chemotherapy/Hormonal Therapy or BSC)

Palliative Radiotherapy or Best Supportive Care (BSC)
Management of Breast Cancer

The management of breast cancer must be multidisciplinary, interdisciplinary, with each discipline respecting the specialty expertise of the other, all for the benefit of the cancer patient.

(A) Most breast cancer (hard, painless, movable, then becomes fixed to the chest wall/skin, with/without nipple retraction) are found by palpation by the patient, her partner or her physician. As tumor site increases, the likelihood that distant metastasis has taken place rises. It is better to detect and treat early (asymptomatic <1 cm diameter tumor size). Mammography can detect very early <1 cm tumor mass and hence effective in screening.

(B) If total mastectomy is anticipated, it is best to confirm the diagnosis with open biopsy. For preliminary screens, FNAB cytology is done. A (-) FNAB should not dissuade the surgeon from excision biopsy if a discrete lump is present, particularly if there is high clinical suspicion of cancer.

Mammography can be done to localize areas with high probability of cancer aiding direction of FNAB.

Review of slides is done to verify presence of cancer for those patients already with biopsy slides.

(C) Majority of breast cancer are invasive ductal carcinoma. Three major cancer types are: noninvasive (intraductal and lobular), invasive, and Paget's disease of the nipple. Poor prognosis types are atypical medullary and not otherwise specified. Other histopathologic findings that correlate with poor prognosis are low nuclear grade and presence of tubule formation.

For treatment purposes, breast cancer may be divided into:

a. Pure non-invasive carcinoma (Stage 0)
   i. ductal carcinoma (Stage 0)
   ii. lobular carcinoma in situ (LCIS)

b. Operable locoregional invasive carcinoma (Stage I, II and some stage IIIA)

c. Inoperable locoregional invasive carcinoma (Stage IIIB, IIIC and some stage IIIA tumors)

d. Metastatic or recurrent carcinoma (Stage IV)

(D) Staging considerations:

History and PE, and at a minimum alkaline phosphatase, chest x-ray, abdominal ultrasound are done for baseline. Bone scan is indicated if the patient has symptoms related to bone or if there is elevated alkaline phosphatase level. CT scan of whole abdomen is indicated if abdominal ultrasound is inconclusive but there are symptoms referable to the abdominal organs.

At a minimum baseline CBC, creatinine, and ECG are done in preparation for treatment.

PET scan can be an option to determine presence of metastatic sites highly suspected but not shown by CT scan/bone scan. For brain metastasis suspect, MRI may be the better option compared to CT scan.

(E) The goal of treatment of in-situ carcinoma is either preventing the occurrence of invasive disease or diagnosing the invasive component when still localized to the breast.

Observation alone is the preferred option for women diagnosed with LCIS because their risk of developing invasive carcinoma is low. Bilateral mastectomy may be considered in special circumstances.

Tamoxifen treatment may be considered in women with DCIS treated with breast conserving therapy, especially in those with ER(+) DCIS treated with mastectomy.

(F) Fresh surgical breast mass specimen must be routinely taken at FIRST surgery for ER/PR assay and level of HER-2/neu expression, needed to plan drug treatment of patient. For stage IV or for those cases not previously performed, it is best to determine even on just the excision biopsy specimen the ER/PR and HER-2 status.

Hormonal therapy has been shown to reduce overall tumor recurrence and mortality in ER(+) women. Tamoxifen or an aromatase inhibitor agent is the usual hormone therapy drug. The best responder would be an ER(+) PR(+) patient; for those premenopausal, tamoxifen can be given; for those post-menopausal, tamoxifen or aromatase inhibitor can be given. For those ER(+)/PR(-), the PR(-) status may be a marker for growth factor overexpression (Her-2 overexpression) and this subgroup of postmenopausal patients may be best started on aromatase inhibitors.

HER-2-neu overexpression denotes an aggressive cancer, resistance to CMF but responsiveness to anti-Her-2-neu immunotherapy (trastuzumab). A
combination of HER-2-neu ≥++/PR(-) connotes resistance to CMF-based regimen and tamoxifen.

(G) The purpose of surgery is to remove the local and regional disease. A number of randomized trials document that in the majority of women with Stage I and II invasive breast CA, mastectomy with axillary dissection versus breast conserving therapy with lumpectomy, axillary dissection and breast irradiation (breast conserving therapy) are medically equivalent primary therapeutic options. MRM still remains the better option for clinical settings with low patient follow-up rates or low resource settings.

Surgical management is the responsibility of the surgical oncologist.

(H) For high risk patients with ≥4 (+)LN and (-)ER or for those premenopausal and (-)LN or with HER-2-neu over expression, anthracycline-containing adjuvant chemotherapy is given. Otherwise, CMF can be given, particularly for elderly and or patients with heart disease; taxanes can also be given particularly for young, ALN(+)-0-3, aggressive and ER/PR(-) tumors.

(I) If adjuvant chemotherapy is indicated, RT should be given after chemotherapy is completed. Radiotherapy is the responsibility of the radiation oncologist.

It was hoped that post-op RT could prevent loco-regional recurrence and improve disease-free and overall survival. It is now evident, however, that this has not occurred to the degree hoped for, probably because remaining tumor burden is too great. Hence, adjuvant systemic chemotherapy is given.

More common chemotherapeutic drugs used currently in breast cancer management (neoadjuvant, adjuvant, or palliative setting) are doxorubicin and the other anthracyclines, cyclophosphamide, fluorouracil, taxanes, navelbine, capecitabine, gemcitabine, methotrexate, vincristine, mitomycin-c, carboplatin, trastuzumab.

Drug management (from hormonotherapy to gene therapy in the adjuvant to palliative setting) is the responsibility of the medical oncologist who does the planning, the administration, and the monitoring of drug therapeutic and safety effects.

(J) Preoperative chemotherapy for large clinical Stage II A and II B tumors and T3N1M0 tumors should be considered for women who meet the criteria for breast conserving therapy except for size.

(K) Metastatic sites for breast cancer are usually the regional LNs, skin, lung, liver, bone, brain, etc. Stage IV breast cancer can be those with:

1. ‘operable-like’ breast mass but with distant metastasis wherein simple mastectomy followed by radiotherapy of target breast and regional LNs sites and symptomatic metastatic sites plus chemotherapy/hormonotherapy, OR wherein radiotherapy to target breast lesion/other symptomatic metastatic sites plus chemotherapy/hormonotherapy can be done,

2. ‘inoperable-like’ breast mass (adhered, ulcerated, etc) with distant metastasis, wherein toiletté mastectomy can be done with chemotherapy/hormonotherapy or radiotherapy or best supportive care.

Surgery, chemotherapy, radiotherapy procedures in Stage IV disease are all palliative in goal, although several patients can respond very well to chemotherapy ± radiotherapy and have significantly long time to disease progression interval. Best supportive care mainly includes management of nutrition, pain, infection, psychological well-being, nursing and rehabilitative care, and other pertinent quality of life patient care.
**Recommended Therapeutics**  
(Drugs Mentioned in the Treatment Guideline)

The following index lists therapeutic classifications as recommended by the treatment guideline. For the prescriber’s reference, available drugs are listed under each therapeutic class.

<table>
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<th>Cytotoxic Drugs</th>
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<tr>
<td><strong>Alkylating Agents</strong></td>
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</table>
| *Cyclophosphamide* | Biomedis Cyclophosphamide  
Cytoxan |  |
| *Melphalan* | Alkeran |  |

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<tr>
<th>Antimetabolites</th>
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| *5-Fluorouracil* | Biomedis Fluorouracil  
Fluracetyl  
Fluroblastin  
Uflahex |  |
| *Capecitabine* | Xeloda |  |
| *Methotrexate* | Biomedis Methotrexate  
Emthexate  
Hextrate  
Pfizer Methotrexate Inj. |  |
| *Tegafur/Uracil* | UFT |  |

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<tr>
<th>Cytotoxic Antibiotics</th>
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| *Doxorubicin HCl* | Adriblastina RD  
Biomedis Doxorubicin HCl  
Caelyx  
Hexal Doxorubicin  
Pfizer Doxorubicin HCl Inj  
Pharmachemie Doxorubicin |  |
| *Epirubicin HCl* | Hexal Epirubicin  
Pharmorubicin |  |
| *Mitomycin C* | Kyowa Mitomycin-C |  |

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<tr>
<th>Mitotic Inhibitors</th>
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</table>
| *Docetaxel* | Biomedis Docetaxel  
Taxotere |  |
| *Vincristine sulfate* | Biomedis Vincristine Sulfate  
Nevexitin |  |

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<tr>
<th>Other Cytotoxics</th>
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| *Carboplatin* | Biovinate  
Crobxatin  
Paraplatin |  |
| *Gemcitabine HCl* | Gemzar |  |
| *Mitoxantrone* | Domitrone  
Hexal Mitoxantrone |  |
| *Paclitaxel* | Biomedis Paclitaxel  
Pharmachemie Paclitaxel  
Taxol |  |

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<th>Hormones and Antagonists in Malignant Diseases</th>
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<tbody>
<tr>
<td><em>Anastrozole</em></td>
<td>Arimidex</td>
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| *Goserelin acetate* | Zoladex  
Zoladex LA |  |
| *Letrozole* | Femara |  |
| *Leuprolelin acetate* | Luprolex |  |
| *Megestrol acetate* | Megace  
Pharmachemie Megestrol Acetate |  |
| *Tamoxifen citrate* | Biomedis Tamoxifen  
Canifen-DS  
Drugmaker's Biotech Tamoxifen  
FenaheX  
Kessar  
Nolvadex-D  
Tamoplex  
Zitazonium |  |

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<th>Immunosuppressants</th>
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<tbody>
<tr>
<td><em>Exemestane</em></td>
<td>Aromasin</td>
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<th>Others</th>
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<tbody>
<tr>
<td><em>Trastuzumab</em></td>
<td>Herceptin</td>
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