المجلس الصحي السعودي
Saudi Health Council

SAUDI BREAST CANCER MANAGEMENT GUIDELINES

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The National Cancer Center (NCC)

@SNCC_SHC

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BREAST CANCER MANAGEMENT GUIDELINES

EVIDENCE LEVELS:

The following evidence levels (EL) were adopted for this guideline:

(EL-1) High Level: well conducted phase III randomized studies or meta-analysis.
(EL-2) Intermediate Level: good phase II data or phase III trials with limitations.
(EL-3) Low Level: observational/ retrospectives study/ expert opinions.

I. ALL BREAST CANCER PATIENTS

1.1 INITIAL PATIENT ASSESSMENT

1.1.1 Obtain detailed clinical assessment including family history; complete physical examination, with emphasis on breast size, tumar size, location and lymph nodes status, document performance status (ECOG PS)

1.1.2 Risk assessment for familial breast cancer (optional) (Appendix 1)

1.1.3 Perform the following laboratory tests: Complete blood count (CBC), differential, liver function test (LFT), renal function, hepatitis profile, electrolytes, calcium, alkaline phosphatase, magnesium, phosphorus; vitamin D level.

1.1.4 Bilateral mammogram, + US breast and Axilla, + MRI breast as indicated (Appendix 2).

1.1.5 Tumor localization (Clip) to be inserted at the time of biopsy .

1.1.6 Consider Fertility counselling if appropriate

1.2 DIAGNOSIS

1.2.1 Confirm histological diagnosis and evaluation of Cell type, grade, hormonal markers (ER, PR), Her2 status, and proliferation index (Ki67) . (Appendix 3) for minimal pathological reporting requirement.

1.2.2 Outside pathology to be reviewed and if inadequate to be repeated.

1.2.3 Core biopsy / FNA of Axillary nodes should be considered as per radiological evaluation.

(Appendix 4)

1.3 STAGING WORK-UP:

1.3.1 Early breast cancer

- ■Chest x-ray
- ■U/S liver

However, every patient will be staged individually based on signs, symptoms, and pathological criteria, for high risk pathology such as TNBC, HER-2 positive BC, then staging will be as in 1.3.2.

Consensus 80%

1.3.2 locally advanced/ metastatic breast cancer

- ■ CT chest, abdomen & pelvis
- ■ Bone scan
- ■ Additional studies as clinically indicated

1.3.4 Indication for Sentinel lymph node:

Sentinel lymph node is indicated in the setting of clinically/ radiological negative Axilla.

1.4 PRE-TREATMENT ASSESSMENT

1.4.1 Discuss all new cases in the multidisciplinary tumor board meeting. .

1.4.2 Echocardiogram or MUGA scan for all HER2 +ve patients planned for HER2 targeted therapy

Age > or equal ٥٥, or high-risk patients such as long standing chronic disease (diabetics or hypertensive) .

1.4.3 General

- ■ Offer available clinical research studies
- ■ Consider family risk for genetic counselling
- ■ Consider fertility counselling if indicated
- ■ Psychological and social support

1.4.4 Final TNM staging based on pathology, if post-surgery, otherwise clinical staging as per TNM (Appendix 4)

II. BREAST CANCER

2.1 DUCTAL CARCINOMA IN SITU (DCIS): Tis N0M0) (refer to surgical guidelines for more details)

2.1.1 Definitive surgery with lumpectomy aiming for 1 cm (10mm) negative surgical margins or mastectomy.

Sentinel lymph node biopsy should be considered for patients who will have mastectomy .

2.1.2 Adjuvant Radio therapy post breast conservative surgery as indicated.

Radio therapy can be omitted in low risk patient : DCIS size less than 15 mm, margins more than 10 mm, age more than 60 and low grade DCIS. (see principle of adjuvant radiation therapy)

2.1.3 For those with ER-positive DCIS, Tamoxifen / AI for risk reduction for ipsilateral and contra lateral breast is not optional, preffered.

2.1.4 Post excision mammogram annually

2.2 LOBULAR CARCINOMA IN SITU (LCIS): Identified on breast biopsy

2.2.1 in Pleomorphic LCIS , surgical excision is indicated.

2.2.2 for other types of LCIS, follow up is sufficient.

III. TREATMENT OF EARLY STAGE INVASIVE BREAST CANCER

(Upfront surgery planned)

3.1LOCAL THERAPY

3.1.1 Surgery

- Breast conserving surgery with sentinel lymph node biopsy

Contraindication for SNB:

- Clinically positive biopsy proven lymph node
- Inflammatory breast cancer.

Contraindication of BCS:

- If radiotherapy is contraindicated for any reason
- A relatively large lesion in a small breast.
- Extensive DCIS by imaging.
- Multicentric tumor/ multifocal.
- Inflammatory BC .
- Retro areolar lesion.

3.1.2 Radiation therapy (See Principle of Radiation Therapy)

- All women who are treated with breast-conserving surgery should have radiation therapy.
- Radiation therapy should follow chemotherapy when chemotherapy is indicated.

3.1.2 Radiation therapy

- All women who are treated with breast-conserving surgery should have radiation therapy.
- Radiotherapy can be omitted in patients age more than 70 years with very low risk of local recurrence AND are willing to take endocrine therapy
- Tumor bed boost is indicated in patients < 50 years old, or with poor pathological features.

- Patients need to be informed about the side effects, including cosmesis, particularly in women with larger breasts size

■. Radiotherapy should be started after wound healing or 3-4 weeks following adjuvant chemotherapy

Indication for radiation therapy post mastectomy:

a. Chest wall radiation therapy
   - ■ Node +ve disease.
   - ■ ≥ T3 / T4 disease.
   - ■ Positive margin or close margin (<1mm).

b. supraclavicular nodal radiation therapy
   - ■ >3 positive lymph nodes.
   - 1-3 metastatic axillary LN with other poor prognostic factors.

c. Axillary nodal radiotherapy
   - ■Incomplete axillary dissection.
   - ■ Patient with axillary sampling.
   - ■Extracapsular invasion.

D. Internal Mammary nodal radiation therapy

- T4 disease
- Medial located tumor with axillary lymph nodes metastasis

E. Dosing schedule
- 40- 42.5 Gy in 15-16 fractions over 3 week
- 45-50.4 Gy in 25-28 Fractions over 5-6 weeks
- Boost dose is 10Gy in 4-5 fractions over one week
- Use bolus as indicated by dosimetric plan where the skin is part of your target volume.
- Treatment breaks should be avoided wherever possible

3.2 Systemic Therapy

(Luminal A), ER-positive, HER2-negative, Ki67 low (less than or equal to 20%) (all should be present)

- Consider ordering Onco-Type DX
- Endocrine therapy alone if oncotype DX recurrence score (RS) is less than 25.
- Chemotherapy may be an option for those younger than 50 years old with RS more than or equal 20.
- Consider short course of chemotherapy in; high tumour burden (four or more positive LN, T3, or high Recurrence score (RS) as per Onco-Type DX

1. Pre-menopausal:
   - Tamoxifen
   - LHRH - Agonist + Tamoxifen
   - LHRH – Agonist + AI (Examastane) especially in women younger than 35 years old, who received chemotherapy.

2. Post-menopausal:
   - Aromatase inhibitors (AI)
   - Tamoxifen

Luminal B Breast cancer:

Luminal B-like (HER2- negative); ER-positive, HER2-negative and either Ki67 high or

HER2 +

ET + CT are indicated for the majority of cases with HER 2 – Luminal B with high recurrence score

Luminal B-like (HER2- positive); ER-positive, HER2-positive, any Ki67, any PgR

CT + anti-HER2 + ET for majority of patients

Notes

- Trastuzumab should be started in parallel with Taxane and then to continue for for 1 year with regular follow-up for cardiac status (Appendix 7)
- The standard duration of Trastuzumab is 12 months. However, 6 months may be an alternative option in selected cases.
- For small Her-2 Positive ER positive BC; the following can be adopted Microinvasive or T1 <0.5 cm consider short course of CT and Trastuzmab or neither.
- Endocrine therapy for all

Triple-negative; ER negative, PgR negative and HER2-negative

Chemotherapy for the majority of patients:

3-4 cycles of Anthracycline based regimen followed by 3-4 cycles of Taxane regimen.

IV. TREATMENT OF LOCALLY ADVANCED INVASIVE BREAST CANCER INFLAMMATORY

Stage IIB, IIIA, IIIB

4.1 Work-up

- As in 1.1, 1.2 and 1.3 (Mammogram + US of affected breast should be available as base line)

4.2 Neoadjuvant Chemotherapy for Her2 amplified tumor.

4.1.1 Three-Four cycles of Anthracycline based regimen followed by 3-4 cycles of Taxane + dual anti Her2 then anti Her2 for 1 year.

4.1.2 TCH (Taxotere/Carboplatin/Herceptin) if Anthracycline is contraindicated.

4.3 Neo-adjuvant therapy for Triple negative breast cancer (TNBC)

4.2.1 3-4 cycles of Anthracycline based regimenfollowed by 3-4 cycles of Taxane regimen.

4.2.2 If BRCA is confirmed triple negative, Taxane/platinum based regimen should be used , if BRCA is unknown, TC should be considered.

4.4 Neo-adjuvant therapy for Hormonal +ve (luminal A)

4.3.1AI for post-menopausal women.

4.3.2 Chemotherapy is an option.

4.5 Assessment response after neoadjuvant chemotherapy.

4.5.1 Clinically every cycle.

4.5.2 Ipsilateral U/S mid therapy.

4.5.3 Ipsilateral U/S / mammography ± MRI at the end of therapy.

Note:

- Change chemotherapy regimen if progress documented clinically by imaging.
- If continue progress, proceed with surgery if feasible.
- If good response, continue chemotherapy all pre-surgery.

4.6 Surgery:

4.6.1 BCS if applicable or MRM (Cases to be discussed in multidisciplinary tumor board).

4.6.2 Inflammatory BC-MRM.

4.7 Radiotherapy (Dr. Yasir new)

Radiotherapy is indicated post neoadjuvant chemotherapy or hormone therapy then mastectomy in

- T3 / T4 disease

- the presence of pathologically positive axillary nodes after neoadjuvant treatment (ypN+)

- positive axillary nodes at presentation even if they become pathologically negative after chemotherapy

4.7 Adjuvant hormonal therapy with Tamoxifen for pre-menopausal and Aromatase

4.7.1 Inhibitor (AI) for post-menopausal and to consider extended treatment for total of 10 years in selected cases.

Follow up of patients treated for early breast Cancer:

- Interval history and physical exam every 4-6 months for 5 years, then every 12months.
- Annual mammography.
- CT/PET CT and MRI imaging should be considered in symptomatic patients as judged appropriate.
- Women on tamoxifen: annual gynaecological assessment every 12 months if uterus present.
- Women on an aromatase inhibitor who experience ovarian failure should have monitoring of bone health with a bone mineral density determination at baseline and periodically thereafter.
- Assess and encourage adherence to adjuvant endocrine therapy.
- Evidence suggests that active lifestyle, achieving and maintaining an ideal body weight (20-25 BMI) may lead to optimal breast cancer outcomes.

V. TREATMENT OF RECURRENT DISEASE:

5.1Local therapy/Regional

- If initial treatment with lumpectomy + radiation therapy (no axillary dissection).
- Completion of mastectomy or second breast conserving surgery.
- If initial treatment with mastectomy + axillary dissection and radiation therapy.
- Surgical resection if possible.
- If initial treatment with mastectomy no prior radiation therapy.

- Surgical resection if possible + radiation therapy to chest wall and supraclavicular and infraclavicular nodes.

5.2 Regional Recurrence

- Axillary recurrence.

5.3 Systemic therapy

- Re-assessmentofER, PR, Her2 status and treat accordingly.
- Hormonal therapy is preferred in hormone sensitive disease.
- In case of loco regional recurrence, which is completely excised, with no systemic disease, there is no evidence that chemotherapy improve overall survival although one study have shown PFS improvement.

- If the local treatment is not satisfactory, then systemic treatment should be considered.

VI. METASTATIC BREAST CANCER:

General considerations

- Metastatic breast cancer (MBC) is generally incurable but Still a treatable disease
- The goals of care are to optimize survival and quality of life.

- The management of MBC is preferable to be done by a comprehensive multidisciplinary team.

- Age alone should not determine the type and intensity of treatment.
- Patient is to be involved in the decision of management plan
- The involvement of supportive palliative team should be encouraged from the time of diagnosis.

6.1 workup for MBC includes a history and physical examination, hematology and biochemistry tests, and imaging of chest, abdomen and bone scan). Brain imaging should be considered only in symptomatic patients.

6.2 The clinical value of routine tumor markers measurement is not well established, their use (if elevated) as an aid to evaluate response to treatment but changing of management should not be based on tumor marker only

6.3 Evaluation of response to therapy should generally occur every 3-4 months for ET or after 3-4 cycles for CT.

6.4 A biopsy of a metastatic lesion is strongly recommended especially for long disease free interval

6.5 The true value of the removal of the primary tumor in patients with stage IV breast cancer is currently unknown but it can be considered in selected patients.

6.6 ER +/HER-2 negative MBC:

- Endocrine based therapy (ET) is the preferred option for hormone receptor positive disease, even in the presence of visceral disease, unless there is concern or proof of visceral crises or endocrine resistance.
- Visceral crisis is defined as severe organ dysfunction as assessed by signs, symptoms, and laboratory studies, leading to a clinical indication for a more rapidly efficacious therapy.
- For pre-menopausal women, ovarian suppression/ablation combined with additional endocrine based therapy is the first choice.

- For Post-menopausal women the preferred 1st line ET is an aromatase inhibitor; the available options include:
  - CDK 4/6 inhibitors + AI
  - Fulvestrant
  - AI
  - Fulvestrant + AI
  - Tamoxifen

- The choice of treatment after the failure of first-line therapy depends on prior therapy; options include:
  - CDK 4/6 inhibitors + Fulvestrant
  - Everolimus + Exemes=tain
  - Fulvestrant
  - Another AI (with a different mechanism of action)
  - Tamoxifen
  - Megestrol acetate

6.7 HER-2 positive MBC:

6.8 For patients with ER-/HER-2+ MBC, the preferred first-line treatment option is Pertuzumab + Trastuzumab + Taxane. Other options include:

- Trastuzumab Emtansine
- Trastuzumab + chemotherapy
- Trastuzumab + other Anti-HER2 therapy

6.9 For patients with ER+/HER-2+ MBC, the preferred first-line therapy is the combination of CT + trastuzumab and pertuzumab is the preferred treatment option. Following completion of chemotherapy, ET is recommended in addition to anti-HER-2 therapy as maintenance.

6.9.1 For patients with ER+/HER-2+ MBC not considered for chemotherapy, the combination of ET + Anti-HER2 therapy is the preferred option.

6.10 In the second line setting, Trastuzumab Emtansine is the preferred option.

Other options include:

- Trastuzumab + another chemotherapy
- Lapatinib + Capecitabine
- Trastuzumab + Lapatinib
- Anti-HER2 + ET

6.11 Chemotherapy for HER-2 negative MBC:

For patients with HER-2 negative MBC for whom CT was chosen as first-line therapy;

- Sequential single-agent chemotherapy is the preferred option.
- Combination CT should be reserved for patients with rapid clinical progression, life-threatening visceral metastases, or need for rapid symptom and/or disease control.
- Imununе therapy can be considered for BRCA negative triple negative breast cancer .
- PARP inhabotir for PRCA mutant

Chemotherapy options include:

- Taxanes
- Anthracyclines
- Capecitabine
- Gemcitabine
- Platinum
- Eribulin
- Ixabepilone

References

1. AGO recommendations on diagnosis and treatment of primary and metastaticbreast cancer, www.ago-online.de.

2. Anglian Breast Cancer Study Group. Prevalence and penetrance of BRCA1 and BRCA2 mutations in a population-based series of breast cancer cases. Br J cancer. 2000; 83:1301-1308.

3. Antonini N, Jones H, Horiot JC, et al. Effect of age and radiation dose on local control after breast conserving treatment: EORTC trial 22881-10882. RadiotherOncol2007; 82:265-271. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17126434.

4. Badwe R, Parmar V, Hawaldar R et al. Surgical removal of primary tumor and axillary lymph nodes in women with metastatic breast cancer at first presentation: a randomized controlled trial. Cancer Res 2013; 73(24 Suppl): S2-02.

5. Bijker N, Meijnen P, Peterse JL, et al. Breast-conserving treatment with or without radiotherapy in ductal carcinoma-in-situ: ten-year results of European.

6. Bonneterre J, Thurlimann B, Robertson JF, et al. Anastrozole versus tamoxifen as first- line therapy for advanced breast cancer in 668 postmenopausal women: results of the Tamoxifen or Arimidex Randomized Group Efficacy and Tolerability study. J CiinOncol2000; 18:3748-3757. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11078487.

7. Burstein HJ, Keshaviah A, Baron AD et al. Trastuzumab plus vinorelbine or taxane chemotherapy for HER2-overexpressing metastatic breast cancer: the trastuzumab and vinorelbine or taxane study. Cancer 2007; 110(5): 965-972.

8. Cardoso* F, Bedard* PL, WinerEP, Pagani 0, Senkus-Konefka E, Fallowfield U, et al, on behalf of the ESO-MBC task force. International guidelines for management of metastatic breast cancer: combination vs sequential single-agent chemotherapy. 1 Natl Cancer Inst2009; 101:1174-81. *co-first authors.

9. Coombes RC, Hall E, Gibson U, et al. A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. N Engl J Med 2004; 350:1081-1092. Available at:

10. Cortes J, O'Shaughnessy J, Loesch D et al. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 openlabel randomised study. Lancet 2011; 377(9769): 914-923.

11. Dupont WD, Page DL. Risk factors for breast cancer in women with proliferative breast disease. N Engl J Med 1985; 312:146-151. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3965932.

12. Edge SB, Byrd DR, Compton CC, et al., eds. AJCC Cancer Staging Manual, 7th Edition. New York: Springer; 2010.

13. Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med 2002; 347:1233-1241. Available at: http://www.nejm.org/doi/ful1/10.1056/NEJMoa022152.

14. Foukakis T, Astrom G, Lindstrom L et al. When to order a biopsy to characterise a metastatic relapse in breast cancer. Ann Oncol 2012; 23(Suppl 10): x349—x35

15. F. Cardoso, A. Costa, L. Norton, D. Cameron, T. Cufer, L. Fallowfield, P. Francis, J. Gligorov, S. Kyriakides, N. Lin, 0. Pagani, E. Senkus, C. Thomssen, M. Aapro, J. Bergh, A. Di Leo, N. El Saghir, P.A. Ganz, K. Gelmon, A. Goldhirsch, N. Harbeck, N. Houssami, C. Hudis, B. Kaufman, M. Leadbeater, M. Mayer, A. Rodger, H. Rugo, V. Sacchini, G. Sledge, L. van't Veer, G. Viale, I. Krop, E. Winer. 1st International consensus guidelines for advanced breast cancer (ABC 1). The Breast 21 (2012) 242-252

16. Gail MH, Costantino JP, Bryant J, et al. Weighing the risks and benefits of tamoxifen treatment for preventing breast cancer. J Natl Cancer Inst1999; 91:1829-1846. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10547390.

17. Goldhirsch A, Wood WC, Coates AS, Gelber RD, Thurlimann B, Senn HJ, Panel members. Strategies for subtypes-dealing with the diversity of breast cancer: highlights of the St. Gallen international expert consensus on the primary therapy of early breast cancer 2011. Ann Oncol 2011;22(8):1736-47.

18. Goss PE, Ingle JN, Martino S, et al. A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. N Engl J Med 2003; 349:1793-1802. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14551341.

19. Goss PE, Ingle JN, Martino S, et al. Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: updated findings from NCIC CTG MA.17. J Natl Cancer Inst2005; 97:1262-1271. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16145047.

20. Hadji P, Aapro MS, Body JJ, Bundred NJ, Brufsky A, Coleman RE, et al. Management of aromatase inhibitor-associated bone loss in postmenopausal women with breast cancer: practical guidance for prevention and treatment. Ann Oncol 2011;22(12):2546-55.

21. Hussain M, Cunnick GH. Management of lobular carcinoma in-situ and atypical lobular hyperplasia of the breast--a review. Eur J SurgOncol2011; 37:279-289.

22. Jakesz R, Jonat W, Gnant M, et al. Switching of postmenopausal women with endocrine-responsive early breast cancer to anastrozole after 2 years' adjuvant tamoxifen: combined results of ABCSG trial 8 and ARNO 95 trial. Lancet 2005; 366:455-462. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16084253.
23. Joensuu H, Bono P, Kataja V, et al. Fluorouracil, epirubicin, and cyclophosphamide with either docetaxel or vinorelbine, with or without trastuzumab, as adjuvant treatments of breast cancer: final results of the FinHer Trial. J ClinOncol2009; 27:5685-5692. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19884557.

24. Krag D, Weaver D, Ashikaga T, et al. The sentinel node in breast cancer--a multicenter Validation study. N Engl J Med 1998; 339:941-946. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9753708.

25. Krag DN, Anderson SJ, Julian TB, et al. Primary outcome results of NSABP B-32, a randomized phase Ill clinical trial to compare sentinel node resection (SNR) to conventional axillary dissection (AD) in clinically node-negative breast cancer patients [abstract]. J ClinOncol 2010;28(Suppl 18): Abstract LBA505. Available at: http://meeting.ascopubs.org/cgi/content/abstract/28/18 supplABA505.

26. Kuehn T, Vogl FD, Helms G, et al. Sentinel-node biopsy for axillary staging in breast cancer: results from a large prospectiveGerman multi-institutional trial. Eur J SurgOncol2004; 30:252-259. Available at: http://www.ncbi.nlm.nih.govipubmed/15028305.

27. Ly BH, Vlastos G, Rapiti E, Vinh-Hung V, Nguyen NP. Local-regional radio-therapy and surgery is associated with a significant survival advantage in metastatic breast cancer patients. Tumori 2010;96(6):947-54.

28. Metcalfe K, Lynch HT, Ghadirian P, et al. Contralateral breast cancer in BRCA1 and BRCA2 mutation carriers. J ClinOncol2004; 22:2328-2335. Available at: http://www.ncbi.nlatnih.gov/pubmed/15197194.

29. Morrogh M, Morris EA, Liberman L, et al. MRI identifies otherwise occult disease in select patients with Paget disease of the nipple. J Am CollSurg2008; 206:316-321. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18222386.

30. National Collaborating Centre for Cancer. Advanced breast cancer: diagnosis and treatment (developed for NICE), www.guidance.nice.org.uk; 2009. website:

31. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines for Breast Cancer, version I, www.nccc.org; 2012.

32. Organisation for Research and Treatment of Cancer randomized phase HI trial 10853--a study by the EORTC Breast Cancer Cooperative Group and EORTC Radiotherapy Group. J ClinOncol2006; 24:3381-3387. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16801628.

33. O'Shaughnessy J, Miles D, Vukelja 5, et al. Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: phase III trial results. J ClinOncol2002; 20:2812-2823. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12065558.

34. O'Shaughnessy JA, Blum J, Moiseyenko V et al. Randomized, open-label, phase II trial of oral capecitabine (Xeloda) vs a reference arm of intravenous CMF (cyclophosphamide, methotrexate and 5-fluorouracil) as first-line therapy for advanced/metastatic breast cancer. Ann Oncol 2001; 12: 1247-1254

35. Patchell RA, Tibbs PA, Walsh JW, Dempsey RJ, Maruyama Y, Kryscio RJ, et al. A randomized trial of surgery in the treatment of single metastases to the brain. N Engl J Med 1990;322(8):494-500.

36. Patil CG, Pricola K, Garg SK, Bryant A, Black KL. Whole brain radiation therapy (WBRT) alone versus WBRT and radiosurgery for the treatment of brain metastases. Cochrane Database Syst Rev 2010 (6): CD006121.

37. Petrelli F, Coinu A, Borgonovo K et al. The value of platinum agents as neoadjuvant chemotherapy in triple-negative breast cancers: a systematic review and meta-analysis. Breast Cancer Res Treat 2014; 144(2): 223-232.

38. Pignol J, Olivotto I, Rakovitch E, et al. Plenary 1: Phase III randomized study of intensity modulated radiation therapy versus standard wedging technique for adjuvant breast radiotherapy [abstract]. Int J RadiatOncolBiolPhys 2006;66(Suppl 1): S1. Available at:http://www.sciencedirect.com/science/article/B6T7X-4M3HN2Y G/2/884fa5eebd14ea7b80e38fc3ea39664c.

39. Robert NJ, Dieras V, Glaspy J, et al. RIBBON-1: Randomized, double-blind, placebo- controlled, phase III trial of chemotherapy with or without bevacizumab (B) for first-line treatment of HER2-negative locally recurrent or metastatic breast cancer (MBC) [abstract]. J ClinOncol 2009;27(Suppl 15): Abstract 1005. Available at:http://meeting.ascopubs.org/cgi/content/abstract/27/15S/1005.

40. Roche H, Fumoleau P, Spielmann M, et al. Sequential adjuvant epirubicin-based and docetaxel chemotherapy for node-positive breast cancer patients: the FNCLCC PACS 01 Trial. J ClinOncol2006; 24:5664-5671. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17116941.

41. Rosselli Del Turco M, Palli D, Cariddi A, et al. Intensive diagnostic follow-up after treatment of primary breast cancer. A randomized trial. National Research Council Project on Breast Cancer follow-up. JAMA 1994; 271:1593-1597. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7848404.

42. Shien T, Nakamura K, Shibata T et al. A randomized controlled trial comparing primary tumour resection plus systemic therapy with systemic therapy alone in metastatic breast cancer (PRIM-BC): Japan Clinical Oncology Group Study JCOG1017. Jpn J ClinOncol 2012; 42: 970-973.

43. Slamon D, Eiermann W, Robert N, et al. BCIRG 006: 2nd interim analysis phase III randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxel (ACT) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (ACTH) with docetaxel, carboplatin and trastuzumab (TCH) in Her2neu positive early breast cancer patients [abstract]. San Antonio Breast Cancer Symposium 2006: Abstract 52.

44. Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 2001;344(11):783-92.

45. Smith 1E, Dowsett M, Yap Y-S, et al. Adjuvant aromatase inhibitors for early breast cancer after chemotherapy-induced amenorrhoea: caution and suggested guidelines. J ClinOncol2006; 24:2444-2447. Available at: .

46. Soran A, Ozmen V, Ozbas S et al. Early follow up of a randomized trial evaluating resection of the primary breast tumor in women presenting with de novo stage IV breast cancer: Turkish Study (Protocol MF07-01). Cancer Res 2013; 73(24 Suppl): 52-03.

47. Temel JS, Greer JA, Muzikansky A, Gallagher ER, Admane S, Jackson VA, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. N Engl J Med 2010;19(363(8)):733-42.

48. Theriault RL. The role of bisphosphonates in breast cancer. J NatlComprCancNetw 2003; 1:232-241. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19768882.

49. Veronesi U, Cascinelli N, Mariani L, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. N Engl J Med 2002; 347:1227-1232. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12393819.

50. Von Minckwitz G, du Bois A, Schmidt M, et al. Trastuzumab beyond progression in human epidermal growth factor receptor 2-positive advanced breast cancer: a german breast group 26/breast international group 03-05 study. J ClinOncol2009; 27:1999-2006. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19289619.

51. Whelan T, MacKenzie R, Julian J, et al. Randomized trial of breast irradiation schedules after lumpectomy for women with lymph node-negative breast cancer. J Natl Cancer Inst2002; 94:1143-1150. Available at: .

52. Wilkinson NW, Shahryarinejad A, Winston JS, et al. Concordance with breast cancer pathology reporting practice guidelines. J Am CollSurg2003; 196:38-43. Available at: http: fiwww.ncbi.nlm.nih.govjpubmed/12517547.

Appendix 1

RISK EVALUATION

Age: ☐ Menarche: ☐ Height (m): ☐ Weight (kg): ☐ Measurements:
BMI: ☐ Metric: ☐ Imperial: ☐

Exercise Level:***
Light: ☐
Moderate: ☐
High: ☐

Nulliparity: ☐
Parity: ☐
Unknown: ☐
Age at first child: ☐

Premenopausal: ☐
Perimenopausal: ☐
Postmenopausal: ☐
No information: ☐
Age at menopause: ☐

HRT Use:
Never: ☐
5 or more years ago: ☐
Less than 5 years ago: ☐
Current user: ☐
Length of use (years): ☐

Age at first baby ☐
Duration bet. pregnancy:

Breast Feeding:
>6 mos: ☐
<6 mos: ☐
1 - 2 yrs: ☐

OCP:
Before first baby: ☐
Long duration >5yrs:

Family History (First Degree):

Mother: Ovarian: ☐ Bilateral: ☐ BC: ☐ Age: ☐

Sister: Ovarian: ☐ Bilareral: ☐ BC: ☐ Age: ☐

Show start up screen

Paternal Gran: Ovarian: ☐ BC: ☐ Age: ☐

Maternal Gran: Ovarian: ☐ BC: ☐ Age: ☐

Affected Nieces
Genetic Testing

Paternal Aunts: No. ☐ Ovarian: ☐ BC: ☐ Age: ☐

Maternal Aunts: No. ☐ Ovarian: ☐ BC: ☐ Age: ☐

Daughters: No. ☐ Ovarian: ☐ BC: ☐ Age: ☐

Previous History of:
BC: ☐ DCIS: ☐

Breast Density:
Raw image: ☐ Digital mammogram: ☐

Previous Breast Biopsy:
Hyperplasia: ☐ Atypical Hyperplasia: ☐ Ovarian Cancer: ☐
Prolieferatal Fibrocyptic: ☐ LCIS: ☐

Smoking: ☐

***

Light — *Does not induce sweating unless it's a hot, humid day. There is no noticeable change in breathing patterns.*

Moderate — *Will break a sweat after performing the activity for about 10 minutes. Breathing becomes deeper and more frequent. You can carry on a conversation but not sing.*

High — *Will break a sweat after 3-5 minutes. Breathing is deep and rapid. You can only talk in short phrases.*

Appendix 2

Main Clinical indications for Breast MRI

1. To define extent of cancer or presence of multifocal or multi centric.
2. For evaluation before and after neoadjuvant therapy.
3. To detect additional disease in women with mammographically dense breast.
4. For identifying primary cancer in women with axillary nodal adenocarcinoma or with Paget's disease of the nipple with breast primary not identified on mammography and ultrasound.

Appendix 3

Minimum core biopsy (Dr. Kush)

Minimal Reporting Guidelines-Breast Carcinoma (Mastectomy & Lumpectomy Specimen)

The Pathology report with breast carcinoma in mastectomy and lumpectomy specimens should at least include all the following items:

- Side
  - Right or left (if bilateral please describe each side individually).
- Procedure/ Specimen Type:
  - Lumpectomy, mastectomy +/- axillary dissection.
- Invasive carcinoma histologic type and variant if applicable
  - See note
- Greatest linear invasive tumor dimension
  - Solitary/ multiple
  - Specify if more than one focus and state the greatest diameter of each focus.
- Histologic grade of invasive carcinoma
  - See note
- Presence or absence of in situ component (DCIS or LCIS)
  - If DCIS present state:

➢ Type, grade, presence or absence of necrosis (comedo type necrosis) and extent of DCIS (% of total tumor volume-see reporting DCIS).

- Lymph vascular invasion
  - State if there is extensive lymphatic/ vascular invasion (>10 lymphatics involved).
  - Specify if dermal lymphatics are involved.
- Surgical margins (for invasive and in situ)
  - Positive margin (at the inked or within less than1 mm), close margin (1-<2 mm), free margin (>2 mm)
  - State the distance of the closest in mm, and state which margin if possible.

- Lymph node status
    - X of Y lymph nodes positive for metastatic carcinoma, size of largest metastasis with or without extra nodal tumor spread.
- Involvement of skin, nipple, or skeletal muscle by invasive carcinoma
    - Skin ulceration, dermal invasion, nipple involvement (Paget's disease, stromal invasion.
- Index microcalcifications
    - Present/ absent
- Status of background breast tissue
    - Atypical hyperplasia, benign mass forming lesions
- Status of estrogen& progesterone receptors, and Her2-neu expression
    - FISH for HER2+ +2 on IHC
    - Strength and extent of positivity of hormonal receptor
    - Her2 testing should be done in an accredited lab
- pTNMtumor stage

Minimal Reporting Guidelines-Ductal Carcinoma in Situ (DCIS)

The Pathology report with DCIS alone should at least include all the following items:

- Type of DCIS
- Presence or absence of necrosis
- Grade
    - Nuclear grade (1, 2 and 3)
- Surgical Margins
    - State the distance of the closest margin in mm, and state which margin if possible.

- Presence or absence of microinvasion/ invasion
    - State the distance of invasive component from the in-situ source
    - State if multiple sites contain micro invasive/ invasion and the maximum distance.

- Index microcalcifications

- ER and PR status

Appendix 4. Staging

Disease stage should be assessed according to the Tumour Node Metastases (TNM) staging system[i].

Primary Tumour (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
Tis (DCIS)	Ductal carcinoma in situ
Tis (LCIS)	Lobular carcinoma in situ
Tis (Paget's)	Paget's disease (Paget disease) of the nipple NOT associated with invasive carcinoma and/or carcinoma in situ (DCIS and/or LCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget's disease are categorized based on the size and characteristics of the parenchymal disease, although the presence of Paget's disease should still be noted.
T1	Tumor ≤20 mm in greatest dimension
T1mi	Tumor ≤1 mm in greatest dimension
T1a	Tumor>1 mm but ≤5 mm in greatest dimension
T1b	Tumor>5 mm but ≤10 mm in greatest dimension
T1c	Tumor>10 mm but ≤20 mm in greatest dimension
T2	Tumor>20 mm but ≤50 mm in greatest dimension
T3	Tumor>50 mm in greatest dimension
T4	Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules)
T4a	Extension to the chest wall, not including only pectoralis muscle adherence/invasion
T4b	Ulceration and/or ipsilateral satellite nodules and/or edema (including peaud'orange) of the skin, which do not meet the criteria for inflammatory carcinoma
T4c	Both T4a and T4b
T4d	Inflammatory carcinoma

Regional lymph nodes (clinical)

NX	Regional lymph nodes cannot be assessed (eg, previously removed)
N0	No regional lymph node metastases
N1	Metastases to movable ipsilateral level I, II axillary lymph node(s)
N2	Metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted; or in clinically detected ipsilateral internal mammary nodes in the *absence* of clinically evident axillary lymph node metastases
N2a	Metastases in ipsilateral level I, II axillary lymph nodes fixed to one another (matted) or to other structures
N2b	Metastases only in clinically detected ipsilateral internal mammary nodes and in the *absence* of clinically evident level I, II axillary lymph node metastases

N3	Metastases in ipsilateralinfraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph node involvement; or in clinically detected ipsilateral internal mammary lymph node(s) with clinically evident level I, II axillary lymph node metastases; or metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or
	internal mammary lymph node involvement
N3a	Metastases in ipsilateralinfraclavicular lymph node(s)
N3b	Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
N3c	Metastases in ipsilateral supraclavicular lymph node(s)

Regional Lymph nodes (Pathological

pNX	Regional lymph nodes cannot be assessed (eg, previously removed, or not removed for pathologic study)
pN0	No regional lymph node metastasis identified histologically
pN0(i-)	No regional lymph node metastases histologically, negative immunohistochemistry (IHC)
pN0(i+)	Malignant cells in regional lymph node(s) no greater than 0.2 mm (detected by H&E or IHC including isolated tumor cell clusters (ITC))
pN0(mol-)	No regional lymph node metastases histologically, negative molecular findings (RT-PCR)
pN0(mol+)	Positive molecular findings (RT-PCR), but no regional lymph node metastases detected by histology or IHC
pN1	Micrometastases; or metastases in 1-3 axillary lymph nodes; and/or in internal mammary nodes with metastases detected by sentinel lymph node biopsy but not clinically detected
pN1mi	Micrometastases (greater than 0.2 mm and/or more than 200 cells, but none greater than 2.0 mm)
pN1a	Metastases in 1-3 axillary lymph nodes, at least one metastasis greater than 2 mm
pN1b	Metastases in internal mammary nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected
pN1c	Metastases in 1-3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected
pN2	Metastases in 4-9 axillary lymph nodes; or in clinically detected internal mammary lymph nodes in the *absence* of axillary lymph node metastases
pN2a	Metastases in 4-9 axillary lymph nodes (at least one tumor deposit greater than 2.0 mm)
pN2b	Metastases in clinically detected internal mammary lymph nodes in the *absence* of axillary lymph node metastases

pN3	Metastases in ten or more axillary lymph nodes; or in infraclavicular (level III axillary) lymph nodes; or in clinically detected ipsilateral internal mammary lymph nodes in the *presence* of one or more positive level I, II axillary lymph nodes; or in more than three axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected; or in ipsilateral supraclavicular lymph nodes
pN3a	Metastases in ten or more axillary lymph nodes (at least one tumor deposit greater than 2.0 mm); or metastases to the infraclavicular (level III axillary lymph) nodes
pN3b	Metastases in clinically detected ipsilateral internal mammary lymph nodes in the *presence* of one or more positive axillary lymph nodes; or in more than three axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected
pN3c	Metastases in ipsilateral supraclavicular lymph nodes

Distant metastases

M0	No clinical or radiographic evidence of distant metastases
cM0(i+)	No clinical or radiographic evidence of distant metastases, but deposits of molecularly or microscopically detected tumor cells in circulating blood, bone marrow, or other nonregional nodal tissue that are no larger

	than 0.2 mm in a patient without symptoms or signs of metastases
M1	Distant detectable metastases as determined by classic clinical and radiographic means and/or histologically proven larger than 0.2 mm

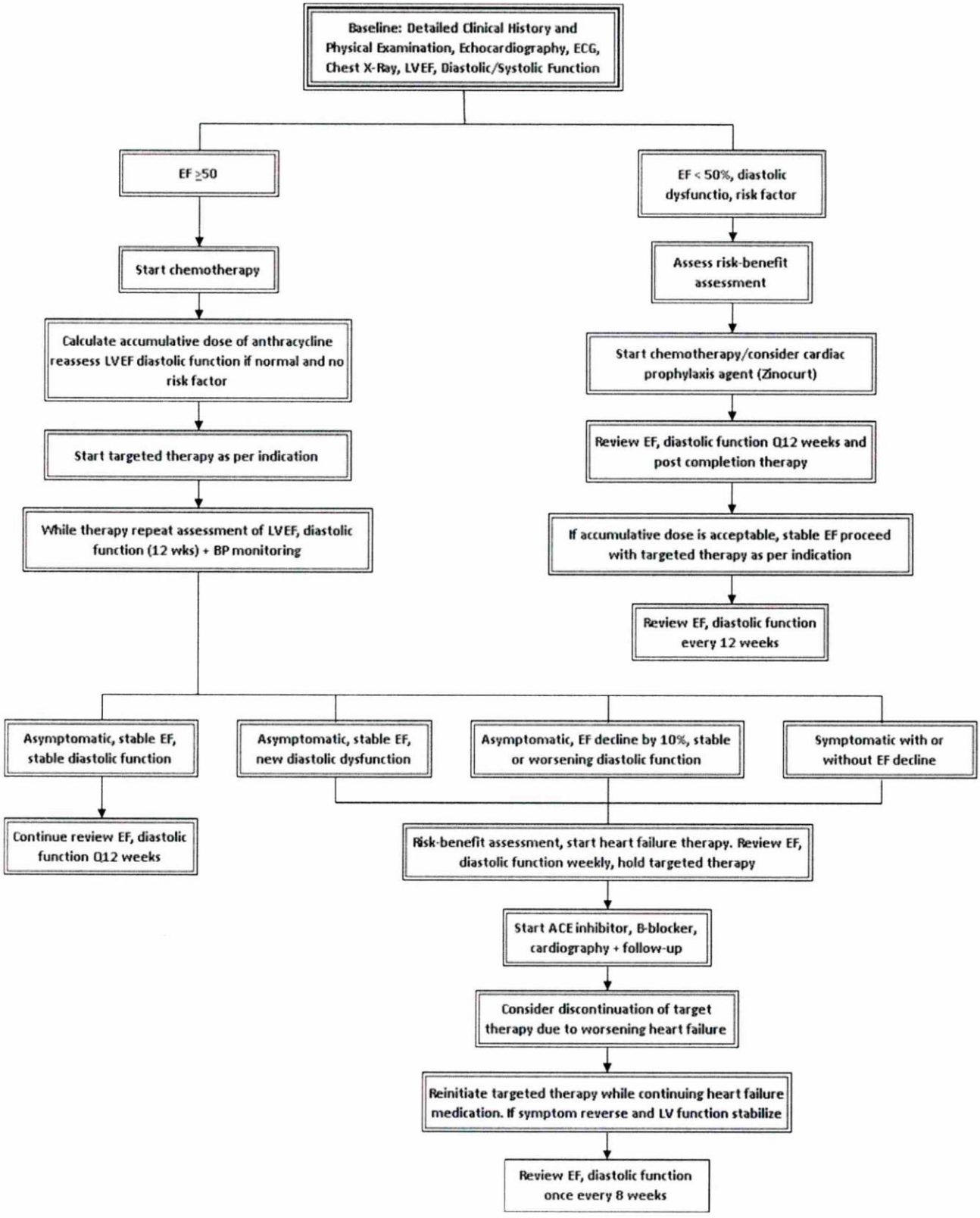
Anatomic stage/ Prognostic groups

0	Tis	N0	M0
IA	T1	N0	M0
IB	T0	N1mi	M0
	T1	N1mi	M0
IIA	T0	N1	M0
	T1	N1	M0
	T2	N0	M0
IIB	T2	N1	M0
	T3	N0	M0
IIIA	T0	N2	M0
	T1	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0

IIIC	Any T	N3	M0
IV	Any T	Any N	M1

Appendix 5

Algorithm for the management of cardiac toxicities



AJCC (American Joint Committee on Cancer). Cancer Staging Manual, 7th edition, Edge SB, Byrd DR, Compton CC, et al (Eds), Springer-Verlag, New York 2010. p.3