



# The Role of Surgery in Stage IV Breast Cancer

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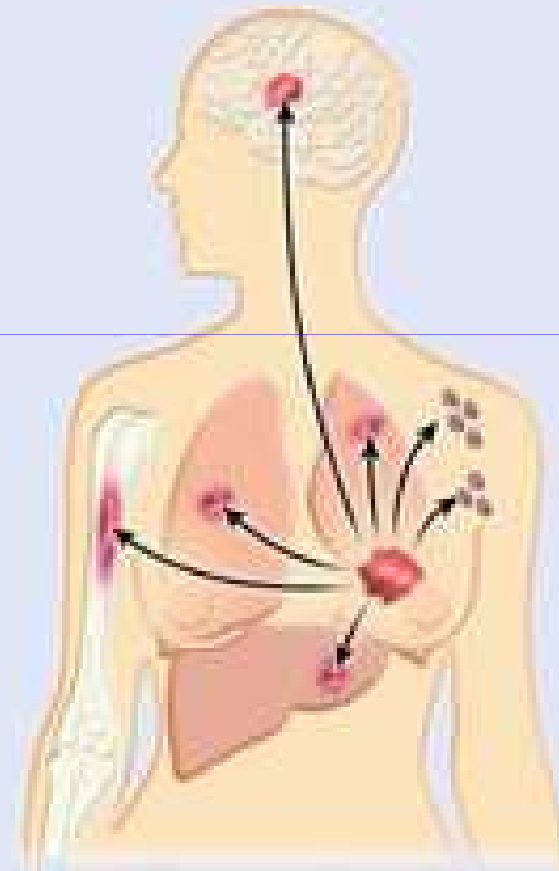
THE UNIVERSITY OF TEXAS  
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CANCER CENTER

# Surgery in Stage IV Breast Cancer

- Overview
  - Impact of resection of the primary on outcomes
    - Survival
    - Chest wall control
    - Distant disease progression
  - Extent of nodal evaluation
  - Role of radiation
  - Prospective trial

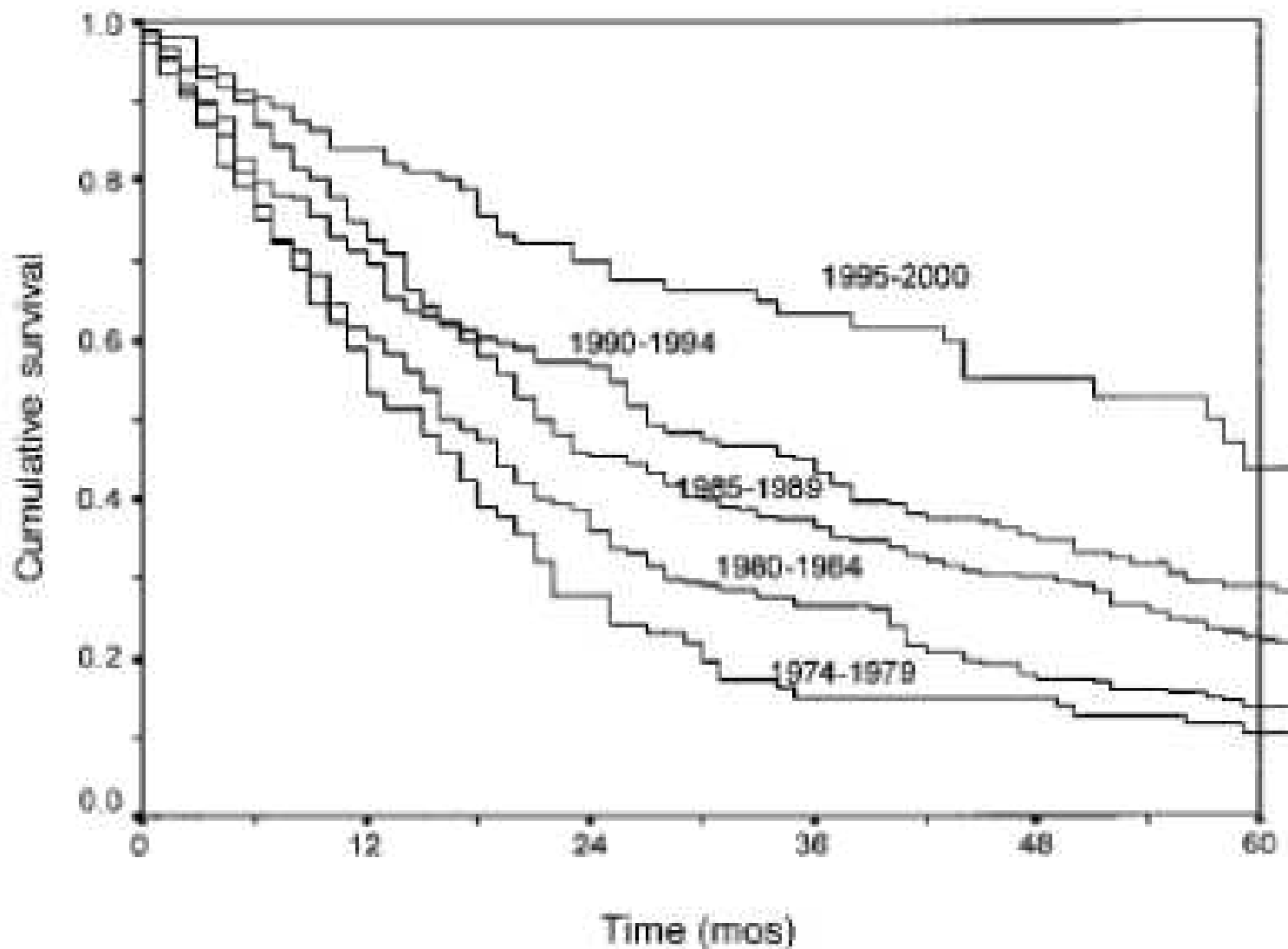
# Stage IV Breast Cancer

- In the U.S.  
~6% present with stage IV disease
- Undeveloped countries: up to 20%



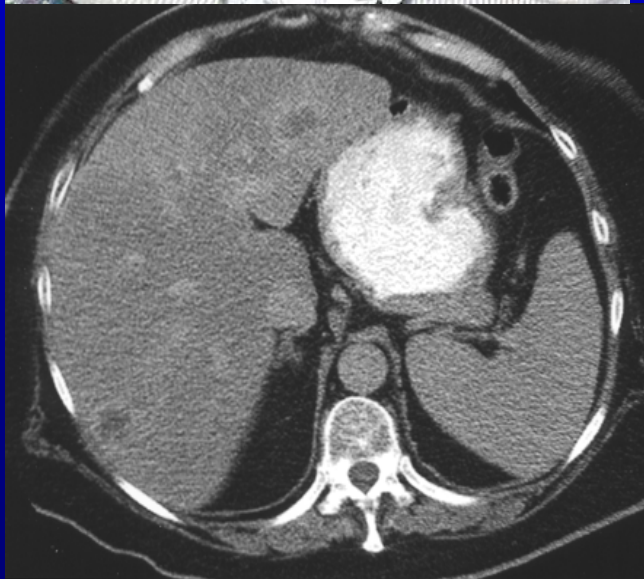
# Surgical Treatment of Stage IV Disease

- National Cancer Institute, U.S. National Institutes of Health
  - “Surgery may be indicated for selected patients. Examples include patients who need mastectomies for fungating/painful breast lesions, parenchymal or vertebral metastases with spinal cord compression , isolated lung metastases, pathologic (or impending) fractures or pleural or pericardial effusions”



Overall survival from time of recurrence.

# Stage IV Breast Cancer



- Stage IV disease is incurable
- Best treatment is systemic therapy
- Surgery is palliative

# Clinical Scenarios

- Patient presents with newly diagnosed breast cancer & bone pain. Bone scan positive.
  - Treatment for the primary?
- Recent BCT, positive nodes, screening bone scan shows metastases.
  - Follow systemic therapy with radiation?
- Local recurrence in the conserved breast, metastatic survey shows metastases.
  - Any treatment for the local disease?

Is there a role for surgical treatment  
of the primary tumor?



# Surgery in Stage IV Disease

- Aggressive local therapy improves survival in metastatic tumors of other organs
  - Colorectal cancer
  - Renal cell carcinoma
  - Gastric cancer
  - Ovarian cancer

Goldberg, et al., *Ann Intern Med* 1998

Flanigan ,et al., *N Engl J Med* 2001

Lin, et al., *J Cancer Res Clin Oncol* 2008

Rafii, et al., *Int J Gynecol Cancer* 2007

# Resection of the Primary Tumor

## Surgical Resection of Primary for Stage IV Breast Cancer

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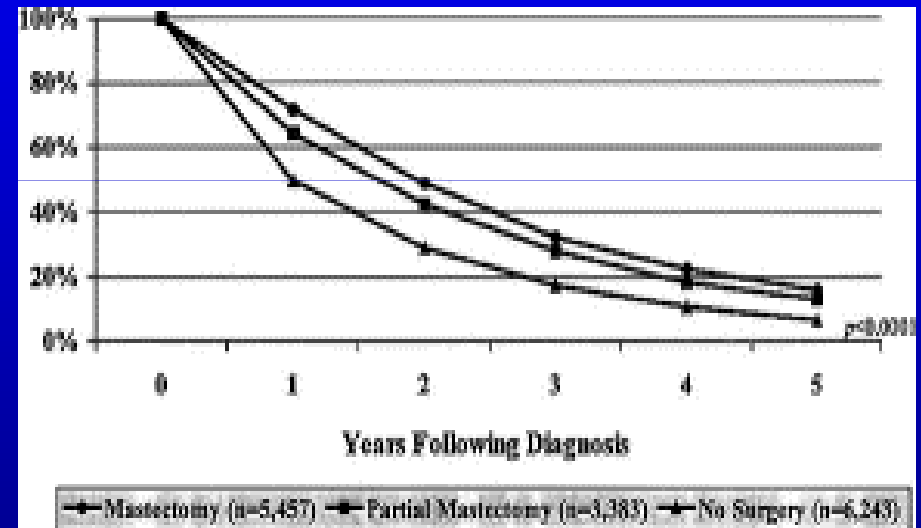
Study	Period	Design	n	Results
Khan 2002	90-93	Retrospective	16,023	Improved survival
Babiera 2006	97-02	Retrospective	224	Improved survival
Rapiti 2006	77-96	Retrospective	300	Improved survival
Gnerlich 2007	99-03	Retrospective	9734	Improved survival
Fields 2007	96-05	Retrospective	409	Improved survival
Bafford 2008	98-05	Retrospective	147	Improved survival

# Surgical Resection of Primary Tumor for Stage IV Breast Cancer

- Khan S, et al.
  - National Cancer Data Base, 1990-1993
  - 16,023 patients treated for stage IV breast cancer
    - Surgery 9162 (57%)
      - Partial mastectomy 3513 (38%)
      - Total mastectomy 5649 (62%)
    - No surgery 6861 (43%)

# Surgical Resection of Primary Tumor for Stage IV Breast Cancer

- 3-yr observed survival
  - No surgery 17.3%
  - Partial mastectomy 27.7%
  - Total mastectomy 31.8%
- Independent prognostic covariates
  - Number metastatic sites
  - Type metastatic burden
  - Extent of resection of primary tumor

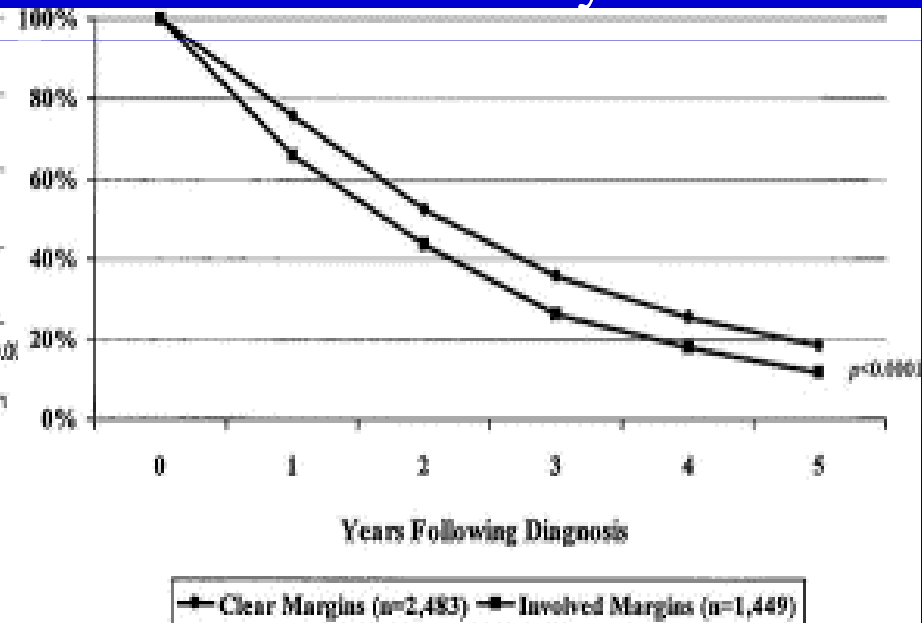
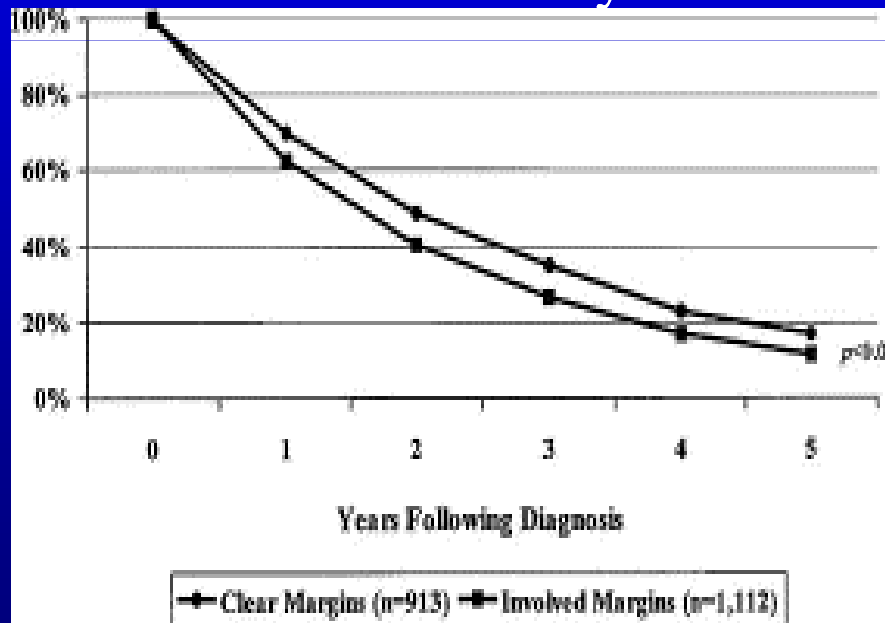


# Surgical Resection of Primary Tumor for Stage IV Breast Cancer

Free surgical margins associated with improved 3-year survival

Observed survival after partial mastectomy

Observed survival after total mastectomy



Khan S, et al., *Surgery* 2002

# Surgical Resection of Primary Tumor for Stage IV Breast Cancer

- Khan et al. Surgery 2002
- Tumor free margins important in outcome
- Overall prognosis improved with surgery (HR of 0.61)
- Treatment in 1990-1993 – older systemic therapy regimens

# Surgical Resection of Primary Tumor for Stage IV Breast Cancer

- Study weakness: selection bias
  - Did patients undergoing surgery have more indolent tumors?
  - Smaller disease burden?
- “data are internally consistent thereby supporting the hypothesis that local therapy is valuable even in the presence of distant disease”

# Surgical Resection of the Primary Tumor in Stage IV Breast Cancer

- Population based observational study – 300 pts
- Geneva Cancer Registry 1977-1996
- Pts with margin negative resection of the primary tumor had a 40% reduced risk of death over pts who had positive margins or no surgery
- Bone only disease fared better

Rapiti E, et al., *J Clin Oncol* 2006



# MDACC Experience

- Retrospective, Single Institution Review
- All patients with intact Stage IV breast cancer between 1997-2002
  - Patients diagnosed with metastasis within 3 mos of diagnosis of breast cancer
- 500 patients evaluated
  - 224 patients met final study criteria
- 118 point review
  - Demographic data
  - Pathological characteristics
  - Treatment
  - Response Evaluation Criteria in Solid Tumors Group (RECIST) at 3 month intervals
  - Final follow-up

# MDACC Experience

- 142 patients who underwent medical therapy alone
- 82 patients who underwent surgical intervention at their breast site
  - 39 segmental mastectomy
  - 43 mastectomy
- Median follow-up 32.1 months
- 38 deaths

# Surgery vs No Surgery

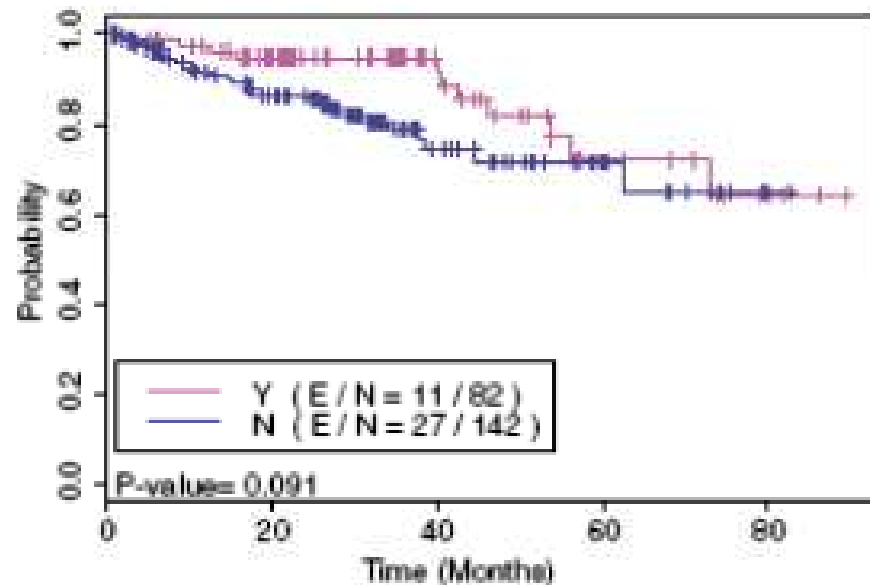


FIG. 1. Overall survival by surgery status. Kaplan-Meier curves show overall survival in the surgery (Y) and non-surgery (N) groups. E/N, number of events/total sample size.

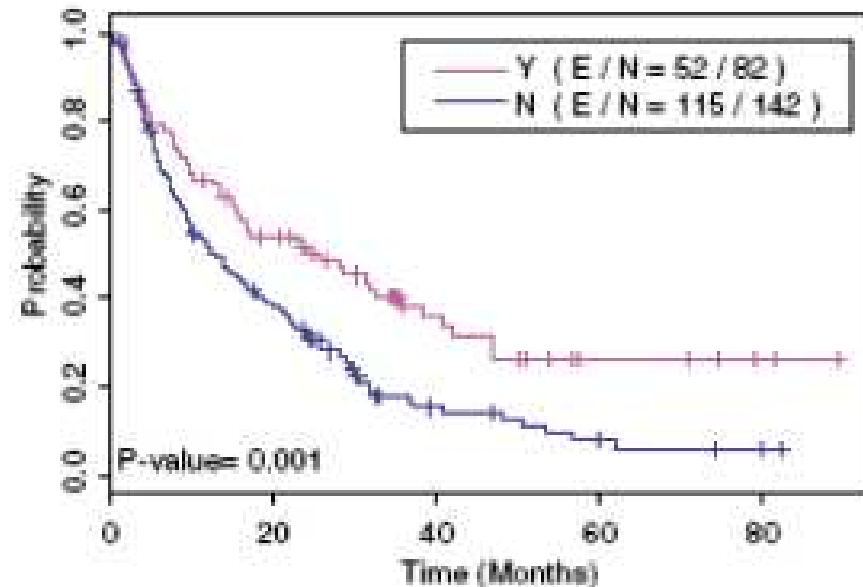


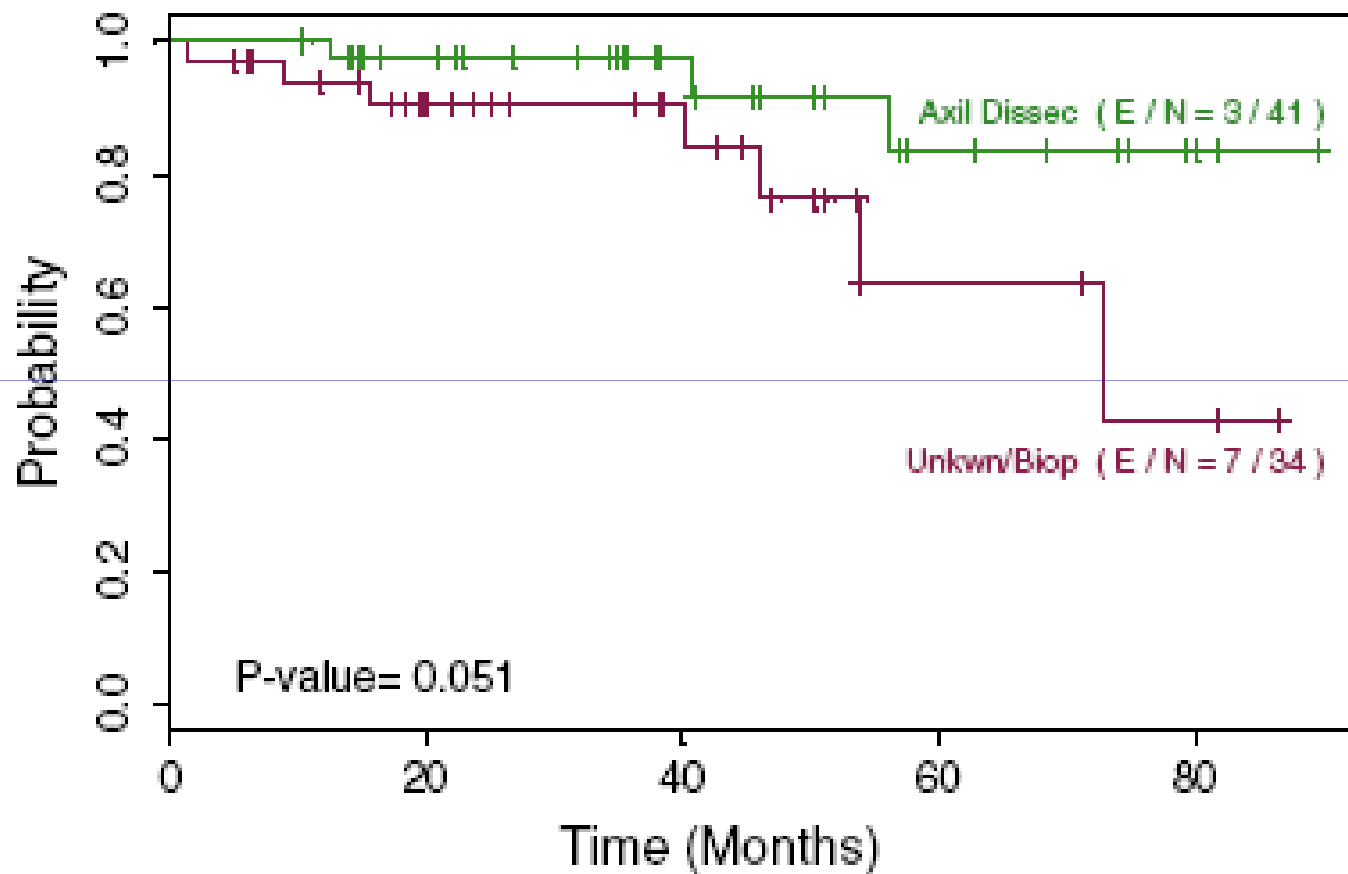
FIG. 2. Metastatic progression-free survival by surgery status. Kaplan-Meier curves show metastatic progression-free survival in the surgery (Y) and non-surgery (N) groups. E/N, number of events/total sample size.

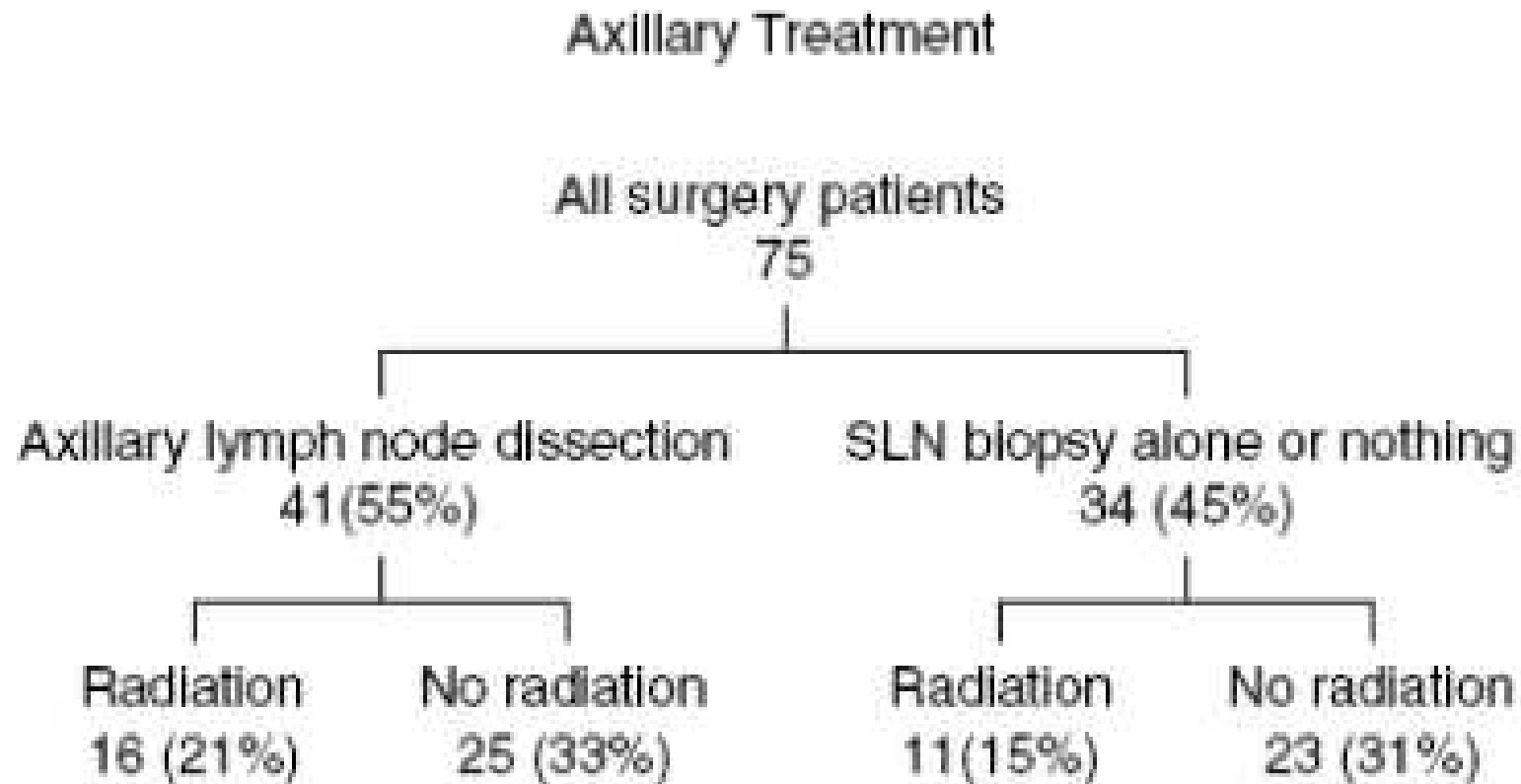
# MDACC Patient Characteristics

- Patients in Surgical Group:
  - Only 1 site of metastasis
  - Chemotherapy as first line treatment
  - Younger age
  - More patients with bone and liver metastases
  - Lower nodal stages
  - More Her 2 positive

# Role for Axillary Evaluation

### Overall Survival by Axillary Evaluation





Rao R, et al. Ann Surg Oncol 2008

# Role of Local-Regional Treatment

## Local-regional treatment

- Surgery vs no surgery of intact primary
  - Surgical – curative vs local control

## Radiation therapy

- Target volume chest wall and draining lymphatics
- PMRT
  - 51 Gy in 1.5 Gy fractions BID
  - 15 Gy boost to chest wall
- No surgery
  - 51 Gy in 34 fractions BID
  - No boost fields except for infraclavicular or supraclavicular involvement



# Prospective Studies

- Prospective Study
  - TBCRC 013
- Randomized Prospective Study
  - ECOG2108
  - MF07-01
  - M1

*A Prospective Analysis of Surgery in  
Patients Presenting with Stage IV Breast  
Cancer*

**TBCRC 013**

# TBCRC 013

- Objectives
  - Primary
    - Characterize patients with stage IV breast cancer while documenting clinical management outcomes
  - Registry
    - Demographics, clinico-pathologic data, blood samples, tissue samples from locoregional and distant disease
  - Consortium of 15 leading institutions

# TBCRC 013

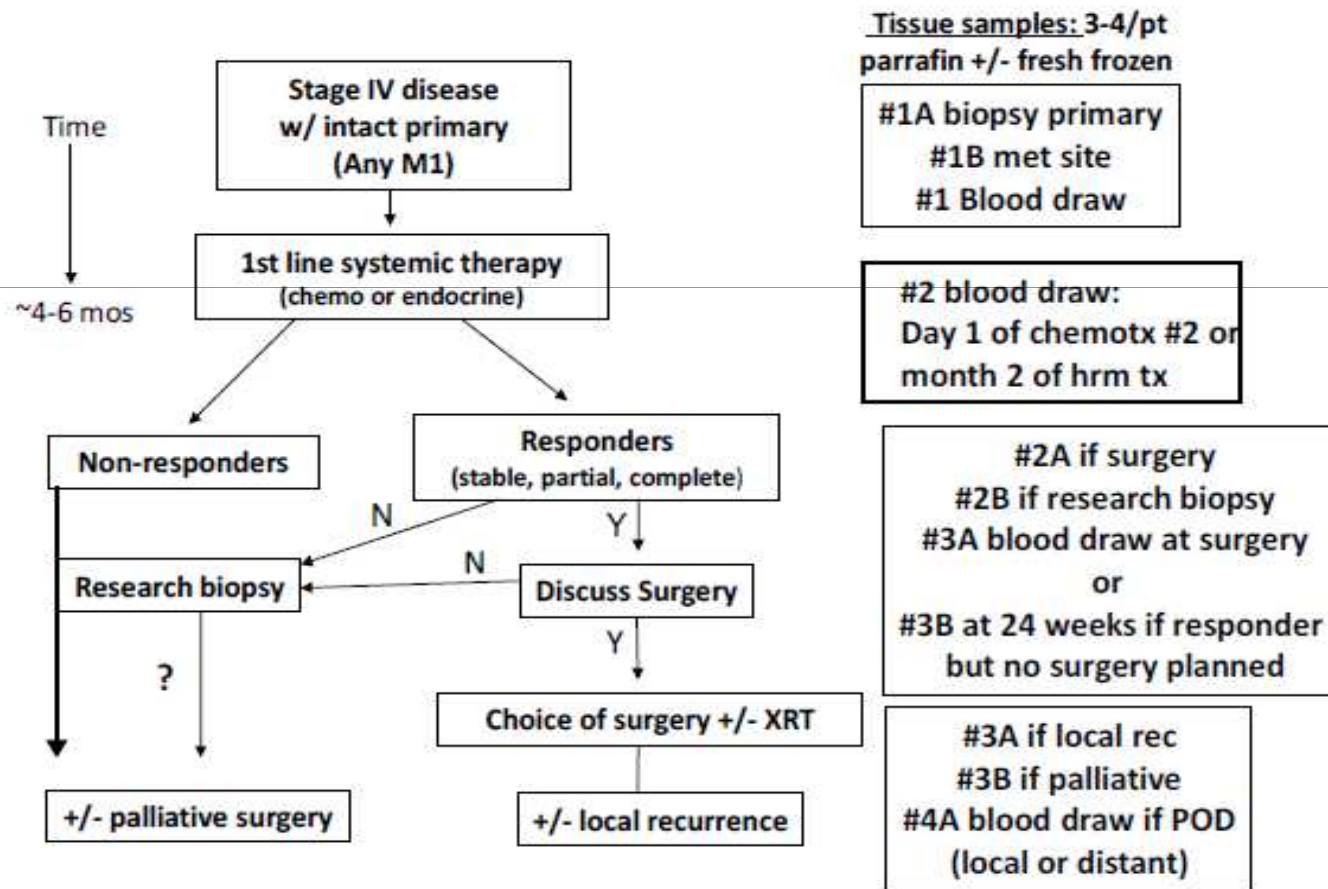
- Aims
  - Measure response to first-line therapy, frequency of surgical referral and proportion of patients undergoing surgery
    - Socio-demographic information
    - Surgical decision-making process
  - Determine incidence of uncontrolled local disease, frequency of surgical palliation
  - Correlate molecular characteristics of primary tumor with conventional prognostic factors

# TBCRC 013

- Aims
  - Perform correlative molecular studies of circulating tumor cells, primary and metastatic tumor samples for future validation studies
    - Correlation of oncoTYPE dx recurrence scores and outcome
    - Patterns of methylation between primary and metastatic sites
    - Tumor endothelial markers between primary and metastatic sites
    - Circulating tumors for genomic analysis

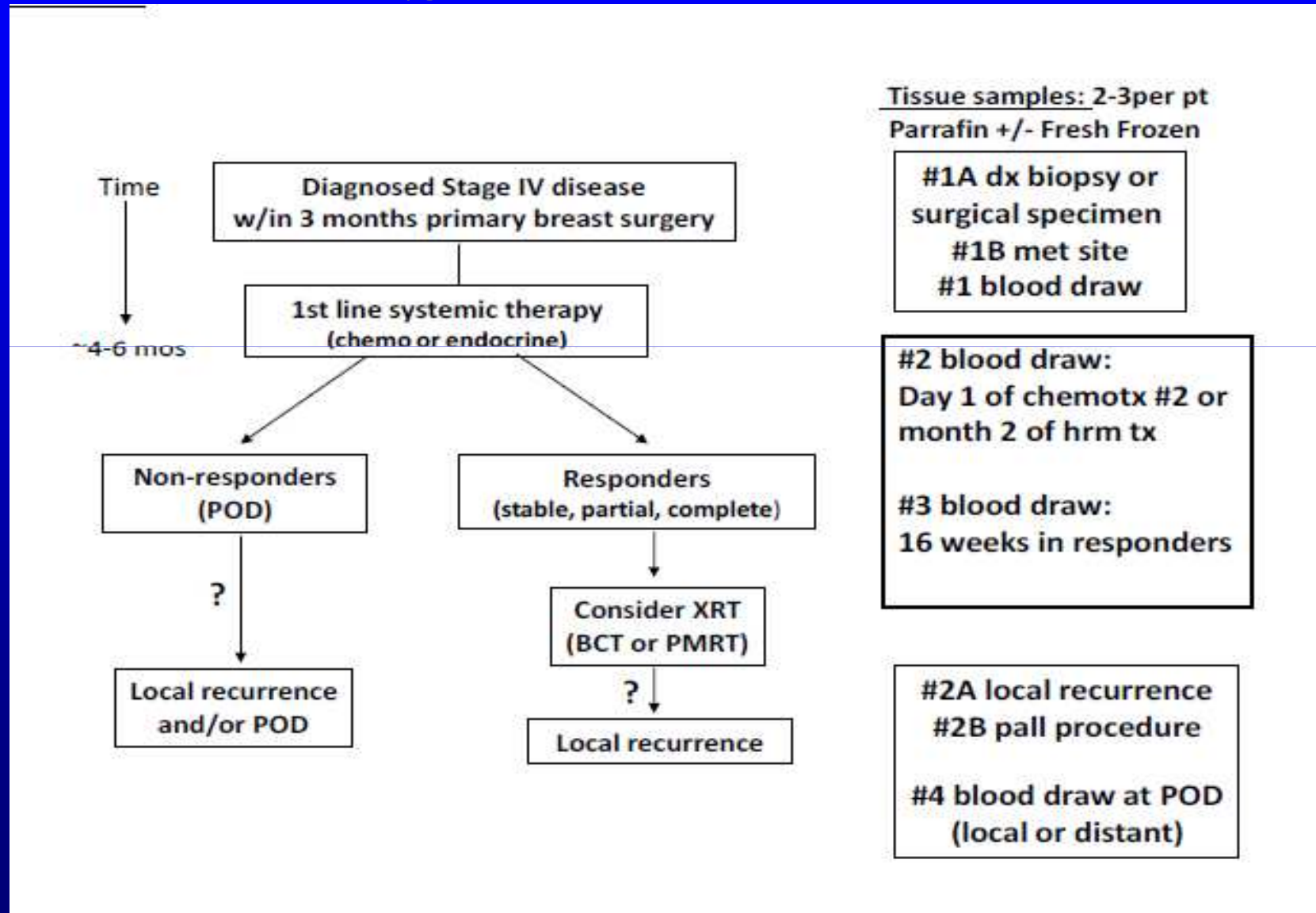
# TBCRC 013

## Scheme A



# TBCRC 013

## Scheme B



A Randomized Phase III Trial of  
the Value Of Early Local Therapy  
for the Intact Primary Tumor in  
Patients with Metastatic Breast  
Cancer

ECOG E2108

PI Seema Khan, MD



# ECOG E2108

## Objectives

- Primary
  - To evaluate whether early local therapy of non-progressing intact primary in women with Stage IV breast cancer will result in prolonged survival compares to those who receive local therapy for palliation only

# ECOG E2108

## Objectives

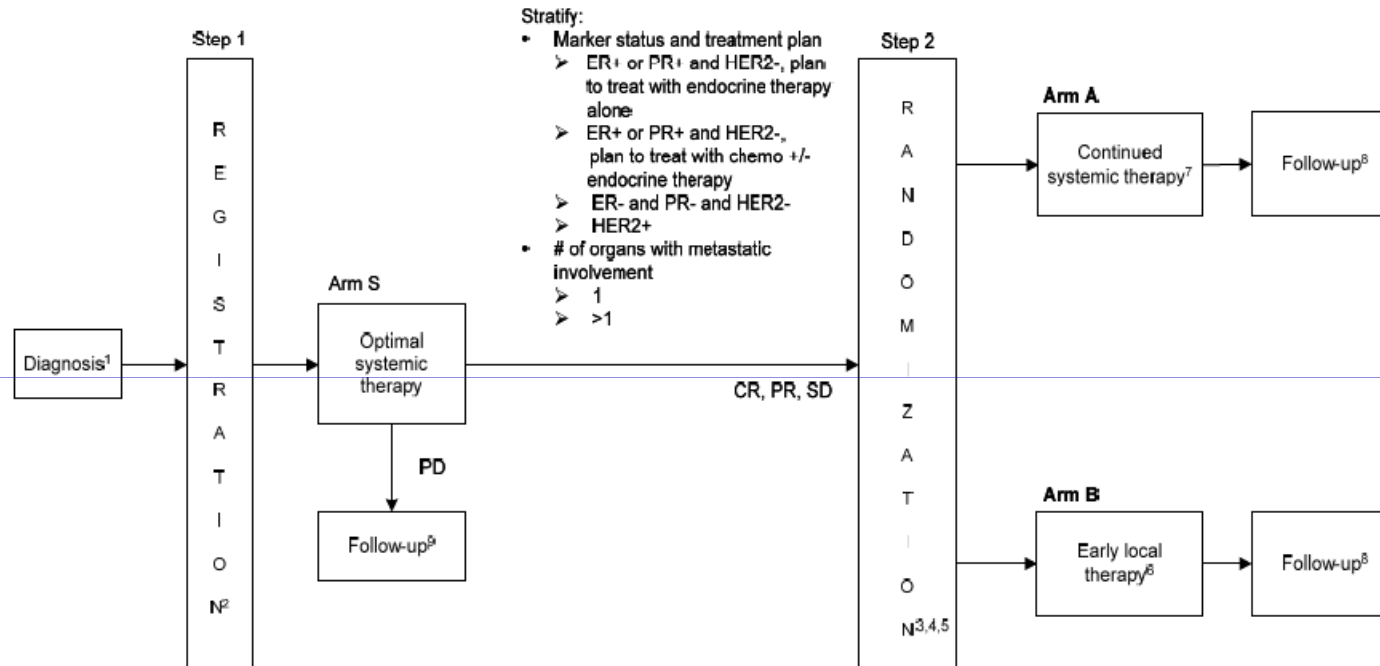
- Secondary Objectives
  - To compare time to uncontrolled chest wall disease between patients who receive local therapy v patients receiving palliative therapy
  - To determine difference in HR QOL between surgical v nonsurgical patients
  - Absolute value of CTC burden at 6 months
  - Tumor and blood specimen collection for future investigation of primary tumor and metastatic lesions and effect of primary tumor resection

# ECOG 2108

- Eligibility
  - de novo stage IV breast cancer unless estimated survival <6 months
- Exclusion
  - Recurrent or bilateral breast cancer

# ECOG E2108

## Schema



Accrual = 880

1. Women with intact primary tumors AND metastatic disease at any site are eligible.
2. Patients may register (Step 1) before or at any time within 10 weeks after initiation of systemic therapy, including after completion of a regimen less than 20 weeks in length.
3. Patients must be randomized (Step 2) within 20 weeks after the start of systemic therapy.
4. Patients may not be randomized (Step 2) less than 16 weeks after the start of systemic therapy.
5. At the time of randomization, patients must have documentation of CR, PR or SD as response to optimal systemic therapy.
6. Early local therapy (Arm B) is defined as surgery and radiotherapy for the primary tumor, following induction systemic therapy. Surgery is to occur within 8 weeks after the end of optimal systemic therapy.
7. Continued systemic therapy is defined as therapy delivered only as needed for control of distant disease.
8. All randomized patients will be followed for treatment and disease status for 5 years post randomization.
9. Patients who are not randomized will be followed for survival for 5 years post registration.

# ECOG E2108

- Total accrual 880 patients for 616 responders
  - Assuming rate of 16 pts/month
  - 55 months of accrual needed
  - Lead site open 5/884

A Randomized Trial Comparing  
Locoregional Resection of Primary  
Tumor with No Surgery in Stage  
IV Breast Cancer at Presentation

MF07-01

Turkish Federation of the National Societies for  
Breast Diseases

# MF07-01

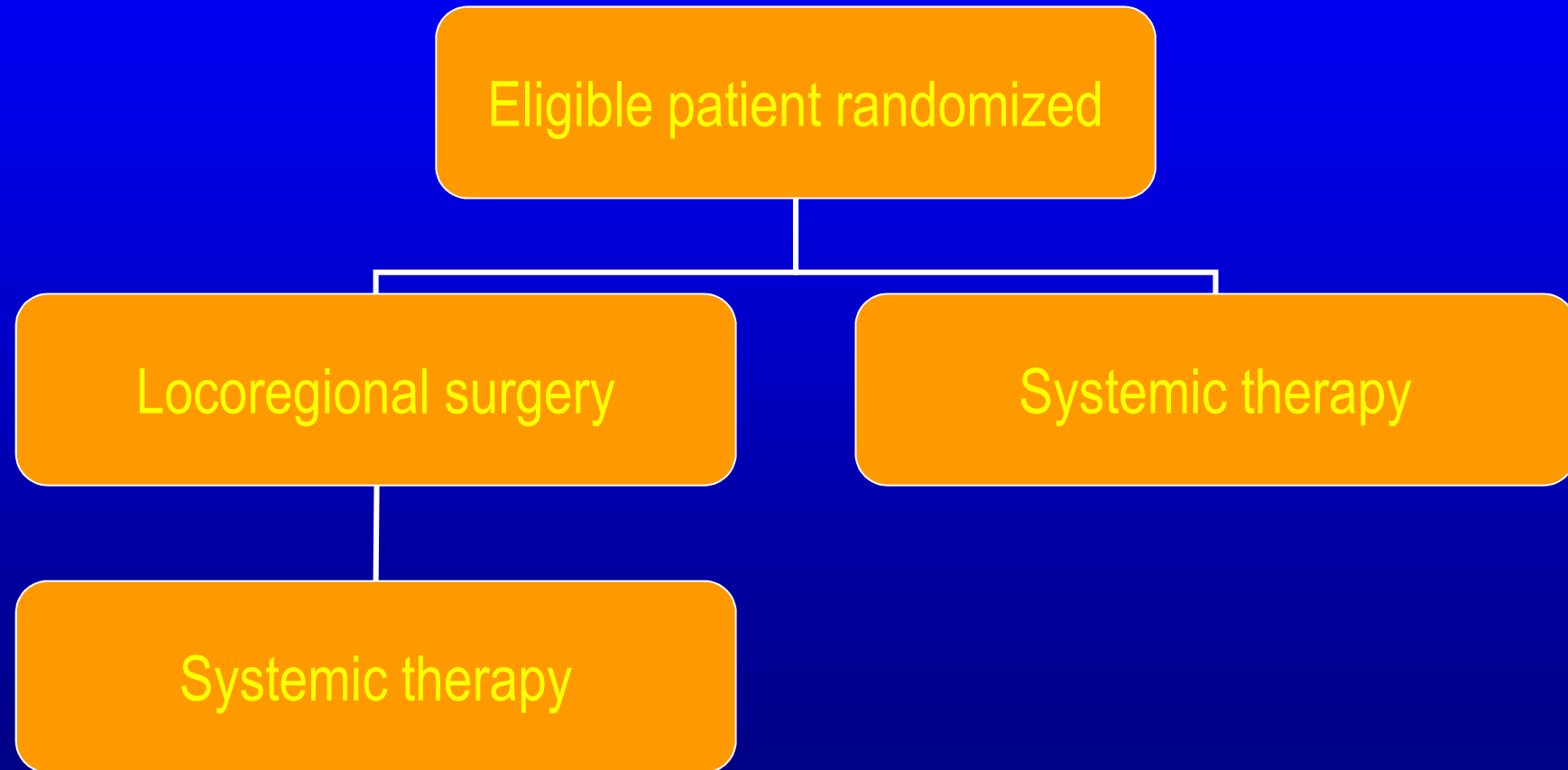
- Primary Aim
  - Determine if locoregional treatment provides survival advantage in Stage IV breast cancer patients.
- Study endpoints
  - Overall survival
  - Progression-free survival
  - QOL measures
  - Morbidity related to surgical procedures

# MF07-01

- Eligibility
  - Surgically resectable disease
  - Good physical condition
    - Able to receive systemic and radiation therapy
- Target accrual
  - 271 patients
- Activated 2007
- Expected to complete accrual 2012
- No interim preliminary data presented



# Treatment Schema



**ROLE OF LOCO-REGIONAL TREATMENT  
IN METASTATIC BREAST CANCER  
AT PRESENTATION  
(M1 Trial)**

**PI R A BADWE, MD**

**TATA MEMORIAL HOSPITAL**

**MUMBAI, INDIA**

## M1 Trial

# Aim and Design

- A randomized controlled trial  
(NCT 000193778)
- To assess the effect of removal of primary tumour on short-term (6 months) disease progression in women with *de novo* metastatic breast cancer.

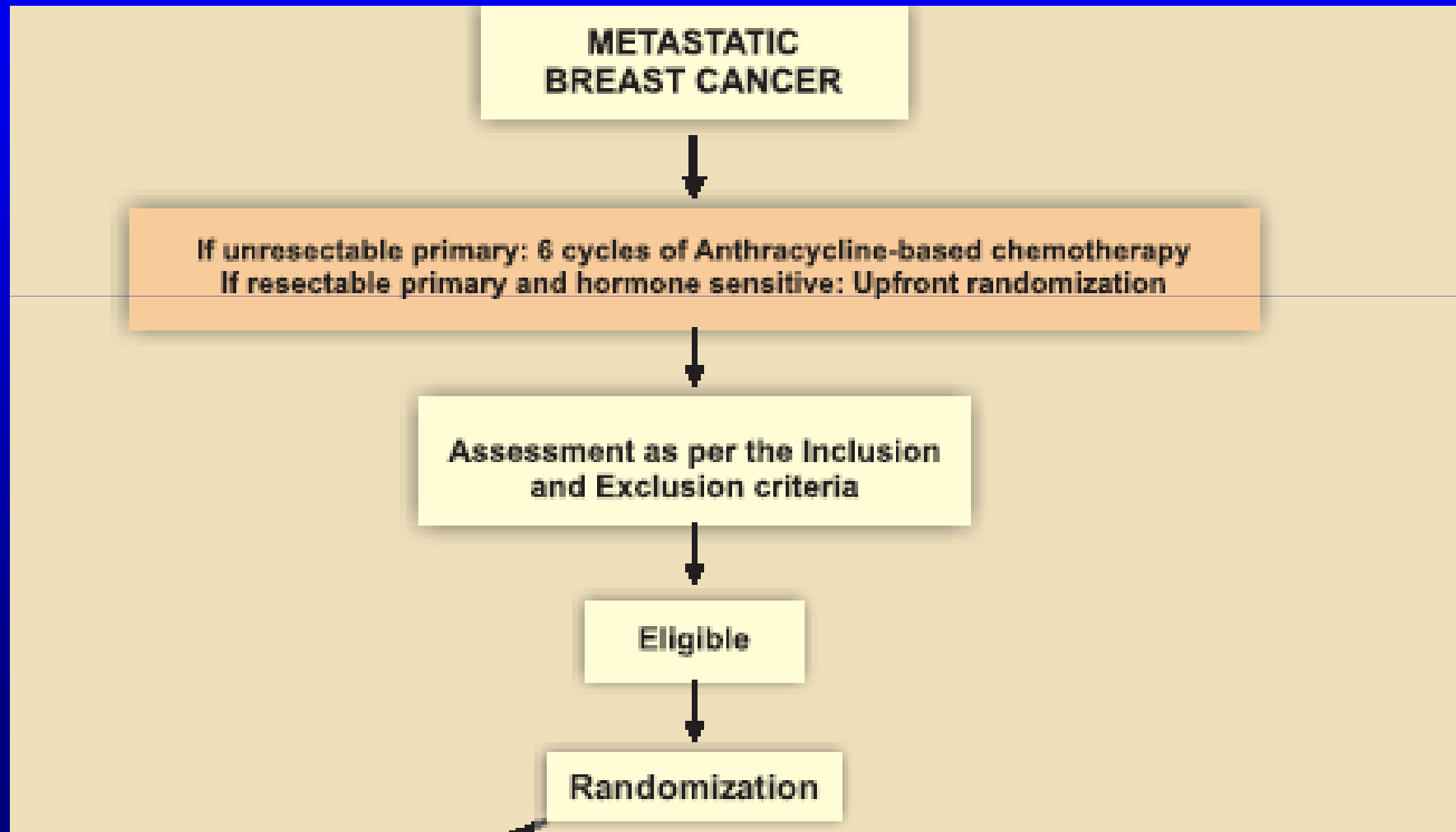
M1 Trial

# Inclusion Criteria

- Women with metastatic breast cancer at first presentation  
(Oligo-metastasis excluded)
- Resectable loco-regional disease at presentation or after chemotherapy

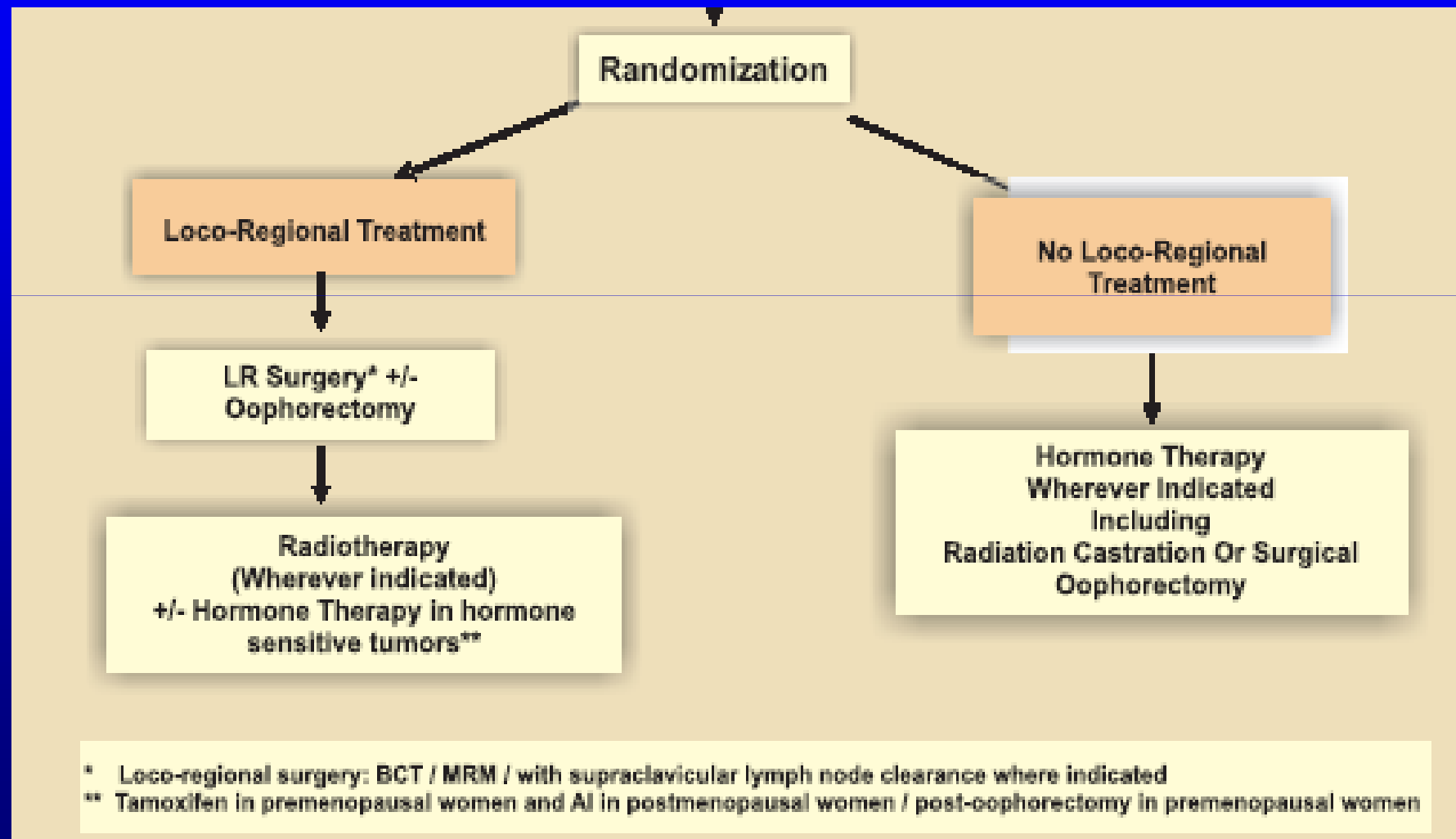
M1 Trial

# Treatment Schema



M1 Trial

# Treatment Schema



# M1 Trial

- Update ASCO Breast 2009
  - n=125
  - 53 LRT
  - 72 NLRT
  - Median f/u 18 months
  - No statistical significance between PFS nor OS
  - Maybe trend towards poorer survival in surgery group
  - Await long-term data

# Summary

- Selection bias
  - Misclassification of disease stage
  - Biology of disease
  - Case selection
  - Younger patients
  - Smaller tumors
  - Fewer axillary nodal metastases
  - Fewer distant metastatic sites

Prospective, randomized clinical trial required to define the role of surgery for patients with stage IV disease



# Reasons not to Resect the Primary Tumor in Stage IV Breast Cancer

- Measurable disease: can be followed for response
- Morbidity of resection
- ? Source of angiostatin which restrains growth of metastases

# Reasons to Resect the Primary Tumor in Stage IV Breast Cancer

- Palliation of symptoms
- Fear of uncontrolled local disease
  - Reduces source of continued shedding of metastatic cells?
  - Increases efficacy of systemic therapy?
  - Prolongs survival?

# Reasons to Resect Primary Tumor

- Uncontrolled local disease may be a source of seeding of distant sites.
- Supported by therapeutic benefit of post mastectomy radiation
- Trends in local and distant recurrence
- Emerging data showing survival benefit of aggressive local therapy for a single metastatic site

# Conclusions

- Participation in clinical trials is critical
- If considering surgery off protocol guidelines include:
  - Define palliative versus therapeutic/curative
    - Likely patients w/ low volume disease
    - Document stability of disease
    - Consider favorable prognostic factors
    - Response to systemic therapy
  - Pursue standard and complete LRT in the therapeutic/curative setting to render patient NED

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- Lei Feng

