The Role of Surgery in Stage IV Breast Cancer

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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”

www.cancer.gov  2011
Overall survival from time of recurrence.

Giordano SH, Cancer 2004
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

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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<th>Period</th>
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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%)

Khan S, et al., Surgery 2002
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

Khan S, et al., *Surgery* 2002
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

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

Babiera GV, Ann Surg Oncol, 2006
Surgery vs No Surgery

FIG. 1. Overall survival by surgery status. Kaplan-Meier curves show overall survival in the surgery (Y) and nonsurgery (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 nonsurgery (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

- **Axil Dissec (E/N = 3/41)**
- **Unkwn/Biop (E/N = 7/34)**

*P*-value = 0.051

Axillary Treatment

All surgery patients 75

Axillary lymph node dissection 41 (55%)
- Radiation 16 (21%)
- No radiation 25 (33%)

SLN biopsy alone or nothing 34 (45%)
- Radiation 11 (15%)
- No radiation 23 (31%)

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

Stage IV disease w/ intact primary (Any M1)

1st line systemic therapy (chemo or endocrine)

Time

~4-6 mos

Non-responders

Responders (stable, partial, complete)

Research biopsy

Discuss Surgery

Choice of surgery +/- XRT

+/− palliative surgery

+/− local recurrence

Tissue samples: 3-4/pt parrafin +/- fresh frozen

#1A biopsy primary
#1B met site
#1 Blood draw

#2 blood draw:
Day 1 of chemotx #2 or month 2 of hrm tx

#2A if surgery
#2B if research biopsy
#3A blood draw at surgery or
#3B at 24 weeks if responder but no surgery planned

#3A if local rec
#3B if palliative
#4A blood draw if POD (local or distant)
TBCRC 013

Scheme B

Time

Diagnosed Stage IV disease w/in 3 months primary breast surgery

1st line systemic therapy (chemo or endocrine)

- 4-6 mos

Non-responders (POD)

? 

Local recurrence and/or POD

Responders (stable, partial, complete)

Consider XRT (BCT or PMRT)

? 

Local recurrence

#1A dx biopsy or surgical specimen

#1B met site

#1 blood draw

Tissue samples: 2-3 per pt

Parrafin +/- Fresh Frozen

#2 blood draw:

Day 1 of chemotx #2 or month 2 of hrm tx

#3 blood draw:

16 weeks in responders

#2A local recurrence

#2B pall procedure

#4 blood draw at POD

(local or distant)
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

Step 1
- Registration

Step 2
- Randomization
- Arm A: Continued systemic therapy → Follow-up^a
- Arm B: Early local therapy → Follow-up^a

Optimal systemic therapy

Arm S
- Diagnosis^b
- CR, PR, SD
- PD
- Follow-up^c

Stratify:
- Marker status and treatment plan
  - ER^+ or PR^+ and HER2^-
  - ER^+ or PR^+ plan to treat with endocrine therapy alone
  - ER^+ or PR^+ plan to treat with chemo +/- endocrine therapy
  - ER^- and PR^- and HER2-
  - HER2^+
  - # of organs with metastatic involvement
    - 1
    - >1

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 16 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
• 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

Eligible patient randomized

Locoregional surgery

Systemic therapy

Systemic therapy

Soran Breast J 2009
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

- **METASTATIC BREAST CANCER**

  - If unresectable primary: 6 cycles of Anthracycline-based chemotherapy
  - If resectable primary and hormone sensitive: Upfront randomization

  - Assessment as per the Inclusion and Exclusion criteria

  - Eligible

  - Randomization
M1 Trial

Treatment Schema

Randomization

Loco-Regional Treatment

No Loco-Regional Treatment

LR Surgery* +/- Oophorectomy

Radiotherapy (Wherever indicated) +/- Hormone Therapy in hormone sensitive tumors**

Hormone Therapy Wherever Indicated Including Radiation Castration Or Surgical Oophorectomy

* Loco-regional surgery: BCT / MRM / with supraclavicular lymph node clearance where indicated
** Tamoxifen in premenopausal women and Al in postmenopausal women / post-oophorectomy in premenopausal women
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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