Stage IV Breast Cancer and the Role for Surgery

Appropriate or Not Appropriate?

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Introduction

SEER data from 1996-2003
- 3-10% of newly diagnosed breast cancer patients will have metastatic disease.
- 5% of white women and 9% of African-American women will present with stage IV disease at initial diagnosis.
- 2007 approx. 11,000 women presented with stage IV breast cancer.

Khan et al. Oncology 2007:21:924
ACS Breast Cancer Facts 2008

Introduction

Convention wisdom and the dictum stated:
Patients with stage IV breast cancer are not surgical candidates. The “toilet mastectomy” or partial mastectomy for primary breast cancer is reserved for symptoms from bleeding, fungating, infected, or painful breast.
The patients prognosis is determined by the tumor burden of the metastatic disease and local therapy would not change their overall survival.

Introduction

Stage IV breast cancer mainstay treatment usually consisted of systemic chemotherapy or hormonal therapy. Radiation is used for isolated soft tissue/skeletal/skin metastasis.
Stage IV Breast CA
Giordano el al. evaluated 843 patients treated with metastatic breast cancer over the last 20 years.
• Noted a steady improvement in patients outcomes.
• 1974-1979 for stage IV breast cancer the median survival was 15 months, and 3 and 5 yrs survival of 15% an 10%.
• 1995-2000 the median survival for stage IV breast cancer was 51 months and 3 and 5 yrs survival of 61% and 40%.

Stage IV Breast CA
1996- Greenberg et al. reported on 1581 patients with metastatic breast cancer:
• 263 patients (16.6%) complete responses.
• 49 patients (3.1%) remained in remission for more than 5 years.
• Others have reported similar responses.

Greenberg, P et al. JCO (1996) 14:2195
Aapro, M et al. Seminars in Oncology (1999) 26(1 suppl 3) :17-21
Piccanti, M et al. Anti-cancer Drugs (1995): 6(suppl 4) 7-11

Stage IV Breast CA
• Studies evaluating circulating tumor cells (CTC) before and after treatment is an independent predictor of survival in patients with metastatic breast cancer.
• Association between the median CTC during treatment predictive of time to progression of disease.
• Surgical resection of the primary breast may assist in restoration of the immune complex by decreasing tumor induced immunosuppression which is related to tumor burden.


Stage IV Breast CA
Other studies suggest removing the primary breast cancer may exacerbate metastases.
Theories:
• Excision of the primary breast cancer will remove inhibition of angiogenesis leading to increase neovascularization.
• Surgical wounding leads to release of growth factor stimulating tumor growth and immune suppression.

“Re-think Old Paradigms”

- In the past, treatment options for stage IV breast cancer were limited around anthracyclines which is often associated with adverse effects.
- In the last decade, newer chemotherapy/hormonal agents and targeted therapy for advanced and metastatic breast cancer has significantly improved Disease Free Survival (DFS) and Overall Survival (OS).
- For example, 2nd and 3rd generation AIs, Taxanes, Trastuzumab (Herceptin) and other HER-2 targeted drugs, Lapatinib (Tykerb).


Surgery and Stage IV Breast Cancer

Over the last decade, several retrospective studies have demonstrated improved survival with surgical resection in patients with metastatic disease.

Hypothesis for the phenomena:

- Cessation of metastatic cells shedding from the primary cancer.
- Surgery decrease the tumor burden and therefore allow systemic therapy to be more effective.
- Surgery may remove some unknown tumorogenic growth factor; angiogenic, inflammatory, or hormonal stimulus for metastatic growth.
- Case selection bias.

Khan et al. (2002) published an analysis of the National Cancer Data Base (NCDB) of The ACS examining patterns of care and outcome in women with Stage IV breast cancer diagnosed between 1990 and 1993.

- 16,023 women were diagnosed with Stage IV breast cancer.
- 6861 (42.8%) received no operation or a variety of diagnostic or palliative procedures.
- 9162 (57.2%) underwent definitive surgery. 3513 (38.3%) patients underwent partial mastectomies and 5649 (61.7%) patients underwent mastectomies.

Surgery and Stage IV Breast Cancer

Khan et al. (2002)
- 3 year survival of 26% in the partial mastectomy group.
- 3 year survival of 35% in the mastectomy group.
- Women treated with surgically resected free margins had a hazard ratio of 0.61 (95% CI).

Conclusion-local therapy in women with stage IV breast cancer should be re-evaluated in a randomized trial comparing surgical resection and systemic treatment vs. systemic treatment alone.


The review controlled for age, comorbidity, tumor grade, histology and sites of metastasis.

Surgery and Stage IV Breast Cancer

Gnerlich et al (2007)
- Patients were categorized into groups with no surgery vs. surgery (partial mastectomy or mastectomy with curative intent).
- Women's surgery status not recorded were excluded.
- Patients were categorized into groups with no radiation therapy or radiation therapy.
- Survival time was calculated using date of diagnosis until time of death or last known to be alive.


Gnerlich et al (2007)-Study Endpoints
- Time to death.
- Recurrence of previously treated primary cancer.
- Progression of metastatic disease.
- Time to recurrence
Surgery and Stage IV Breast Cancer
Gnerlich et al (2007)

Results:
• 4578(47%) had surgery for their breast cancers and 5156(53%) did not have surgery.
• The median age in the surgery group was 62 yrs compared to a median age in the non surgery group of 66yrs.
• Among the women who underwent surgery their tumors were more likely to be less than 5CM, grade 3, ER pos. compared to women who did not go to surgery.


Surgery and Stage IV Breast Cancer
Gnerlich et al (2007)

Results:
• At the end of the study period in 2003, 24% of women who underwent surgery were alive compared to 16% of women who did not undergo surgery. (p<.001)
• Crude HR for women undergoing surgery from death was .57(95% CI), indicating 43% of women are less likely to die if they had surgery.
• Even women in the surgery group who went on to die during the study period had a longer median survival compared to the non surgery group. 18 months compared to 7 months.


Surgery and Stage IV Breast Cancer
Gnerlich et al (2007)

Conclusions:
• Limitation of a retrospective review of the SEER database.
• Survival was improved in surgery group compared to the non surgery group. Particularly in the bone only metastasis surgery group (median survival 31.9 months vs.15.4 months) in the bone metastasis non surgery group. (p0.0001) adj HR 0.53 (95%CI)
• Randomized trials are need.


Surgery and Stage IV Breast Cancer
Cady et al (2008) performed a matched pair analysis of Stage IV breast cancer with and without resection of the primary breast cancer. This was an attempt to avoid selection bias.
• 808 patients were identified from MGH, Brigham Women’s Hospital (BWH) and the Massachusetts Death Certificate Database diagnosed between 1970 and 2002. The patients were followed until 2005
• Male breast cancers were eliminated from the study or if patients had a second non breast cancer malignancy.
• 622 patients for the final analysis

Cady, B. Ann of Surg Onc 200815(12):3384
Surgery and Stage IV Breast Cancer

Cady et al (2008) evaluated:
- Age
- Decade of diagnosis
- Cancer characteristics-size, type, grade, receptor status, node status.
- Organ site of principal metastatic disease
- Extent of metastasis
- Margin status of surgical specimen
- Type of systemic treatment, chemotherapy, hormonal, radiation
- Type of surgical procedure mastectomy, lumpectomy, biopsy only
- Sequence of therapy

Cady, B. Ann of Surg Onc 200815(12):3384

Surgery and Stage IV Breast Cancer

Cady et al (2008) Matched:
- Age
- Date of Diagnosis
- Location of metastases-bone, viscera, soft tissue, and distant lymph node.
- ER status
- Use of systemic treatment
- Definitive primary breast surgery or not.

Cady, B. Ann of Surg Onc 200815(12):3384

Surgery and Stage IV Breast Cancer

- 168 patients had bone only metastases.
- 100 patients had viscera (brain, lung, liver) only metastases.
- 308 patients had multiple sites of metastases, bone viscera, distant lymph nodes.
- 388 patients (62%) no definitive surgery.
- 234 patients (38%) had surgery with a curative intent (MRM or partial mastectomy with axillary surgery).

Cady, B. Ann of Surg Onc 200815(12):3384

Surgery and Stage IV Breast Cancer

- Confirmed 95 (15%) patients survived greater than 5 years.
- In this group median age was 54 compared the group not survival 5 years, median age is 60
- 87% were ER pos.
- 72% had bone only metastases.
- Only in the bone only metastases group was a survival advantage identified if chemo is used before surgery.

Cady, B. Ann of Surg Onc 200815(12):3384
Surgery and Stage IV Breast Cancer


- Authors did identify some problems with the study
- Retrospective analysis may have selection bias with patient incorrectly staged.
- Incorrect classification of the operations performed.
- Higher proportion of patients with oligometastases, bone only metastases, younger age, ER pos status, and good response to systemic therapy had better DFS and OS.

Conclusions:

Survival for stage IV for breast cancer is dependent on the extent of local and metastatic disease, ER status, and tumor grade and age.

Ruiterkamp J. et al reviewed 10 studies comparing primary breast surgery for stage IV patients to no surgery.

- All studies were retrospective.
- Analysis only of studies with a control group of patient who underwent surgery compared to patients with no surgery.
- In 7/10 studies noted significant overall survival if the breast was treated with curative intent.
- In a multivariate analysis the breast surgery was an independent factor for improved survival with a HR 0.65 (95% CI) (0.47-0.71).
Surgery and Stage IV Breast Cancer

Ruiterkamp J. et al. and Khan S. et al also demonstrated some additional survival benefit when axillary surgery was performed at the time of the breast surgery. Several studies have demonstrated uncontrolled regional axillary disease can act as a source for systemic seeding.


Surgery and Stage IV Breast Cancer

Ruiterkamp et al concluded:
“Stage Migration Bias”
Patients who benefit from surgery probably have smaller tumors and asymptomatic metastatic disease and already have a better survival advantage at the start.
Randomized clinical trials are needed.

Surgery and Stage IV Breast Cancer

Resection of metastatic disease

- Elias reviewed 5 prospective studies for patients undergoing liver metastectomy for a total 210 patients.
- The 3 yrs survival varied between 35-71%.
- In their own study 54 patients with stage IV breast cancer underwent surgery for resection of liver metastases.
- All patients had intra-operative liver ultrasound.
- 20 (46.7%) patients had additional liver metastases and therefore underwent a different resection that the pre-op plan.
- 44 patient had curative resection and 10 were palliative.
Surgery and Stage IV Breast Cancer
Resection of metastatic disease

- All but two patients had neoadjuvant chemotherapy.
- 25 patients had posthepatectomy hepatic arterial infusion chemotherapy.
- DFS was 34% and 22% at 3 years and 5 years.
- OS was 50% and 42% at 3 years and 5 years.


Surgery and Stage IV Breast Cancer
Resection of Metastatic Disease

Singletary et al reviewed 8 retrospective studies looking at primary lung resection in patients with stage IV breast cancer.
- 744 patients.
- Some patients were treated with systemic therapy and others no systemic therapy.
- Median survival ranged from 42-79 months.
- The 5 yrs actuarial survival ranged from 35-80% and
- The 10 yrs actuarial survival 8-60%.


Surgery and Stage IV Breast Cancer
Resection of Metastatic Disease

Friedal et al in this study with the largest series of patient undergoing lung resection with metastatic breast cancer with 467 patients reported:
- a median survival of 30 months.
- DFS of 36 months.
- OS at 5 yrs survival of 45% and 10 yrs survival of 26%.


Surgery and Stage IV Breast Cancer
Resection of Metastatic Disease

Flickinger et al reported in a multi-institutional study suggested radio-surgery for solitary brain metastases has survival advantages over whole brain radiation.
Jawahar et al noted no survival advantage in 103 patients.

Algorithm for Stage IV Breast Cancer

Distant Metastases at diagnosis: Neoadjuvant chemotherapy

Disease Response

Patient resectable: Curative surgery and Post-op radiation if indicated

Patient unresectable or medically unable to undergo surgery: Curative radiation to primary tumor and LN

Disease Progression

Second line Chemotherapy with or without targeted therapy

Surgery and Stage IV Breast Cancer - Conclusion

1997 speech by Blake Cady provides a nice summary: “In the land of Surgical Oncology, Cancer Biology is King, and Case Selection is Queen. Technical maneuvers and alternative surgical approaches are the prince and princess of the realm.

Occasionally the prince and the princess revolt and attempt to rule the realm. They are almost always defeated by the powerful forces of the King and Queen: Cancer biology and careful case selection”. Randomized multi-institutional studies will make the laws!

Lunar View of Earth Sunrise

Apollo 11 June 20, 1969

“Ronin” the Wonder Dog