# A Retrospective Study Evaluating the Impact of Loco-regional Surgery in Metastatic Breast Cancer at the Time of Initial Diagnosis

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# List of Abbreviations

| | |
|---|---|
| 3D | Three Dimensional |
| ACS | American Cancer Society |
| AJCC | American Joint Committee on Cancer |
| AR | Androgen Receptor |
| ASIR | Age-Standardized Incidence Rate |
| ASTRO | American Society for Radiation Oncology |
| BCAC | Breast Cancer Association Consortium |
| BCS | Breast Conservative Surgery |
| BCSS | Breast Cancer-Specific Survival |
| BLBC | Basal-Like Breast Cancer |
| BMI | Body Mass Index |
| BRCA1/2 | BReast CAncer 1 & 2 |
| CA 15-3 | Cancer Antigen 15-3 |
| CCL2 | C-C motif Ligand 2 |
| CDK4/6 | Cyclin-Dependent Kinases 4 & 6 |
| CEA | CarcinoEmbryonic Antigen |
| CK | CytoKeratins |
| CR | Complete Response |
| CTCs | Circulating Tumor Cells |
| CXCL12 | C-X-C motif chemokine 12 |
| DCIS | Ductal Carcinoma InSitu |
| DCIS | Ductal Carcinoma *In Situ* |
| DFI | Disease Free Interval |
| DIN | Ductal Intraepithelial Neoplasia |
| DMFS | Distant Metastasis Free Survival |
| ECM | ExtraCellular Matrix |
| ECOG | Eastern Cooperative Oncology Group score |
| EFS | Event-Free Survival |

| | |
|---|---|
| · EMA | Epithelial Membrane Antigen |
| · ER | Estrogen Receptor |
| · FES | $^{18}$F-fluoroEStradiol |
| · FFTP | First Full-Term Pregnancy |
| · FH | Family History |
| · FISH | Fluorescent In Situ Hybridization |
| · GEP | Gene Expression Profiling |
| · Her2 | Human Epidermal Growth Factor Receptor 2 |
| · HIS | Human Invasion Signature |
| · HR | Hazard Ratio |
| · HR | Hormonal Receptor |
| · IDC | Invasive Ductal Carcinomas |
| · IHC | ImmunoHistoChemical assessment |
| · IL-1β | InterLeukin 1 beta |
| · ILC | Invasive Lobular Carcinomas |
| · LCIS | Lobular Carcinoma InSitu |
| · LFS | Li-Fraumeni Syndrome |
| · LIN | Lobular Intraepithelial Neoplasia |
| · LVI | Lymphatic Vascular Invasion |
| · MBC | Metastatic Breast Cancer |
| · MHT | Menopausal Hormonal Therapy |
| · MP | MammaPrint |
| · MRI | Magnetic Resonance Imaging |
| · MRM | Modified Radical Mastectomy |
| · mTOR | mammalian Target Of Rapamycin |
| · NCCN | National Comprehensive Cancer Network |
| · NCI | National Cancer Registry |
| · NE | Not Estimated |
| · NOS | Not Otherwise Specific |
| · NST | No Special Type |

| | |
|---|---|
| · ODX | Oncotype DX™ |
| · OS | Overall Survival |
| · PD | Progressive Disease |
| · PET | Positron Emission Tomography |
| · PFS 1 | Time for the first progression |
| · PFS | Progression Free Survival |
| · PNI | Perineural Invasion |
| · PR | Partial Response |
| · PR | Progesterone Receptor |
| · PS | Performance Status |
| · RANKL | Receptor Activator of Nuclear factor Kappa-B Ligand |
| · RCTs | Randomized Controlled Trials |
| · RECIST | Response Evaluation Criteria In Solid Tumors |
| · RFA | RadioFrequency Ablation |
| · RR | Relative Risks |
| · RS | Recurrence Score |
| · SBRT | Streotactic Body RadioTherapy |
| · SD | Stable Disease |
| · SDF1 | Stromal cell-Derived Factor 1 |
| · SEER | Surveillance, Epidemiology, and End Results |
| · SERD | Selective Estrogen Receptor Down-regulator |
| · SMA | Smooth Muscle Actin |
| · SPECT | Single Photon Emission CT |
| · SPSS | Statistical Package for Social Science |
| · SREs | Skeletal-Related Events |
| · SRS | Stereotactic RadioSurgery |
| · TACE | Transcatheter Arterial ChemoEmbolization |
| · TDLU | Terminal Duct-Lobular Unit |
| · TMEM | Tumor MicroEnvironment of Metastasis |
| · TNBC | Triple Negative Breast Cancer |

| | |
|---|---|
| · TNM | Tumor–Node–Metastases staging system |
| · UICC | Union Internationale Contre le Cancer |
| · UK | United Kingdom |
| · VEGF | Vascular Endothelial Growth Factor |
| · VEGFR | Vascular Endothelial Growth Factor Receptor |
| · WBRT | Whole Brain Radiotherapy |
| · WHO | World Health Organization |

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# Abstract

Breast cancer is the most common malignant tumor among women worldwide. Despite the advances in the diagnosis and management of breast cancer, 6–10% of affected patients present metastatic breast cancer at diagnosis and 30–40% will develop metastases during the evolution of their disease. The appearance of metastases, as a sign of incurability, constitutes a major problem of care. The recent therapeutic strategies and emergence of new drugs have not only helped to extend the median survival time (around 30 months now) but also to improve the quality of patients' lives. The mainstay of treatment in metastatic breast cancer is systemic therapy, which includes chemotherapy, endocrine therapy and targeted therapy. Traditionally, loco-regional treatment (surgery or radiotherapy) has been used only for control of fungation and bleeding. However, metastatic breast cancer patterns have undergone some changes with increasingly sensitive imaging modalities, resulting in potential stage migration. This allows clinicians to better identify metastatic breast cancer patients with an improved prognosis and the potential to benefit from a more aggressive loco-regional or systemic treatment approach.

Our study analyzed retrospectively the impact of loco-regional surgery on the outcome of patients with breast cancer found to be metastatic at their initial diagnosis, and found a clear survival benefit in the patients underwent surgery for their primary breast tumor. The results of the current study contribute to the growing body of literature addressing the question of whether surgical resection of the primary tumor in patients presenting de novo with stage IV disease improves survival. Findings from this and other studies provide support for a prospective, randomized trial to more definitively test the hypothesis that better control of local disease in stage IV breast cancer patients will improve survival. Other important questions that should be addressed are the optimal timing of surgery, the optimal chemotherapy regimen, and methods of and indications for resection of site(s) of metastasis.

We do not at present recommend 'routine' breast surgery or definitive local treatment in women with known metastatic breast cancer receiving standard palliative treatments.

**Keywords** : ODX: Oncotype DX™, MRM: Modified Radical Mastectomy; TNM: Tumor–Node–Metastases staging system

# Epidemiology

## The global burden:

Cancer constitutes a huge burden on society in more and less economically developed countries alike. The incidence of cancer is increasing because of the growth and aging of the population, as well as an increasing prevalence of established risk factors such as smoking, physical inactivity, overweight, and changing reproductive patterns associated with urbanization and economic development. ***(Torre et al., 2015)***

Based on GLOBOCAN estimates, about 14.1 million new cancer cases and 8.2 million deaths occurred in 2012 worldwide. Over the years, the burden has shifted to less developed countries, which currently account for about 57% of cases and 65% of cancer deaths worldwide, with breast cancer remaining the leading cause of cancer death among females in less developed countries (Fig 1.1). ***(Torre et al., 2015)***

Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death among females worldwide, with an estimated 1.7 million cases and 521,900 deaths in 2012. Breast cancer accounts for 25% of cancer cases and 15% of cancer deaths among females. More developed countries account for about one-half of all breast cancer cases and 38% of deaths. International variation in breast cancer incidence rates reflects differences in the capability of early detection as well as presence of risk factors. ***(Schottenfeld, 2006)***

In the timeline between 1980 and the late 1990s, breast cancer incidence rates rose approximately 30% in Western countries, likely because of changes in reproductive factors and the use of menopausal hormonal therapy (MHT) and more recently because of increased screening. Declining incidence rates in those countries in the early 2000s have been attributed to the reduced use of MHT. Beyond changes in MHT use, declining or

stable incidence rates in Western countries may also be due to plateaus in participation in mammographic screening. ***(DeSantis et al., 2011; Youlden et al., 2012)***

Concerning breast cancer death rates, they have been stable or decreasing since around 1990 in Northern America and higher-resource European countries. These reductions have been attributed to early detection through mammography and improved treatment, although the respective contributions of each are unclear. Breast cancer incidence rates have been rising in many countries in South America, Africa, and Asia. The reasons are not completely understood but likely reflect changing reproductive patterns, increasing obesity, decreasing physical activity, and some breast cancer screening activity. Mortality rates in these countries are also increasing, most likely due to lifestyle changes associated with westernization compounded by the delayed introduction of effective breast cancer screening programs and, in some cases, limited access to treatment. ***(Bosetti et al., 2012; Autier et al., 2011)***

Approximately 5% to 10% of breast cancers are metastatic at diagnosis; of these, approximately one-fifth will survive 5 years, depending on prognostic factors, up to 30% of node-negative and up to 70% of node-positive breast cancers will relapse. The prevalence of metastatic disease is high because many women live with this disease for several years. ***(Cardoso et al., 2012)***

In the United States, approximately 6-10% of new breast cancer cases are initially Stage IV or metastatic. This is sometimes called "de novo" metastatic disease, meaning from the beginning. For 2012 this means new cases of Stage IV were in the range of 13,776 - 22,096. ***(American Cancer Society (ACS) Cancer Facts and Figures 2012)***

## Age distribution:

Half of breast cancers are diagnosed within the screening age bracket, which is between 50 and 69 years, while around 6.6% of all breast cancer cases are diagnosed in women less than 40 of age, 2.4% in women less than 35, and 0.65% in women less than 30; if plotted on a curve, the cumulative incidence of breast cancer seems to follows an exponential function below the age of 40 after which it seems to rise linearly. (Fig. 1.2 & 1.3) ***(Anders et al., 2009; Benson et al., 2012)***

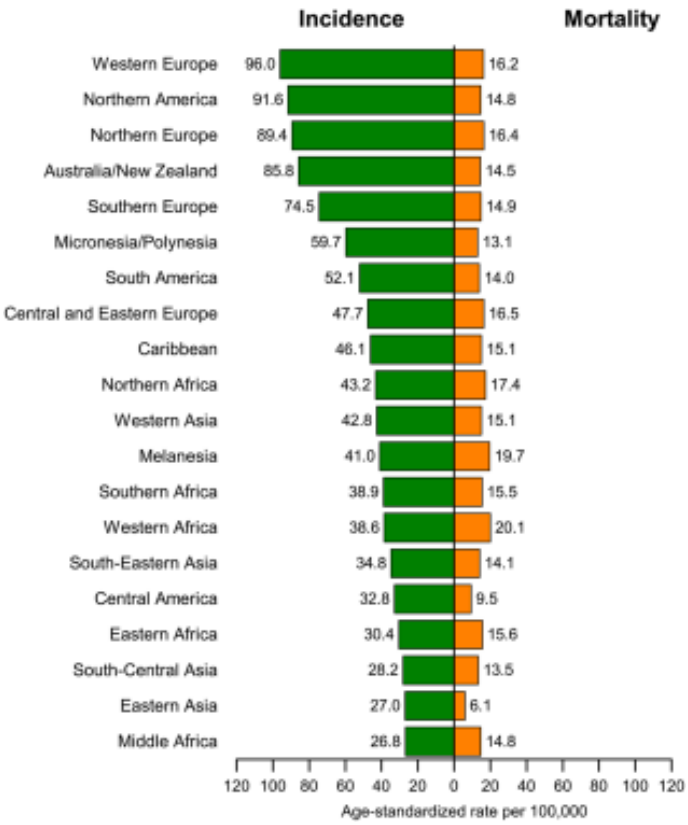


Fig (1.1): Breast Cancer Incidence and Mortality Rates by World Area in 2012. ***(Torre et al., 2015)***

A statistically significant increase (1976–2009) has been reported in the age-standardized incidence rate (ASIR) for distant stage (metastatic) breast cancer diagnosed in women at age 25–39