Factors associated with better survival after surgery in metastatic breast cancer patients

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Abstract Women with Metastatic Breast Cancer (MBC) and an intact primary have long been treated with systemic therapy alone. Local therapy is not considered unless for palliative reasons. However, several studies have suggested local treatment in the form of Surgery for the primary improves overall survival in certain groups of MBC patients. We evaluated the factors influencing the outcome in this group of patients. In a retrospective review of our prospective database, we identified the patients who presented with MBC and underwent surgery for primary tumour (2004–2009). Patients' surgical details and clinicopathological factors were reviewed. The overall survival of the MBC patients who underwent surgery was evaluated and

compared depending on the various clinicopathological factors. Out of 196 patients with MBC, 48 underwent surgery of the primary tumor during their treatment course. Median overall survival was better in patients with young age (≤ 40 years), Estrogen receptor(ER) positive tumors (31.4 months vs 21.2 months), single metastatic site vs multiple metastatic sites (43.4 months vs 26.69 months). We also found that patients with low level of suspicion for metastases fared better than those with high level of suspicion (43.4 months vs 20.9 months). Our data analysis suggested that for MBC patients who undergo surgery, survival is significantly worse in patients with pathological T4 lesions and there is a trend towards better survival in younger patients and in those who have ER positive tumour, Her2neu negative tumour, single site of metastases and patients with low level of metastatic suspicion. However these factors need to be evaluated in a randomized trial comparing with patients who have not undergone surgery.

Keywords Metastatic breast cancer · Surgery · Survival · Factors

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Introduction

Conventionally it has been thought that once metastases have occurred, aggressive local therapy provides no survival advantage for breast cancer patients. Hence surgical treatment of the breast primary tumour in patients who present with stage IV breast cancer and an intact primary tumor has only been palliative. Potentially curative surgical treatment of the primary tumor or metastatic site (lung/liver) has not been considered for these patients. Khan et al. [1] challenged this approach and showed that patients of metastatic breast cancer (MBC) treated with surgery showed statistically significant survival benefit over those not treated with surgery.

The median survival for metastatic breast cancer patients is 18 to 24 months, although the range extends from a few months to several years [1, 2].

Patients experiencing long-term survival tend to be young with an excellent performance status and limited metastatic disease. For such patients, an intensified multidisciplinary approach combining systemic therapies with local treatment (surgery, radiation) may not only prevent local complications, but also prolong overall survival.

In this study, we reviewed our patients of MBC operated for the primary tumor and have tried to define the subset of patients who might probably benefit from multidisciplinary approach.

Materials and Methods

We identified all patients who presented at our institute (January 2004 to December 2009) with the initial diagnosis of MBC and had undergone resection of primary tumour during the course of treatment.

Information collected included the patient (Age, menstrual status) and tumour characteristics (Stage, receptor status, metastatic site/s), type of surgery (BCS/MRM) and details of follow up (Table 1).

Primary end point was Overall survival determined from date of diagnosis to the date of last follow up.

Patients were categorized into different groups and survival was compared using Kaplan Meier survival curves and *p* value was calculated using log rank test. Statistical significance was defined as a *p* value < .05. Calculations were performed using spss software (Version 11.0).

One criterion for categorisation was ‘The level of suspicion’ for metastases. Some of our patients had suspicious radiological features of metastatic site, and on account of the same, patients were labelled as metastatic eg. A small focal lesion in liver not amenable to CT guided FNAC/Biopsy, multiple hot spots in spine which could be degenerative. Such patients were grouped under low level of suspicion. Whereas patients who had histologically confirmed metastases were grouped under high level of suspicion of metastases.

Results

A total of 196 cases of MBC were treated at our center from Jan 2004 to Dec 2009. Of these, 48 patients underwent surgery during their course of treatment.

Their median age was 51.50 (Range: 30 years–75 years) years. Median overall survival of these patients is 26.63 months (95 % CI – 16.69–36.57). Median follow up was for 19.7 months ranging from 1.53 months to 64.67 months.

Most of the patients had negative margins at resection (45/48). Forty-seven patients had mastectomy and only one patient had wide local excision (lumpectomy) as the treatment of primary.

Chemotherapy in neoadjuvant setting was received by 41 patients and 6 received adjuvant chemotherapy. Thirty-six patients received taxol based whereas nine patients received non taxol based chemotherapy.

Median survival of the patients less than or equal to 40 years of age was 11.367 months whereas the same for patients with age more than 40 years was 28.8 months (*p*=0.059) (Table 1).

Table 1 Patient and Tumor characteristics of patients with metastatic breast cancer who underwent surgery during their course of treatment. (Univariate analysis)

Patient Characteristics	Groups	Number of patients	Median overall survival (in months)	<i>p</i> value
Age	<= 40 year	8	11.36	0.059
	>40 year	40	28.8	
Menstrual status	Premenopausal	23	26.63	0.664
	Postmenopausal	20	28.8	
ER status	Positive	19	31.4	0.193
	Negative	22	21.2	
PR status	Positive	17	31.4	0.38
	Negative	24	21.2	
Her2neu status	Positive	12	28.8	0.43
	Negative	25	43.4	
T stage	T0–T3	17	>64.4	0.043
	T4	27	19	
Site of metastases	Bone mets	14	31.4	0.638
	Extraskelatal	32	23.3	
Number of metastases	Single	11	43.4	0.435
	Multiple	34	26.6	
Level of suspicion	Low/Unconfirmed	10	43.4	0.08
	High/Confirmed	32	20.9

Fig. 1 Kaplan meier curve to compare survival according to ER status

Nineteen patients had ER positive tumours whereas 22 patients had ER negative tumours. Median survival of the ER positive patients was 31.4 months whereas for ER negative patients it was 21.2 months ($p=0.193$) (Fig. 1).

Her-2 negative patients had better survival as compared to Her-2 positive patients (Median survival: 43.4 months Vs 28.8 months). But the difference didn't reach statistical significance ($p=0.427$) (Fig. 2).

Median survival of the patients with only bone metastases was better than the patients who had soft tissue metastases (31.4 months Vs 23.3 months) but the difference was not statistically significant and survival curves were approaching each other (Fig. 3) And the patients with single metastatic lesion fared much better than those with multiple metastatic sites (Median survival: 43.4 months Vs 26.6 months) ($p=0.435$) (Fig. 4).

Fig. 2 Kaplan meier curve to compare survival according to Her2neu status

Fig. 3 Kaplan meier curve to compare survival according to metastatic site

In our study, we found out that patients who had low level of suspicion of metastatic disease survived longer than those who had confirmed metastases (Median survival: 43.4 months Vs 20.9 months). Difference though was not sufficient to reach statistical significance but definitely showing trend towards better survival in low suspicion group ($p=0.08$) (Fig. 5).

We divided the patient in two groups depending on the pathological T stage of the primary lesion. All T4 lesions were included in one group and rest into other group (T1–T3).

The median overall survival in T4 lesion group was 19 months which is significantly worse than in the other group (T1–T3) (>64.6 months) (p value: 0.043) (Fig. 6).

Fig. 4 Kaplan meier curve to compare survival according to number of metastases

Fig. 5 Kaplan meier curve to compare survival according to level of suspicion of metastases

Discussion

It is very important to understand the biology of metastases in carcinoma breast to assess the appropriateness of surgical treatment in these patients.

Newer hypotheses for metastasis in breast cancer challenged the concept that metastasis is a late event in tumorigenesis. Recent advances in molecular biology, have resulted in three new models of metastasis in breast cancer: (A) the parallel evolution (or circulating tumor cell) model, (B) the gene expression of the primary tumor predicts metastasis model, and (C) the breast cancer stem cell model [3].

The parallel evolution hypothesis suggests that circulating tumor cells (found in blood) or disseminated tumor cells

(found in bone marrow and secondary organs such as liver, bone, or lung) are found early in tumorigenesis, and are independent of the primary tumor characteristics [4].

Lang JE and Babiera GV [5], in their review of role of Locoregional Resection in Stage IV Breast Cancer, explained the molecular basis of locoregional resection in metastatic breast cancer and also concluded that surgery is an important tool that offers hope for prolonged survival for these Stage IV patients in the setting of comprehensive multidisciplinary breast cancer treatment.

In a pooled analysis of nine studies including 4,703 breast cancer patients who had Stage I through III disease, Braun and colleagues [6] found bone marrow micro metastases in 30.6 % of breast cancer patients.

Conceptually, early stage patients who have micrometastatic disease are not much different from Stage IV breast cancer patients with minimal metastatic burden or Stage IV, no evidence of disease (NED) breast cancer patients. Since surgery is standard of care for the patients with early-stage breast cancer patients who have micro metastatic disease, then it seems reasonable to perform surgical intervention for the Stage IV patients.

Improved imaging technology has resulted in the diagnosis of stage IV disease even in patients with low tumour burden. This resulted in increase in the number of women classified as stage IV which otherwise would be staged as stage II or III in the absence of such advanced imaging modalities (e.g. PET scan). These patients would have been treated aggressively with multimodality therapy.

Danna et al. [2] indicated that primary tumor removal reverses immune suppression caused by bulky tumour even in the presence of extensive metastatic disease.

In a retrospective review of data from National Cancer Database of the American College of Surgeons covering the years 1990 through 1993, Khan et al. [1] showed that resection of the primary tumor provided a statistically independent survival benefit, after adjustment for the extent and type of metastatic disease and type of systemic therapy. They found that women who underwent surgical resection of the primary tumor with free margins had a better 3-year survival rate than women not surgically treated (35 % vs. 26 %). There was no difference in survival between the partial mastectomy and total mastectomy groups provided tumour was resected with negative margins. They also found that tumor size was only weakly predictive of survival and that the extent of nodal involvement did not predict survival in women with distant metastatic disease (Table 2).

Carmichael and colleagues [7] reported a retrospective, small, single institution case series of 20 Stage IV breast cancer patients who underwent local surgery. They reported a median survival after breast surgery of 23 months. Ten of the patients (50 %) were alive with no evidence of local disease at 20 months median follow-up. The study authors

Fig. 6 Kaplan meier curve to compare survival according to pathological T stage

Table 2 An overview of few studies about role of surgery in metastatic breast cancer patients

Study	Type of study	Patients undergoing surgery/No. of patients of MBC	Survival		<i>p</i> value	HR	Factors significantly affecting survival (Multivariate analysis)
			No surgery	Surgical resection of primary			
Khan S et al. [1] 2002	Retrospective, Population based	9162/16023	17.3 %*	PM - 27.7 %*, TM-31.8 %*	<0.0001	0.61	Surgical resection of the primary tumor, systemic therapy, number of metastatic sites, and type of metastatic disease
Barbiera G et al. [9], 2006	Retrospective, single institutional	82/224	NA	NA	0.0007	0.54	Number of metastatic sites, and Her2/neu status
Rapiti et al. [8], 2006	Retrospective, population based	127/300	12 %***	Negative margin - 27 %, Positive margin - 16 %***	<0.05 for negative margin	0.5	Local surgery with -ve margin, age <50 year, N0 disease, ER + ve status, absence of visceral or CNS metastases and hormonal treatment.
Gnerlich J et al. [10], 2007	Retrospective, Population based	4578/9734	21 months ****	36 months****	0.001	0.63	Surgery for primary tumour
Blanchard DK et al. [11], 2008	Retrospective population based	153/242	16.8 months ****	27.1 months****	<0.0001	NA	Surgery for primary tumour.
Cady et al. [12] 2008	Retrospective, single institutional	234/622	NA	NA	NA	NA	Young age, ER +, bone only metastasis
Shien et al. [13] 2009	Retrospective, single institutional	160/326	22 months ****	27 months****	0.049	0.89 (0.79–1)	Nil
Mcguire K et al. [14], 2009	Retrospective, single institutional	154/566	20 %**	33 %**	0.0012	NA	NA
Ruiterkamp J et al. [15], 2009	Retrospective population based	288/728	14 months ****	31 Months ****	<0.01	0.62	Surgery, number of metastatic sites <1, use of systemic treatment and age <50 year
Bafford et al. [16] 2009	Retrospective, institutional	61/147	4.13 year [#]	2.36 year [#]	0.003	0.47	Surgery, ER + status, Her2+ status, no CNS metastasis
Leung et al. [17] 2010	Retrospective, single institutional	52/157	13 months ****	25 months****	0.06	NA	Chemotherapy
Vohra L et al. [18], 2011	Retrospective, single institutional	127/205	32 months **	49 months**	0.0001	NA	NA

* - 3 year observed survival, ** -Overall survival, *** - 5 year breast cancer specific survival, **** - Median survival in months, *PM* partial mastectomy, *TM* total mastectomy, # - Mean survival in years

concluded that surgical resection does have a role in the management of limited Stage IV breast cancer with an intact primary tumor. This study has some limitations, especially given that no control group was implemented in the study design, questioning the significance of these findings. No receptor status of tumors, grade, or rationale for surgical treatment was provided. No details of the specific multimodal treatment regimen were provided (Table 2).

Rapiti et al. [8] present the results of a retrospective study of the impact of surgical therapy of the primary tumor on survival outcomes in patients with metastatic disease at the time of the initial diagnosis of breast cancer. They found that patients operated for resection of the primary tumor had a 50 % reduction in breast cancer mortality compared with women who did not undergo surgery. Similar to the study by Khan et al. [5], authors found that the survival benefit was limited to women with postresection tumor-free margins, but a statistically significant survival benefit for axillary surgery was not observed (Table 2).

Rao et al. [19] also proved that resection of the intact primary tumor and axillary nodes if performed within 3 months of diagnosis in these patients, there is an advantage in terms of improved progression-free survival. They also showed that patients with only one site of metastasis fared better.

McGuire et al. [14] in their study at Moffitt Cancer Centre compared overall survival of metastatic breast cancer patients undergoing breast conservation surgery with those who underwent mastectomy. They also considered factors like number and sites of metastases and tumor receptor status, as well as adjuvant and neoadjuvant chemotherapy and radiation but difference in survival between the groups of none of the factors reached statistical significance level.

Recently, Ruitercamp et al. [15] and Vohra et al. [18] also suggested that surgical excision of primary tumour is significantly associated with better survival (Table 2).

Cady et al. [12] challenged this concept by conducting matched pair analysis of metastatic breast cancer patients from database of patients entered into the tumor registries of the Massachusetts General Hospital (MGH) and the Brigham and Women's Hospital (BWH) over 40 years. They concluded that improved 5-year survival of metastatic breast cancer patients who undergo surgery for excision of primary is probably due to selection of patients with expected better prognosis for surgery. These better prognostic factors are likely to be estrogen receptor positive tumours, bone-only metastases, oligometastatic disease and good response to initial systemic therapy (Table 2).

But still there is sufficient evidence to review our approach towards metastatic breast cancer patients diagnosed with distant metastases at the initial breast cancer presentation. As evident from study at The M.D. Anderson Cancer Center (Houston, TX) [20] and a study by Nieto et al. [21], a subset of patients have had prolonged survival. The M.D.

Anderson Cancer Center (Houston, TX) has reported a 15-year disease-free survival rate of 24 % in 134 patients with solitary locoregional recurrences or metastases treated with multimodality treatment including surgery whereas Nieto et al. found that 51.6 % of 60 patients with minimal metastatic disease treated with surgery and/or radiation therapy and high-dose chemotherapy were alive and disease free at the median follow up of 62 months.

Hence we have attempted to define the subset of patients who will benefit maximally with multimodality approach including surgery for primary tumour in spite of being presented with metastatic breast cancer.

In our study the number of patients with positive resection margins and patients who underwent lumpectomy was very low.

Patients who were younger (<50 year) had trend towards better prognosis in this study. This is consistent with the finding in multivariate analysis in various studies [8, 12, 13, 15] comparing surgery Vs no surgery in metastatic breast cancer.

Patients with ER positive tumours had longer median overall survival in our group of patients. Two retrospective analyses [8, 16] had also noted that the survival in ER + ve metastatic breast cancer patients is better.

We found that survival in patients with only bone metastases was similar to the patients who had visceral metastases. Leung et al. [17] also found similar survival in patients with only bone metastases Vs visceral metastases (Median survival: 17 months for both groups, Log Rank $P = 0.91$; Wilcoxon $P = 0.51$). Rapiti et al. [8] found that presence of visceral metastases is significantly associated with poorer survival.

In our study, patients who had only a single metastatic lesion (either in bone or soft tissues or visceral) had fared better than those with multiple metastatic lesions. Other investigators [1, 9, 15] have also reported in multivariate analysis, that either single or oligometastatic lesions have better survival than multiple metastatic lesions.

When the patients were divided according to pathological T stage, the patients with T1–T3 disease had significantly better survival. Since majority of our patients (85 %) had neoadjuvant chemotherapy, lower T stage represents tumours responding to chemotherapy and vice versa. This observation can be helpful in deciding whether to subject a patient of metastatic breast cancer for surgery or not.

We also looked at the survival in patients according to radiological level of suspicion. The patients who have had low level of radiological suspicion of metastatic disease had better overall survival, thus emphasizing the need for more aggressive local therapy in this subset of patients. This finding is important in context of patients in the developing countries where there is lack of adequate facilities or expertise to histologically confirm the diagnosis of metastatic disease.

Limitation of our study is that it is a retrospective study thus we cannot negate the selection bias. Number of patients was small which might be the reason for inability to find statistically significant difference in majority of variables.

Conclusions

There is statistically significant survival benefit in pT1–pT3 lesions and, there is a trend towards better survival in patients who are ER positive, Her-2 neu negative, single metastatic site and patients with low level of suspicion of metastatic disease. Thus patients with these characteristics can be considered for multimodality therapy, including surgery, more aggressive than only palliation. However there is a need for randomized controlled trial to confirm these findings.

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