



Effect of Surgery or Radiotherapy of the Breast on Survival in Metastatic Disease: a Retrospective Cohort Study

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Abstract

Evidence to justify survival benefit of local therapy of the breast (LT) for breast cancer patients who are metastatic at presentation (MBC) is weak. The aim of this study is to evaluate the outcome of LT on survival in MBC patients. Patients who had received (1) radiotherapy, (2) surgery, (3) surgery and radiotherapy as LT, and (4) no LT in four groups of 25 were evaluated for 1- and 4-year cause-specific survival (CSS). One- and 4-year CSS in four groups were (1) 76% and 60%, (2) 84% and 56% (3) 80% and 52%, and (4) 48% and 16%, respectively. When controlling for age and site of metastasis as covariates, grouping significantly correlated with survival: $F(3, 94): 2.93, P 0.04$. Post hoc analysis revealed that the mean survival of group 2: ($M 23.39, SE 2.53$) was higher than group 4: ($M 13.63, SE 2.52, P = 0.03$). Surgery as a single modality LT for MBC may provide survival benefit.

Keywords Metastatic breast cancer · Local treatment · Radiotherapy · Surgery

Introduction

Metastatic breast cancer is an incurable condition. Systemic treatment is the mainstay of palliative treatment in this disease state and is categorized to hormone therapy (HRT) or chemotherapy. Systemic treatment can prolong survival, control cancer-related complications, and increase the quality of life and function of metastatic patients. A small proportion of patients with limited metastases may have prolonged survival exceeding 10 years [1, 2]. Each year there is 1–2%

improvement in survival rates of patients with metastatic breast cancer. This is largely due to improvements in systemic treatment [3].

Most metastatic cases present before the 5th year of treatment of a localized disease and only approximately 6% of patients present with de novo metastatic disease [1, 4]. Some evidence suggests that metastatic shed develops early in the disease course [5]; this can be controlled by a good functioning immune system. It has been proposed that removal of the primary tumor in the metastatic setting may enhance host immune response, reduce tumor burden, eliminate the source of tumor seeding, and improve delivery of systemic treatment [3], but on the contrary, surgery may induce stress, immunosuppression, and tumor seeding [6–8].

Several retrospective reports and meta-analyses have shown a prolonged survival for patients that had received local therapy of the primary (LT) [9–17]. Two prospective trials have shown no benefit for LT in initial good responders to chemotherapy [18, 19] but one did [20]. Consequently, there is no strong evidence that there is an added survival benefit from LT in metastatic breast patients and therefore this is not a standard practice. Institutional experiences, patient preferences, and degree of response to initial chemotherapy contribute to decision for LT. This is achieved after being discussed in a multidisciplinary team [21]. Evidence for an effect of radiotherapy of the primary

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on survival is even less. This study answers this question that if there is a difference in cause-specific survival (cancer-related death) in metastatic patients that had received surgery alone, radiotherapy alone, or surgery plus radiotherapy, after controlling for probable covariates.

Patients and Methods

The participants of this retrospective cohort were women with stage IV breast cancer at presentation who were referred to the oncology department between March 2009 and March 2013. The patients were selected by simple sampling of their medical records in Omid hospital, Isfahan, Iran. In order to comply with the ethical standards, all patients received a phone call while sampling, the purpose of the study and the method was explained to her or her family, and after obtaining informed consent, patients were included. Patients were excluded if they or their family members were not able to respond to calls and for whatever reason were unwilling to participate in the study. Information on forms (demographic, clinical, therapeutic, etc.) were completed from medical records and through phone calls and if necessary a date of appointment was set. We reviewed the patients in terms of their living status and their death history was recorded. All death certificates were reviewed and information of those who had died outside the same hospital was obtained by interviewing families. Patients who had non-cancer-related death (e.g., accidents and cerebrovascular stroke) were excluded from the study, and other patients were replaced. To be noted, initial tumor staging was not recorded for all metastatic patients. LT was defined as local surgery (lumpectomy or modified radical mastectomy), or radiotherapy (with or without targeting regional lymph nodes), or both. Four separate groups of 25 individuals with the following characteristics were grouped as:

1. Patients who received radiotherapy at the site of the primary tumor but not surgery
2. Patients who had not received radiotherapy at the site of the primary tumor, but had undergone surgery
3. Patients who received surgery followed by radiotherapy of the site of the primary tumor
4. Patients who did not receive radiotherapy at the initial site and did not undergo surgery for the primary tumor

The primary endpoint of the study was cancer-related death. One- and 4-year survival rates were studied. Also, other factors expected to be effective in the development of the outcome (death) such as age, the location of metastasis, duration of chemotherapy sessions, HRT and type of drug used for it, tumor size, and primary tumor surgery, were also surveyed.

Results

The average age of 100 patients was 52.4 (range 27–87). Demographic data are listed in Table 1. Data about tumor size was frequently missing. Fifty-six percent of all 100 cases received some kind of HRT in a phase of their disease course. Mean CSS was higher in patients who had received HRT (M 21.57, SD 11.61) compared with those who had not (M 17.23, SD 13.98). This difference was marginally significant (Mann-Whitney U 944.5, P 0.046). The four treatment groups did not differ in terms of site of metastasis (bone, viscous, or multiple sites), age distribution, tumor size, or duration of chemotherapy (less than or equal or greater than six courses). But the difference between the groups was significant in HRT status (Table 1). The highest 1-year CSS rate was equal to 84% in group 2: patients who had obtained primary tumor surgery, without radiotherapy, and in second place, it was for patients who did tumor surgery with radiotherapy (80%). Patients who underwent radiotherapy to the primary site of the tumor without surgery, stood in the third place (76%). Also, the highest 4-year survival rate was related to patients who had received radiotherapy at the site of the primary site of the tumor without surgery (60%), and in the second place, it was related to patients undergoing primary tumor surgery without radiotherapy (56%). Then, in the third rank were patients undergoing primary tumor surgery and radiotherapy with a 4-year survival rate of 52%. Ultimately, patients who did not have primary tumor site surgery and radiotherapy had the lowest 1 and 4 year CSS (48% and 16%). Kaplan-Meier plots are shown in Fig. 1. In order to study the effect of treatment group on survival, Levene's test for equality of variances was performed which according to P 0.2, the heterogeneity of variances hypothesis was rejected. ANOVA analysis showed that the effect of groupings on survival was significant: $F(96.9) = 3.0$ $P = .03$. Post hoc comparison using Tukey's HSD test showed that the mean survival in group 2: only surgical treatment, ($M = 23.39$, $SE = 2.53$) and group 4: no treatment, ($M = 13.63$, $SE = 2.52$) was significantly different ($P = .03$). This effect was not significant in other comparisons of groups 3: radiotherapy and surgery ($M = 19.70$, $SE = 2.54$) and 1: radiotherapy alone ($M = 21.93$, $SE = 2.53$). Using the ANCOVA analysis, age was controlled as a general prognostic factor, as well as the location of metastasis in groups of single bone metastasis, single visceral organ metastasis, and multiple sites of metastases. ANCOVA showed that the effect of treatment group on survival was still significant: $F(3, 94) = 2.93$ $P = .04$. In contrary when including parameters of receiving HRT in the model, the treatment group effect of grouping on survival was not significant: $F(2, 95) = 2.38$ $P = .07$.

Table 1 Demographic data

| Parameter | subtype | Group 1 RT (N = 25) | Group 2 Sur. (N = 25) | Group 3 Sur. +RT (N = 25) | Group 4 No LT (N = 25) | Total (N = 100) | Statistical value | P value |
|--------------------|-----------------------|------------------------|--------------------------|------------------------------|---------------------------|--------------------|--------------------------------|---------|
| Age means (SD) | | 53.1 (14.2) | 49.5 (12.5) | 55.7 (15.1) | 51.5 (13.0) | | .905 ^a | 0.44 |
| Tumor stage | T1 | 4 | 5 | NA | 2 | 11 | 9.307 ^β | 0.41 |
| | T2 | 11 | 11 | 8 | 3 | 33 | | |
| | T3 | 5 | 5 | 6 | NA | 16 | | |
| | T4 | 2 | 2 | NA | NA | 4 | | |
| Site of metastasis | Only brain | 3 | 2 | 1 | 6 | 12 | 9.364 ^β | 0.40 |
| | Only bone | 12 | 9 | 8 | 10 | 39 | | |
| | Viscerus (lung/liver) | 4 | 3 | 5 | 2 | 14 | | |
| | Multiple | 6 | 11 | 11 | 7 | 37 | | |
| Surgery | lumpectomy | – | 4 | 8 | – | 12 | 1.75 ^β ^γ | 0.32 |
| | MRM | – | 21 | 17 | – | 38 | | |
| Hormone therapy | None | 9 | 12 | 7 | 20 | 47 | 17.77 ^β | 0.007 |
| | Tamoxifen | 12 | 9 | 8 | 4 | 33 | | |
| | AI | 6 | 4 | 8 | 1 | 19 | | |
| Cht. | None | 5 | 1 | 2 | 5 | 13 | 7.810 ^β | 0.25 |
| | Less than 6 courses | 3 | 6 | 5 | 8 | 22 | | |
| | 6 courses and more | 17 | 18 | 18 | 12 | 65 | | |

^a ANOVA statistical F, ^β Pearson's chi-square, ^γ difference calculated between group 2 and 3. *RT*, radiotherapy to the primary site; *Sur.*, surgical treatment of the primary site; *LT*, local treatment of the primary; *Cht.*, chemotherapy; *AI*, aromatase inhibitor; *MRM*, modified radical mastectomy; *SD*, standard deviation

Discussion

This study was conducted to investigate the role of LT in metastatic breast cancer patients and the benefit of surgery and/or radiotherapy as a LT approach. By exploring the subset analysis, the effect of some other factors on CSS were also examined. The mean age of women with breast cancer in this study was slightly higher than the results of a national study within the locale, which reported 49.6 years [14]. The age difference between groups was not significant neither were tumor size, chemotherapy duration, and site of metastases, but hormonal status was.

The results of this study indicated that patients with metastatic breast cancer who received none of the local breast cancer treatments (surgical or radiotherapy) survived less. Some recent studies have appealed that LT in patients with metastatic breast cancer can increase survival [12], while some prospective studies rejected this premise. The National Comprehensive Cancer Network (NCCN) and European Society of Medical Oncology (ESMO) guidelines include surgery, radiotherapy, and regional chemotherapy as possible treatment options for some patients with localized metastatic disease. Surgical treatment may be considered after initial systemic therapy for patients with impending complications, such as bleeding, pain, fungation, or ulceration [22, 23].

Some of reported independent variables for prognosis for LT managed metastatic patients are age [16], response to

initial chemotherapy and receiving systemic therapy [10, 15], Karnofsky performance status [24], Tumor [12], and nodal [16] staging, grade of tumor [12], hormonal treatment or ER and PR status [16, 25], and Her-2 status [26], Number of metastatic sites [15], and site of metastasis [15, 27]. Therefore, survival advantage in LT managed metastatic patients might be a consequence of good prognostic factors per se. The common approach for LT is lumpectomy or mastectomy without reconstruction and without radiotherapy [21], but attaining clear surgical margins [11, 15] and addressing disease in the axilla [22] also affected survival in some studies and are recommended and occasionally practiced. Oligometastatic patients are also more subject to LT. Circumstantially, surgery may have been obtained before detecting metastasis in a patient with a low likelihood of metastasis [10, 24].

The surgery alone group had the highest 1-year CSS. This result is concordant to a recent study that evaluated a number of outcomes such as local relapse-free survival and overall survival in metastatic breast patients who had received different LT modalities. The best outcome fitted to patients treated with surgery alone [12]. The patients who had received radiotherapy in our study were treated with 45–50 Gy to the breast as well as nodal basins similar to [28–31]. The results showed that although CSS was higher in both groups who had received radiotherapy than those who had not, this difference in survival was not statistically significant in post hoc analysis.

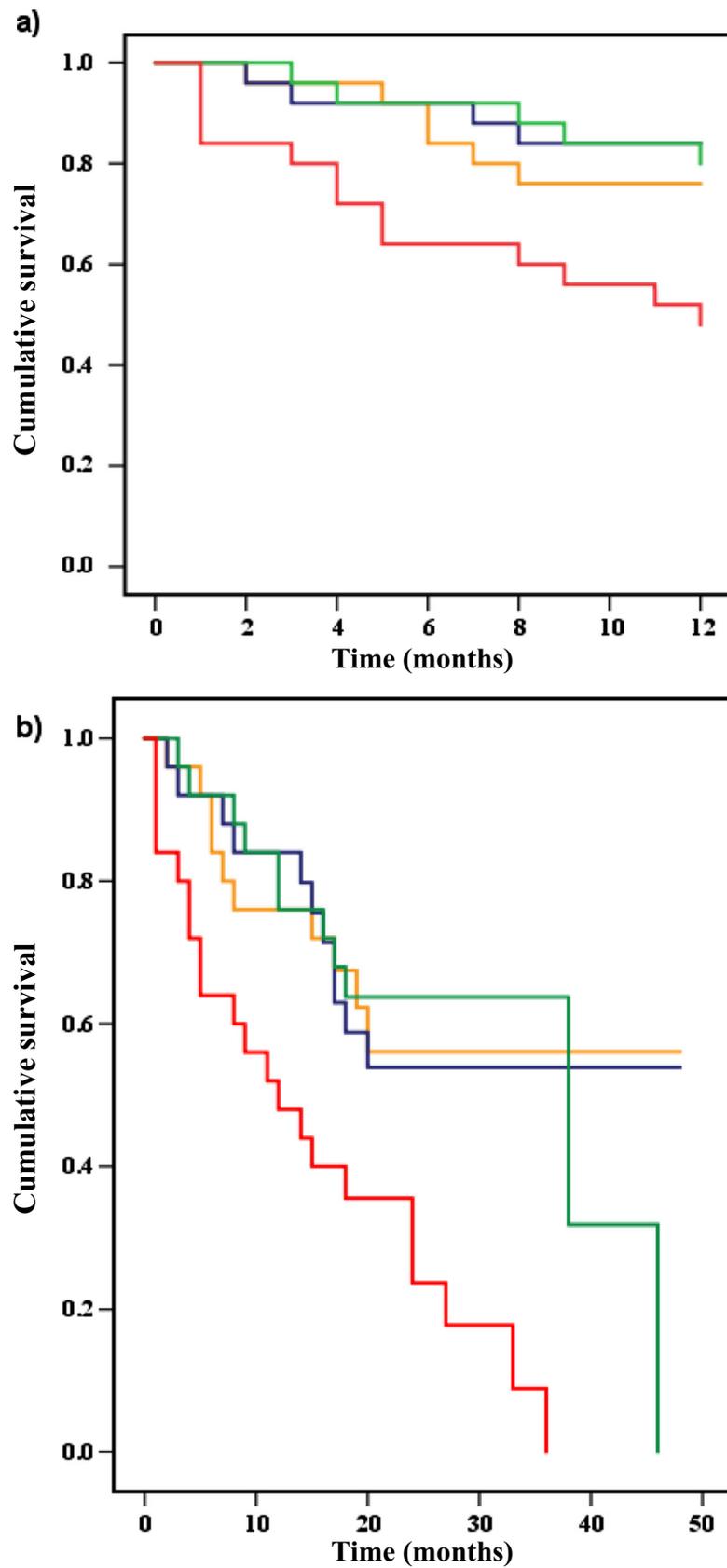


Fig. 1 Kaplan-Meier plots for **a** one-year and **b** 4-year cause-specific survival for each treatment. Lines show radiotherapy (orange), surgery (blue), surgery and radiotherapy (green), and no treatment (red) of the primary site of metastatic breast cancer

Long-term pooled data have shown that radiotherapy provides a survival benefit in early stage invasive breast cancer when compared to controls [32]. The effect of radiotherapy as an LT on survival in metastatic patients is not well studied. The incurable status of metastatic disease supposedly overpowers any marginal survival benefit of breast radiotherapy, though there is modest evidence that breast radiotherapy and the amount of delivered dose independently correlate with survival in metastatic patients [12, 28, 30]. Hence, patients who are supposed to live longer are occasionally proposed LT treatments in addition to systemic therapy by their radiation oncologists. This may explain why the effect of treatment stratification on survival was not significant when including the favorable factor of HR status in analysis. HRT targeting estrogen and progesterone receptors may control disease progression years before the need for switching to chemotherapy after a mean 8–12 months of first-line and a mean 4–6 months of second-line HRT [24]. Given the fact that the difference of CSS was marginally significant in patients receiving HRT compared to those who had not, hormone receptor status may be a confounding factor for survival advantage of LT in this study. Alternatively, one study showed that patients selected for receiving radiotherapy had better outcome when the hormone status was favorable and hormone sensitivity may independently affect the response to LT [31]. The effect of patient- and tumor-related factors on LT of metastatic patients should be evaluated thoroughly in future studies.

Conclusion

This study showed that after adjusting the groups for possible covariates, breast cancer patients that had received surgery as a LT for metastatic disease favored meaningfully compared to those that had not received any LT, however, hormone receptor status was still an important parameter that was in association with higher survival in patients receiving LT. It is not clear that if the hormone status of the tumor was merely responsible for all survival benefits observed in patients receiving LT. This study was not able to find an independent effect of LT (either surgery or radiotherapy) on survival when factors of HRT were included in ANCOVA. More comprehensive studies are still needed to reach a definitive conclusion for choosing patients for LT.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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