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Local Resection of Primary Tumor in Upfront Stage IV Breast Cancer

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Keywords

Local resection · Metastatic breast cancer · Stage IV breast cancer

Summary

Background: This study aimed to identify the association of local surgery of the primary tumor in metastatic breast cancer (MBC) patients with overall survival (OS) and prognostic factors. **Patients and Methods:** Patients with primary MBC (1990–2006) were included in our retrospective analysis (n = 236). 83.1% had surgery for the primary tumor. OS was evaluated using Kaplan-Meier estimates. Predictive factors for OS were determined. **Results:** Median follow-up was 123 months for all patients still alive at the time of analysis. In univariate analysis, patients with surgery of the primary tumor had significantly prolonged OS (28.9 vs. 23.9 months). Within the surgery group, patients with MBC limited to 1 organ system had a better outcome (39.3 vs. 24.9 months), as did asymptomatic patients. Independent risk factors for shorter OS were hormone receptor negativity, symptoms, and involvement of ≥ 1 organ system. **Conclusion:** Patient selection for local therapy was confounded by a more favorable profile and a lesser tumor burden before surgery, which might implicate a bias. Nevertheless, our univariate results indicate that local surgery of the primary tumor in MBC patients could be considered as part of the therapeutic regimen in selected patients. However, larger patient numbers are needed to prove these findings in the multivariate model.

Thomas Kolben and Theresa M. Kolben contributed equally to this work.

Introduction

In the United States and Western Europe, approximately 5% of breast cancer (BC) patients present with stage IV at their primary diagnosis [1]. Stage IV BC is defined as BC that has metastasized to distant organs. The standard therapeutic approach is palliative; systemic therapy is considered the mainstay of treatment [2, 3]. Local resection of the primary tumor is recommended for symptom control, e.g. for ulceration and bleeding or alleviation of pain. A substantial survival benefit due to resection of the primary tumor is not expected for stage IV BC. The development of new systemic therapy regimens and new agents has led to a significant increase in the overall survival (OS) of patients suffering from metastatic disease [4]. With this gain in survival time, the risk of local progression and associated problems also increases, which justifies considering local resection as part of the initial treatment approach.

Additionally, several retrospective studies reported an association of local resection with increased survival time [5, 6].

It has been assumed that a decrease of circulating tumor cells (CTCs) by surgical reduction of the total tumor volume (including tumor stem cells as a source of CTCs) decreases the rate of new metastasis and is therefore associated with a better prognosis [7].

Another reason for longer survival after resection of the primary tumor might be an activation of autoimmunity and an increase in drug efficacy [8].

With the availability of more sensitive imaging modalities such as positron emission tomography/computed tomography (PET/CT), the profile of metastatic breast cancer (MBC) has changed. Patients with metastatic disease can be diagnosed earlier, which confronts us with a new group of patients with 'low tumor burden'. These patients might be good candidates for local resection.

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Table 1. Patient demographics

	No local surgery	Local surgery	p	Total
Age, median (range), years	57 (33–93)	58 (28–86)	ns	58 (28–93)
Patients, n (%)	40 (16.9)	196 (83.1)		236 (100.0)
T stage, n (%)				
T1–3	23 (57.5)	129 (65.8)	ns	152 (64.4)
T4	17 (42.5)	67 (34.2)		84 (35.6)
Grade, n (%)				
G1 and G2	30 (75.0)	88 (44.9)	0.001	118 (50.0)
G3	10 (25.0)	108 (55.1)		118 (50.0)
HR status, n (%)				
Positive	33 (82.5)	146 (74.5)	ns	179 (75.8)
Negative	7 (17.5)	50 (25.5)		57 (24.2)
HER2 status, n (%)				
Positive	4 (10.0)	25 (12.8)	ns	29 (12.3)
Negative	21 (52.5)	89 (45.4)		110 (46.6)
Missing	15 (37.5)	82 (41.8)		97 (41.1)
Organ systems involved, n (%)				
1	14 (35.0)	125 (63.8)	<0.001	139 (58.9)
2	10 (25.0)	44 (22.4)		54 (22.9)
3	10 (25.0)	22 (11.2)		32 (13.6)
> 3	6 (15.0)	5 (2.6)		11 (4.7)
Location of metastasis, n (%)				
Bone only	8 (20.0)	84 (42.9)	0.009	92 (39.0)
Sing. visc./soft	6 (15.0)	40 (20.4)		46 (19.5)
Multiple	23 (57.5)	66 (33.7)		89 (37.7)
+CNS	3 (7.5)	6 (3.1)		9 (3.8)
Symptoms, n (%)				
No	7 (17.5)	94 (48.0)	<0.001	101 (42.8)
Yes	33 (82.5)	102 (52.0)		135 (57.2)
First-line systemic treatment, n (%)				
Chemotherapy	18 (45.0)	109 (55.6)	ns	127 (53.8)
Endocrine	22 (55.0)	87 (44.4)		109 (46.2)
Lost to follow-up, n (%)	6 (15.0)	11 (5.6)	0.03	17 (7.2)

HR = Hormone receptor; Sing. visc./soft = single visceral organ/soft tissue (≙ 1 organ); multiple = ≥ 2 organs; +CNS = CNS involvement ± other; ns = not significant.

To our knowledge, up to now, final results from only 2 prospective studies are available focusing on the question whether local therapy of the primary tumor in stage IV BC has an effect on the prognosis and survival of such patients [9, 10]. A number of promising randomized trials investigating this topic are underway (still recruiting or in follow-up), summarized by Shien [11].

The purpose of our study was to identify the potential impact of surgical therapy of the primary tumor in patients with primary stage IV BC.

Patients and Methods

Between 1990 and 2006, 236 patients with primary MBC treated at the University Hospital Munich Grosshadern were included in this retrospective analysis. 16.9% of these patients had received no local surgical treatment, whereas 83.1% had undergone surgery. Exclusion criteria from our analysis were as follows: radiation as the only local treatment, no systemic treatment, non-resectable primary tumors, and death within 30 days of presentation. Patient demographics are presented in table 1.

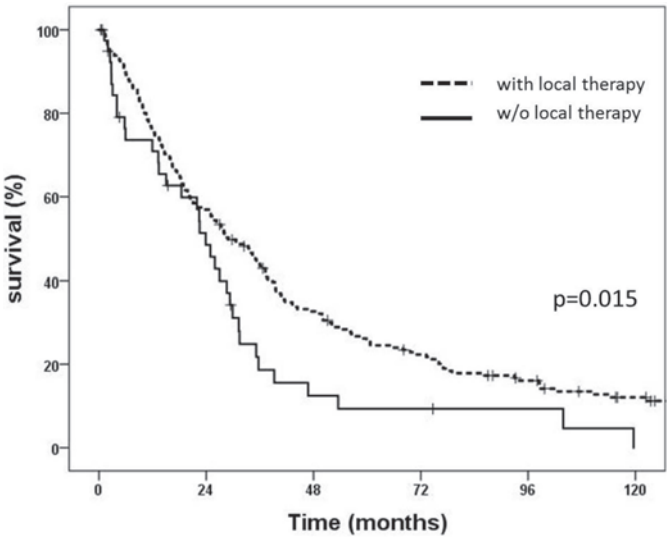

Fig. 1. Overall survival (OS) in relation to local surgery in M1 patients (no local surgery vs. local surgery): median OS (95% confidence interval) 23.9 (19.3–28.5) vs. 28.9 (22.2–35.7) months; p = 0.015.

Patients in the non-surgery group were significantly more likely to have metastases to multiple organ systems (57.5 vs. 33.7%) and involvement of the central nervous system (CNS) (7.5 vs. 3.1%) ($p < 0.001$). Patients without surgery presented significantly more frequently with symptoms (82.5 vs. 52.0%) ($p < 0.001$).

Most patients who underwent surgery received systemic therapy after surgery (139/196, 70.9%). The remaining patients (57/196, 29.1%) were treated with primary systemic therapy (chemo or endocrine therapy) followed by surgery within 3–6 month of the tumor being diagnosed.

Starting with the official approval of trastuzumab for MBC in Germany in 2000, most patients received trastuzumab if treated with chemotherapy (n = 10; no surgery: n = 2, surgery: n = 8). Trastuzumab was not used in patients with endocrine first-line treatment or anthracycline-based first-line chemotherapy.

Kaplan-Meier estimates were used to evaluate OS which was specified as the time interval from primary diagnosis of MBC to death from any cause. The log-rank test was used to assess survival differences between groups in the univariate analysis.

Multivariate Cox proportional hazards regression models were used to identify potential prognostic factors associated with survival.

A test for interaction was performed for an exploratory subgroup analysis of the differential effect of surgery on prognosis.

All analyses were carried out with SPSS software (IBM SPSS Version 22; IBM Corp., Armonk, NY, USA). All tests were two-sided using a significance level of 0.05.

Results

Median follow-up after the primary diagnosis was 27 (1–218) months (median follow-up for all patients still alive at the time of analysis was 123 (27–180) months). At the time of analysis, the observed mortality was 87.2% (206/236 patients), 17 patients were lost to follow-up, and 13 patients were still alive.

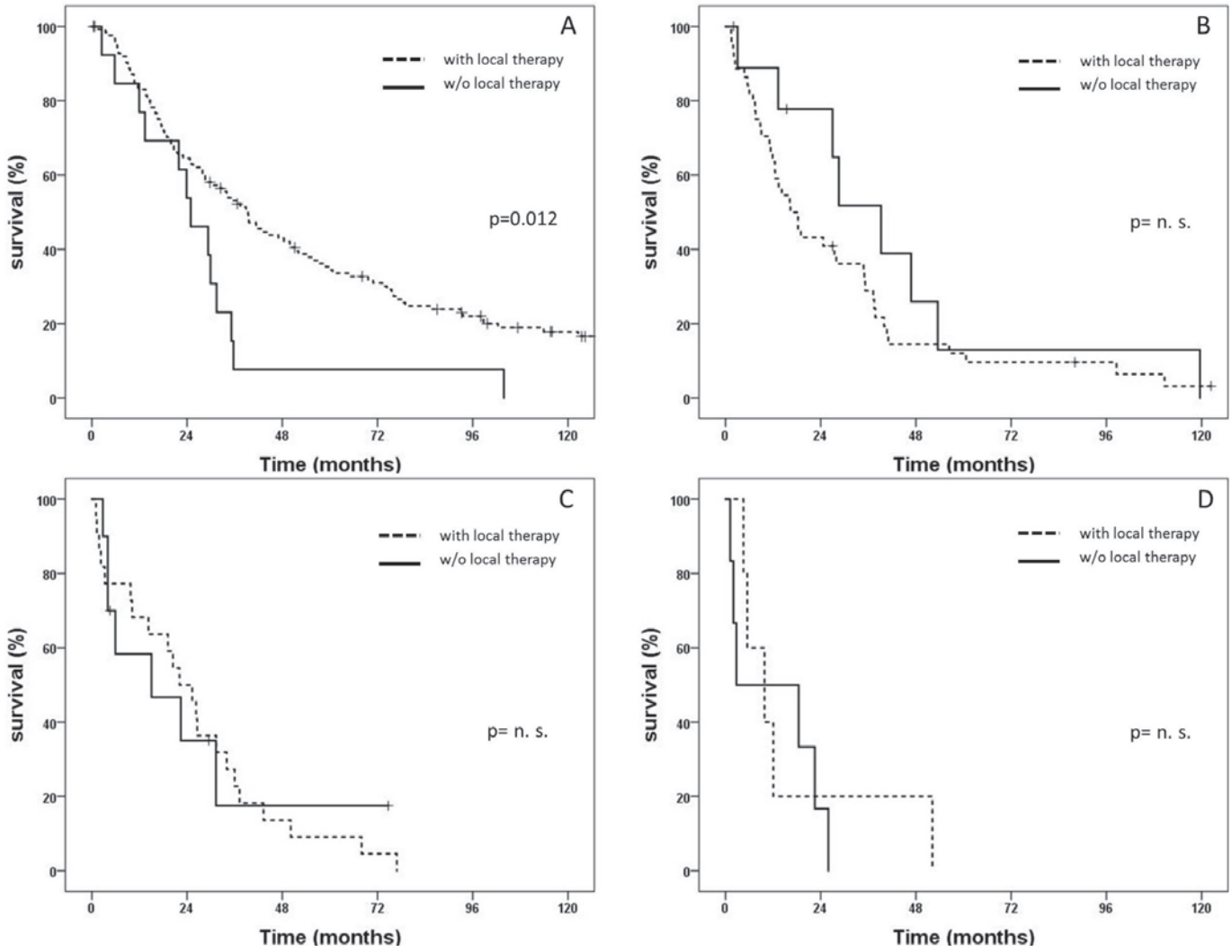

Fig. 2. Number of metastases and overall survival (OS) in relation to local surgery (no local surgery vs. local surgery. **A** M1 patients with metastases limited to 1 organ system: median OS (95% confidence interval (CI)) 24.9 (16.3–33.6) vs. 39.3 (31.4–47.3) months; p = 0.012. **B** M1 patients with metastases limited to 2 organ systems: median OS (95% CI) 39.2 (23.2–55.2) vs. 16.3 (10.3–22.4) months; not significant (ns). **C** M1 patients with metastases limited to 3 organ systems: median OS (95% CI) 15.0 (7.2–38.0) vs. 22.1 (13.9–30.3) months; ns. **D** M1 patients with metastases to > 3 organ system: median OS (95% CI) 2.8 (0.0–22.5) vs. 9.8 (0.5–19.2) months; ns.

In the univariate model, patients with surgical therapy of the primary breast tumor had significantly prolonged median OS of 28.9 (22.2–35.7) vs. 23.9 (19.3–28.5) months (p = 0.015) (fig. 1).

The association of local treatment with OS compared to no local surgery was not homogenous across all subgroups. In more advanced disease groups, local treatment was not associated with a significant OS prolongation. Local surgery did not show any significant effect on survival outcome in patients with involvement of 2 organ systems (16.3 (10.3–22.4) vs. 39.2 (23.2–55.2) months; not significant), 3 organ systems (22.1 (13.9–30.3) vs. 15.0 (7.2–38.0) months; not significant), and more than 3 organ systems (9.8 (0.5–19.2) vs. 2.8 (0.0–22.5) months; not significant). However, patients with MBC limited to 1 organ system had significant prolongation of OS after local surgery (39.3 (31.4–47.3) vs. 24.9 (16.3–33.6) months; p = 0.012) (fig. 2).

Patients with metastatic disease limited to 1 visceral organ or 1 soft tissue system, presented with prolonged OS in the surgery group (27.3 (17.4–37.2) vs. 13.4 (0–29.8) months; p = 0.042). A considerable prolongation of OS was also observed in patients with bone metastases only (43.3 (33.3–53.3) vs. 24.9 (16.6–33.3) months; p = 0.115) (fig. 3).

Patients with metastases to multiple organ systems (19.0 (10.6–27.4) vs. 25.9 (14.1–37.7) months; not significant) or any CNS involvement (2.1 (0–6.5) vs. 2.8 (2.7–2.8) months; not significant) had no significant improvement in survival after surgery (fig. 3).

Patients who were asymptomatic at presentation had a significantly higher increase in OS after surgery (37.5 (23.8–51.2) vs. 15.0 (11.5–18.6) months; p = 0.029) compared to symptomatic patients (24.7 (17.3–32.2) vs. 23.9 (19.3–28.5) months; not significant).

In the multivariate analysis, patients with hormone receptor-negative BC were significantly more likely to have shorter survival (relative risk (RR) 1.6; p = 0.004). The RR of dying increased with an increasing number of involved organ systems (p < 0.001). The risk for shorter survival was significantly higher in patients presenting with symptoms at diagnosis (p < 0.001) (table 2).

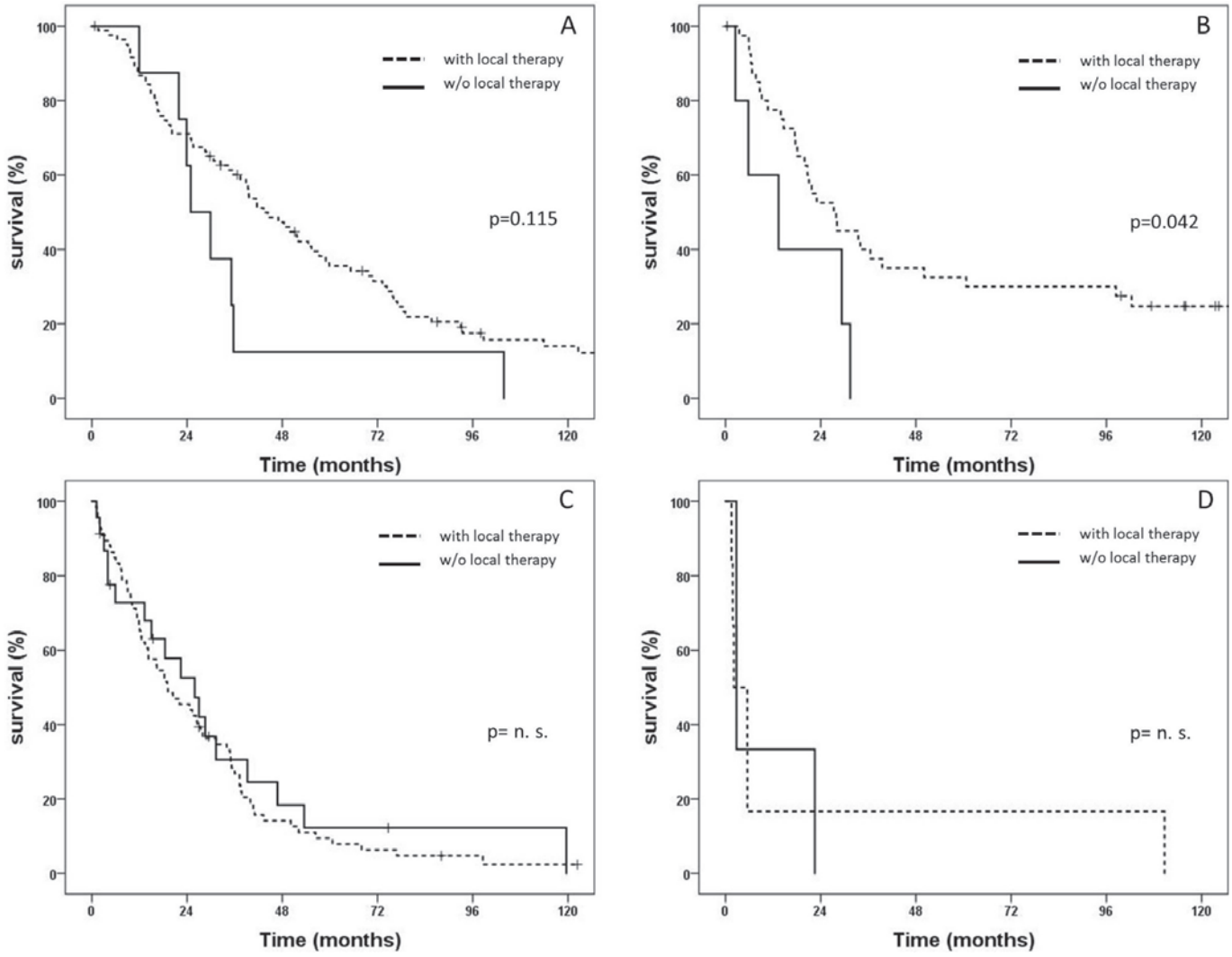

Fig. 3. Location of metastases and overall survival (OS) in relation to local surgery (no local surgery vs. local surgery). **A** M1 patients with metastases limited to the bone: median OS (95% confidence interval (CI)) 24.9 (16.6–33.3) vs. 43.3 (33.3–53.3) months; p = 0.115. **B** M1 patients with singular metastases to visceral or soft tissue only (1 organ system only): median OS (95% CI) 13.4 (0–29.8) vs. 27.3 (17.4–37.2) months; p = 0.042. **C** M1 patients with metastases to multiple organ systems: median OS (95% CI) 25.9 (14.1–37.7) vs. 19.0 (10.6–27.4); not significant (ns). **D** M1 patients with central nervous system involvement: median OS (95% CI) 2.8 (2.7–2.8) vs. 2.1 (0–6.5) months; ns.

Table 2. Multivariate analysis

	RR (95% CI)	p
HR negative vs. positive	1.6 (1.2–2.2)	0.004
2 organs vs. 1 organ involved	1.5 (1.1–2.2)	0.013
3 organs vs. 1 organ involved	2.0 (1.3–3.0)	0.002
> 3 organs vs. 1 organ involved	3.3 (1.8–6.3)	<0.001
Symptomatic vs. asymptomatic disease	1.7 (1.3–2.3)	<0.001

Covariables included in the Cox regression model: tumor stage, grade, HR status, number of involved organs, type of metastases, symptoms, local treatment, menopausal status, type of systemic treatment (non-significant results not shown: tumor stage, grade, type of metastases, local treatment, menopausal status, type of systemic treatment).
RR = Relative risk; CI = confidence interval; HR = hormone receptor.

The exploratory analysis of particular groups revealed surgery not to be associated with a homogenous effect on survival across the subgroups. In general, cases with a lower tumor load (e.g. less involved organ systems or asymptomatic disease) had a higher benefit from surgery. The test for interaction was significant for number of involved organ systems, location, and symptoms (fig. 4).

A landmark analysis limiting the presented data to only patients who survived for more than 6 months revealed similar results. Pa-

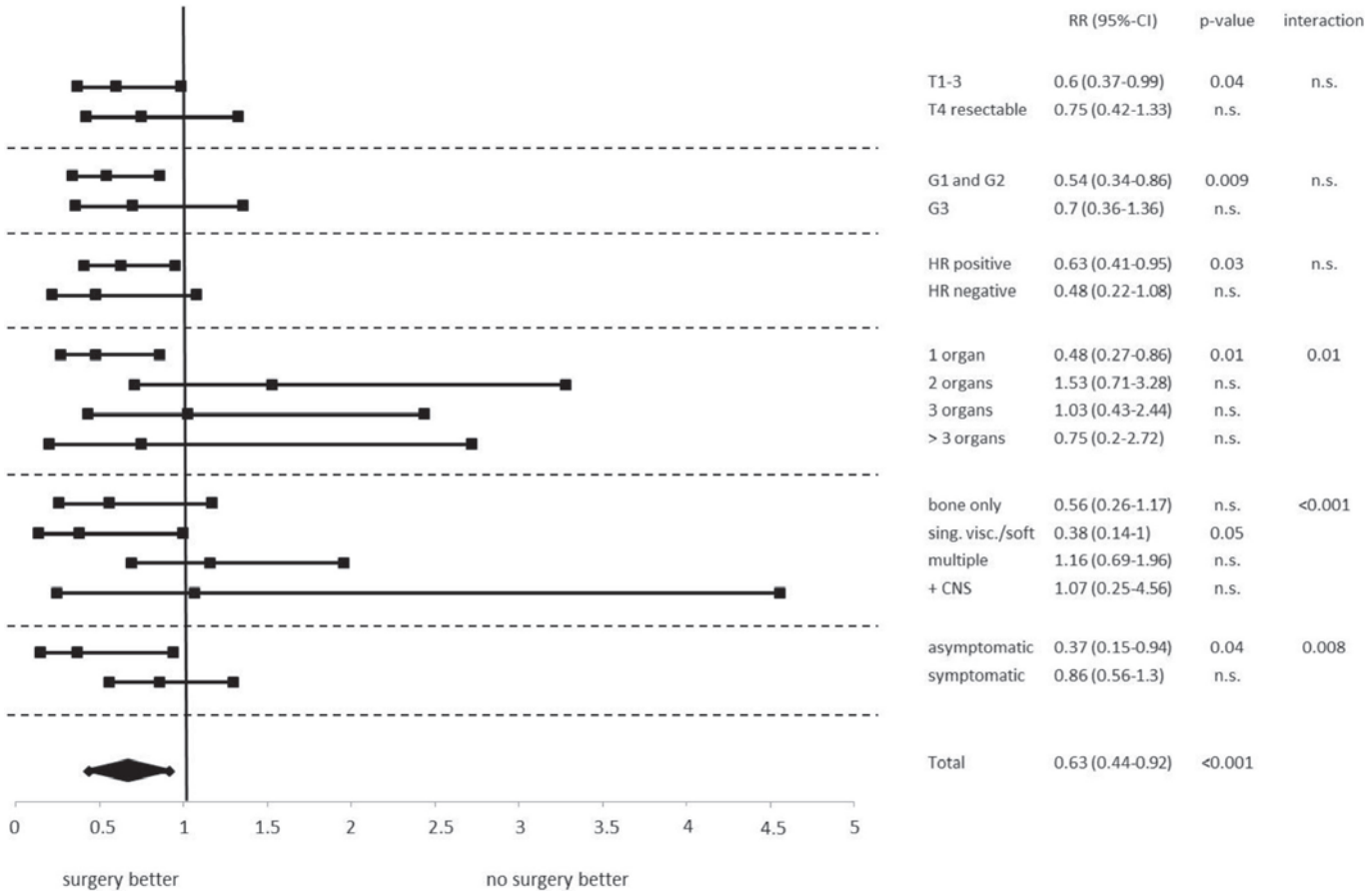

Fig. 4. Exploratory subgroup analysis. RR< 1 ≙ surgery favorable, RR > 1 ≙ surgery unfavorable (RR = Relative risk; CI = confidence interval; interaction = test of interaction; ns = not significant; HR = hormone receptor; sing. visc./soft = single visceral organ/soft tissue (≙ 1 organ); multiple = ≥ 2 organs; +CNS = CNS involvement ± other).

tients with bone metastasis only, metastases limited to 1 organ system, or asymptomatic disease had a considerably better prognosis in the surgery group, whereas all other groups showed no association with an effect of surgery (data not shown).

Discussion

In the univariate analysis, those patients with metastatic disease who had the primary tumor surgically removed showed significantly improved OS, which is consistent with other studies [5, 6, 12].

Different hypotheses exist to explain this positive effect of local surgery in the advanced stage of the disease. However, the true mechanism remains unclear. Removal of the primary tumor and thereby reduction in the total tumor burden is supposed to be associated with reduced tumor-induced immunosuppression [8] and decreased self-seeding of the primary tumor to distant sites [13], which again could be due to a reduction in CTCs [14]. Associated removal of BC stem cells, which can be the source of chemo-resistant clones, could influence outcome in a positive way by making metastases more sensitive to chemotherapeutic regimens [15].

The benefit of local surgery in MBC patients is not supported by results of a prospective randomized controlled trial conducted in India with 350 patients. This cohort received initial treatment with 6 cycles of anthracycline-based chemotherapy or endocrine therapy, and only patients who responded well to chemotherapy were enrolled in the study. Surgery did not extend survival in this trial. After 2 years, 41.9% of those who underwent breast surgery followed by radiotherapy were alive compared to 43.0% of women who received no local therapy [9]. The exclusion of non-responders to chemotherapy is in contrast to our study which did not exclude patients with a poor prognosis or low response to systemic treatment.

The prospective Indian trial focused on patients with a higher risk profile, while in our retrospective study the number of patients with low-risk metastases was substantially higher.

Consistent with the Indian randomized trial, we were unable to observe any substantial benefit from surgery in patients with high-risk metastases (limiting the analysis to patients who did not survive the first 6 months after diagnosis). Focusing on the low-risk patients, however, we could see a survival benefit in the surgery group in all univariate-analyzed subgroups (in patients with a documented survival of more than 6 months). However, in our multivariate model, no effect of local surgery was seen.

Regarding the inclusion criteria for patients, our study is more comparable to another prospective randomized study conducted in Turkey [10]. In this study, the survival rate after 40 months of median follow-up was significantly higher in the surgery group (46 vs. 37 months). The treatment algorithm differed between the 2 prospective studies. In contrast to the Indian study, all the Turkish women assigned to locoregional therapy received systemic therapy after breast-conserving surgery and breast irradiation – not before. Furthermore, patients with HER2-positive tumors were treated with trastuzumab.

In our analysis, the majority of patients who were treated surgically received systemic therapy after the surgery (71%). Pre- or postoperative systemic treatment did not result in significantly different outcome.

Besides the survival benefit found in the total cohort after local surgery, the Turkish investigators, similar to us, also identified subgroups who had a significant benefit from local surgery, i.e. patients with less aggressive tumor biology and patients with metastases limited solely to the bone [10].

This is strikingly similar to our univariate findings. We also observed a significant prolongation of survival in patients with disease limited to the bone in the surgery group.

In a review focusing on surgery in metastatic patients, Hartmann et al. [16] state that based on current data, locoregional treatment in primary MBC should not be routinely recommended in patients with asymptomatic primary tumors. In contrast, our data suggest that survival was longer especially in asymptomatic patients of the surgery group.

Patients with involvement of only 1 organ system were treated more often with surgery of the primary tumor, which is consistent with the findings of a meta-analysis of 10 studies including almost 29,000 patients with MBC [17].

Yet, in our analysis, the decision for local treatment was biased by the extent and presentation of the metastatic disease. Patients with more advanced MBC seemed to not benefit from removal of the primary tumor. A reason for this could be that a reduction in total tumor burden loses its effect once a certain tumor load is reached.

There are some limitations to our analysis: One obvious limitation is the retrospective and monocentric design. The selection of patients for local therapy was confounded by a more favorable profile and lesser tumor burden (higher proportion of oligometastatic patients, and bone metastases only) before surgery, which might implicate a selection bias.

To address the problem of bias by including patients who died early following the primary diagnosis of MBC, we performed a landmark analysis limiting the presented data to only patients who survived more than 6 months. In doing so, patients were excluded in whom poor tumor biology would have dictated the survival endpoints independent of local intervention. The results were almost identical.

A possible strength of our analysis is the substantial follow-up and patient numbers. However, the latter still seems too small to confirm an effect of local surgery in the multivariate model.

A current review supports the potential OS benefit we observed in the local surgery group in patients with oligometastatic disease, especially if limited to the bone [18].

The treatment of MBC will always be a multimodal approach influenced by the patient's age and comorbidities as well as specific tumor characteristics.

Despite the enormous problem of bias in a retrospective trial, especially in the complex situation of MBC, our univariate data were similar to those of the 2 randomized trials published so far [9, 19].

According to our analysis, asymptomatic patients and those with only 1 involved organ system (especially bone only) could be considered low-risk, while patients with symptomatic disease or more than 1 involved organ system or CNS metastases should be considered high-risk.

Essentially, surgery of the primary tumor should only be offered to metastatic high-risk patients if local control seems helpful in the context of palliative treatment. In contrast, for patients with low-risk metastases, surgery could potentially provide a small but significant survival benefit and could be offered more liberally.

Patients with oligometastatic disease to the bone and limited metastatic disease burden might be potential candidates for local surgery in that situation.

However, since local surgery lacked significance in the multivariate model, we suggest to investigate this topic with larger patient numbers.

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Disclosure Statement

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References

1 Siegel R, Naishadham D, Jemal A: Cancer statistics, 2013. CA Cancer J Clin 2013;63:11–30.
2 Arbeitsgemeinschaft Gynaekologische Onkologie e.V.: Empfehlungen Gynaekologische Onkologie Kommission Mamma: Version 1, 2014. *www.Ago-online.De/fileadmin/downloads/leitlinien/mamma/maerz2014/de/2014d_22_besondere_situationen_und_lokalisationen_in_der_metastasierten_situation.Pdf.*
3 National Comprehensive Cancer Network (NCCN): Clinical Practice Guidelines in Oncology: Breast Cancer, version 1, 2016. *www.nccn.org/professionals/physician_gls/pdf/breast.Pdf.*
4 Andre F, Slimane K, Bachelot T, Dunant A, Namer M, Barrelier A, Kabbaj O, Spano JP, Marsiglia H, Rouzier R, Delaloge S, Spielmann M: Breast cancer with synchronous metastases: trends in survival during a 14-year period. J Clin Oncol 2004;22:3302–3308.

5 Ruiterkamp J, Voogd AC, Bosscha K, Tjan-Heijnen VC, Ernst MF: Impact of breast surgery on survival in patients with distant metastases at initial presentation: a systematic review of the literature. Breast Cancer Res Treat 2010;120:9–16.

6 Petrelli F, Barni S: Surgery of primary tumors in stage IV breast cancer: an updated meta-analysis of published studies with meta-regression. Med Oncol 2012; 29:3282–3290.

7 Budd GT, Cristofanilli M, Ellis MJ, Stopeck A, Borden E, Miller MC, Matera J, Repollet M, Doyle GV, Terstappen LW, Hayes DF: Circulating tumor cells versus imaging – predicting overall survival in metastatic breast cancer. Clin Cancer Res 2006;12:6403–6409.

8 Danna EA, Sinha P, Gilbert M, Clements VK, Pulaski BA, Ostrand-Rosenberg S: Surgical removal of primary tumor reverses tumor-induced immunosuppression despite the presence of metastatic disease. Cancer Res 2004;64:2205–2211.

9 Badwe R, Hawaldar R, Nair N, Kaushik R, Parmar V, Siddique S, Budrukkar A, Mittra I, Gupta S: Locoregional treatment versus no treatment of the primary tumour in metastatic breast cancer: an open-label randomised controlled trial. Lancet Oncol 2015;16:1380–1388.

10 Soran A, Ozmen V, Ozbas S, Karanlik H, Muslumanoglu M, Igci A, Canturk Z, Utkan Z, Ozaslan C, Evrensel T, Uras C, Aksaz E, Soyder A, Ugurlu UM, Col C, Cabioglu N, Bozkurt B, Sezgin E, Johnson R, Lembersky BC: A randomized controlled trial evaluating resection of the primary breast tumor in women presenting with de novo stage IV breast cancer: Turkish study (protocol MF07–01). J Clin Oncol 2016;34(suppl):abstr 1005.

11 Shien T, Doihara H: Resection of the primary tumor in stage IV breast cancer. World J Clin Oncol 2014;5:82–85.

12 Pathy NB, Verkooijen HM, Taib NA, Hartman M, Yip CH: Impact of breast surgery on survival in women presenting with metastatic breast cancer. Br J Surg 2011;98:1566–1572.

13 Norton L, Massague J: Is cancer a disease of self-seeding? Nat Med 2006;12:875–878.

14 Cristofanilli M, Budd GT, Ellis MJ, Stopeck A, Matera J, Miller MC, Reuben JM, Doyle GV, Allard WJ, Terstappen LW, Hayes DF: Circulating tumor cells, disease progression, and survival in metastatic breast cancer. N Engl J Med 2004;351:781–791.

15 Goldie JH, Coldman AJ: A mathematic model for relating the drug sensitivity of tumors to their spontaneous mutation rate. Cancer Treat Rep 1979;63:1727–1733.

16 Hartmann S, Reimer T, Gerber B, Stachs A: Primary metastatic breast cancer: the impact of locoregional therapy. Breast Care (Basel) 2014;9:23–28.

17 Harris E, Barry M, Kell MR: Meta-analysis to determine if surgical resection of the primary tumour in the setting of stage IV breast cancer impacts on survival. Ann Surg Oncol 2013;20:2828–2834.

18 Criscitiello C, Giuliano M, Curigliano G, De Laurentiis M, Arpino G, Carlomagno N, De Placido S, Golshan M, Santangelo M: Surgery of the primary tumor in de novo metastatic breast cancer: to do or not to do? Eur J Surg Oncol 2015;41:1288–1292.

19 Soran A OV, Ozbas S, Karanlik H, Muslumanoglu M, Igci A, Canturk Z, Utkan Z, Ozaslan C, Evrensel T, Uras C, Aksaz E, Soyder A, Ugurlu U, Col C, Cabioglu N, Bozkurt B, Dagoglu T, Uzunkoy A, Dulger U: Early follow up of a randomized trial evaluating resection of the primary breast tumor in women presenting with de novo stage IV breast cancer; Turkish study (protocol MF07–01). SABCS 2013;S2–03.