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ORIGINAL ARTICLE – BREAST ONCOLOGY

Primary Tumor Extirpation in Breast Cancer Patients Who Present with Stage IV Disease is Associated with Improved Survival

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Abstract. Purpose. Previous evaluation of our institutional experience with stage IV breast cancer patients with an intact primary tumor (IPT) did not reveal an overall survival (OS) benefit for surgery at 32.1 months median follow-up. We assessed the impact of surgery after 74.2 months median follow-up, and the effect of systemic therapy and local radiotherapy (RT).

Methods. We reviewed the records of all patients presenting from 1997 to 2002 with stage IV disease with an IPT. Cox proportional hazards modeling was used to assess differences in survival between treatment groups.

Results. Seventy-four (35.6 %) of 208 patients underwent resection of the IPT. After adjustment for covariates, surgery was associated with improved OS ($p = 0.04$). Multivariable analysis revealed that estrogen receptor (ER) positivity ($p = 0.002$) and having only a single focus of metastatic disease ($p = 0.05$) were also associated with improved OS. Surgery was highly associated with receipt of RT ($p = 0.0003$). RT was significantly associated with improved survival ($p = 0.015$) in an exploratory analysis.

Conclusions. Stage IV breast cancer patients with an IPT treated surgically had significantly improved OS. Radiation to the primary was also associated with improved survival, but this was evident only with adjustment for the effect of surgery. These findings may be limited by selection bias. Completion of ongoing prospective randomized trials is needed to conclusively determine whether stage IV patients with an IPT should be offered aggressive locoregional therapy.

Surgery for the primary tumor in stage IV breast cancer has traditionally been reserved for palliation of bleeding or ulceration, under the assumption that it offered no survival benefit. With advancements in systemic therapy, the survival of metastatic breast cancer patients has improved.[1] Level II and III evidence supports the hypothesis that metastatic breast cancer is potentially curable for selected patients with oligometastases treated with a multidisciplinary approach.[2–4] Our institutional experience demonstrated improved metastatic progression-free survival after median follow-up of 32.1 months. A trend towards improved survival at this short follow-up interval did not reach statistical significance.[5] Our median survival has now been reached (56 months for the longest surviving cohort) and our median follow-up (74 months) well exceeds our median survival, reflecting that this dataset is now mature.

In this update, we evaluated the overall (OS) and progression-free survival (PFS) in this population after a longer median follow-up interval (74.2 months) to determine if a survival benefit could be demonstrated from local surgical treatment. We also assessed whether a survival benefit could be demonstrated for local radiation therapy. Finally, we investigated the impact of margin status, site and number of metastases, and treatment with systemic therapy.

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PATIENTS AND METHODS

Patient Selection

We reviewed the records of all patients at our institution presenting from 1997 to 2002 with metastatic breast cancer and an intact primary tumor (IPT). Institutional review board approval was obtained prior to data collection. We utilized our previously reported 224-patient dataset but excluded 16 patients for duplicate records (2 patients), missing information (1), sarcoma histology (2), or delayed diagnosis of metastatic disease more than 3 months after surgery (1).[5] We also excluded 10 patients who underwent surgery at an interval of >36 months after presentation, to more clearly assess the impact of surgery on survival, rather than the effect of prolonged systemic therapy. Patients were included only if metastases were diagnosed within 3 months from their primary cancer diagnosis.

Data Collection

We recorded evidence of disease progression, survival status, and date of last follow-up. Specific details of multidisciplinary treatment were noted for all patients, including receipt of radiation therapy (RT), upfront (i.e., within 6 months of diagnosis) cytotoxic chemotherapy (UC), or induction therapy (IT)—defined as either chemotherapy or hormonal therapy prior to surgical treatment. The *AJCC Cancer Staging Manual*, *6th Edition* was used to describe tumor size and nodal involvement.[6]

Statistical Analyses

The associations between surgical treatment and patient characteristics were analyzed with the Chi squared test. OS and PFS were estimated by the Kaplan–Meier method. The log-rank test was used to compare survival differences between surgical and nonsurgical patients. Multivariate analysis was performed using the Cox proportional hazards model.

We also analyzed the effects of RT and IT by the Kaplan–Meier method, and by multivariable analysis with two Cox proportional hazards models fitted separately to include use of surgery and radiation, given their association. All tests were two-sided.

RESULTS

Of the 208 patients who presented with metastatic disease with an IPT, 74 (35.5 %) underwent surgery for the breast primary and 134 (64.4 %) did not. Forty-four patients (59.5 %) had proven metastatic disease prior to surgery, while 30 were found to be metastatic within 3 months after the date of surgery. Among patients who had surgery more than 6 months after the diagnosis of metastatic breast cancer, 21 (80 %) had surgery for treatment rather than palliative purposes.

Patient characteristics for the surgical and nonsurgical groups are presented in Table 1. Median age at presentation was 52.5 years (range 21–88 years). Median follow-up time from presentation was 74.2 months (62 months for surgical patients, 74.8 months for nonsurgical patients). The interval from presentation to surgery ranged from 0 to 35 months; 75 % of patients underwent surgery within 8.8 months of diagnosis. Multiorgan metastatic disease was more prevalent in the nonsurgical group (27.6 vs. 17.6 %); the groups were also imbalanced with respect to regional nodal disease, which was more common in the nonsurgical group (77.5 vs. 60 %, $p = 0.013$). Patients in the surgical cohort were more likely to receive chemotherapy (73 vs. 53 %, $p = 0.013$).

Within the surgical cohort, 33 underwent breast-conserving surgery (BCS) while 41 underwent total mastectomy. Thirty-two percent of surgical patients also received local RT (9 after BCS, 15 postmastectomy), versus 12 % of the nonsurgical patients ($p = 0.0003$). Use of RT did not correlate with type of surgery ($p = 0.39$). Seventy-eight percent of surgical patients received UC, versus 61 % of nonsurgical patients ($p = 0.01$); nonsurgical patients more frequently received hormonal therapy only (43 vs. 23 %). Forty-one percent of surgical patients received IT, whereas by definition nonsurgical patients did not receive IT.

One hundred thirty-five patients had died by the time of this report (134 of breast cancer, 1 of other causes). One hundred eighty-three patients experienced progression of disease; of these, 160 had metastatic progression.

Median survival for the entire cohort was 44.4 months (56.1 months for the surgical group, 37.2 months for the nonsurgical group). Figure 1 depicts Kaplan–Meier curves demonstrating superior outcomes in the surgical cohort for OS ($p = 0.002$, Fig. 1a) and PFS ($p < 0.0001$, Fig. 1b). Receipt of RT was also associated with a nonsignificant trend towards improved OS ($p = 0.097$, Fig. 2) and PFS ($p = 0.059$). Neither use of IT ($p = 0.28$) (Fig. 3) or UC ($p = 0.12$) nor use of anthracycline chemotherapy ($p = 0.35$) was associated with better OS.

Effect of Surgery

Table 2 displays the results of a multivariate analysis assessing the effect of surgery on OS. After adjustment for covariates, surgery was associated with improved OS compared with no surgery [$p = 0.04$, hazard ratio (HR) 0.58, 95 % confidence interval (CI) 0.35–0.98]. Estrogen

TABLE 1 Patient demographic information by surgery status

Variable	No surgery	Surgery	*p* value
Race			
Other	46 (34.3 %)	28 (37.8 %)	0.61
White	88 (65.7 %)	46 (62.2 %)	
Histology			
Infiltrating ductal	72 (58.5 %)	52 (72.2 %)	0.13
Infiltrating lobular	14 (11.4 %)	7 (9.7 %)	
Other	37 (30.1 %)	13 (18.1 %)	
T stage			
T0/Tis/TX/T1	20 (15.3 %)	5 (8.5 %)	0.06
T2	36 (27.5 %)	26 (44.1 %)	
T3	29 (22.1 %)	16 (27.1 %)	
T4a/T4b/T4c	40 (30.5 %)	9 (15.3 %)	
T4d	6 (4.6 %)	3 (5.1 %)	
N stage			
N0	29 (22.5 %)	24 (40 %)	0.013
N1–3	100 (77.5 %)	36 (60 %)	
Number of metastatic sites			
1	94 (70.1 %)	60 (81.1 %)	0.09
>1	40 (29.9 %)	14 (18.9 %)	
Metastatic sites			
Liver	18 (13.4 %)	26 (35.1 %)	0.003
Bone	63 (47 %)	26 (35.1 %)	
Lung	16 (11.9 %)	9 (12.2 %)	
Multiple	37 (27.6 %)	13 (17.6 %)	
ER status			
Positive	87 (68 %)	38 (59.4 %)	0.24
Negative	41 (32 %)	26 (40.6 %)	
PR status			
Positive	66 (52 %)	28 (43.8 %)	0.28
Negative	61 (48 %)	36 (56.3 %)	
HER2 status			
Positive	28 (25.5 %)	20 (35.7 %)	0.17
Negative	82 (74.5 %)	36 (64.3 %)	
Systemic therapy			
Chemotherapy only	71 (53 %)	54 (73 %)	0.013
Hormonal therapy only	58 (43.3 %)	17 (23 %)	
Both	1 (0.7 %)	1 (1.4 %)	
None	4 (3 %)	2 (2.7 %)	
Trastuzumab			
No	108 (80.6 %)	57 (77 %)	0.54
Received	26 (19.4 %)	17 (23 %)	
Radiation			
No	118 (88.1 %)	50 (67.6 %)	0.0003
Received	16 (11.9 %)	24 (32.4 %)	

ER estrogen receptor, *PR* progesterone receptor, *HER2* human epidermal growth factor receptor 2

receptor positive status was also associated with improved OS ($p = 0.002$, HR 0.40, 95 % CI 0.22–0.72). Positive nodes ($p = 0.04$, HR 0.55, 95 % CI 0.31–0.97) also correlated with improved OS.

Effect of Radiotherapy

Kaplan–Meier analysis showed a nonsignificant survival advantage for use of RT, potentially confounded by the fact that surgical treatment was highly associated with RT ($p = 0.0003$). Therefore, RT was fitted in a separate multivariate model controlling for collinearity with surgery (Table 3). The results revealed that use of RT was significantly associated with improved survival ($p = 0.015$, HR 0.47, 95 % CI 0.25–0.87). On subset analysis of the 74 surgical patients, use of RT ($n = 24$) was associated with improved OS on univariate analysis ($p = 0.02$) but not on multivariate analysis ($p = 0.10$, 95 % CI 0.19–1.18).

Effects of Axillary Surgery or Radiation

We performed a subset analysis of the 74 patients treated surgically to determine if there was an incremental benefit for axillary treatment as part of surgery to the IPT. On univariate analysis, we noted a trend towards improved survival among the 39 patients who had an axillary procedure (sentinel node or complete axillary dissection) compared with the 35 patients who had no axillary procedure ($p = 0.06$). Of the 35 surgical patients who had no axillary surgery, five received axillary radiation; a trend towards improved OS was noted in comparison with the 30 patients who underwent resection of their breast tumor without axillary surgery or radiation ($p = 0.08$), but the number of patients in the axillary radiation group was small.

Effect of Resection Margin Status

Positive margin status was more prevalent in patients who underwent BCS rather than mastectomy ($p < 0.0001$). Patients undergoing surgery with negative margins ($n = 52$) demonstrated a PFS advantage compared with patients undergoing surgery with a positive margin ($n = 22$, $p = 0.03$), but not better OS ($p = 0.43$). However, when compared with all other patients (including the 22 patients with surgery with positive margins, the nonsurgical patients with non-clinically measurable tumor, and the nonsurgical patients with measurable tumor), patients treated with surgery with negative margins had a statistically significant advantage in both PFS ($p < 0.0001$) and OS ($p = 0.0002$).

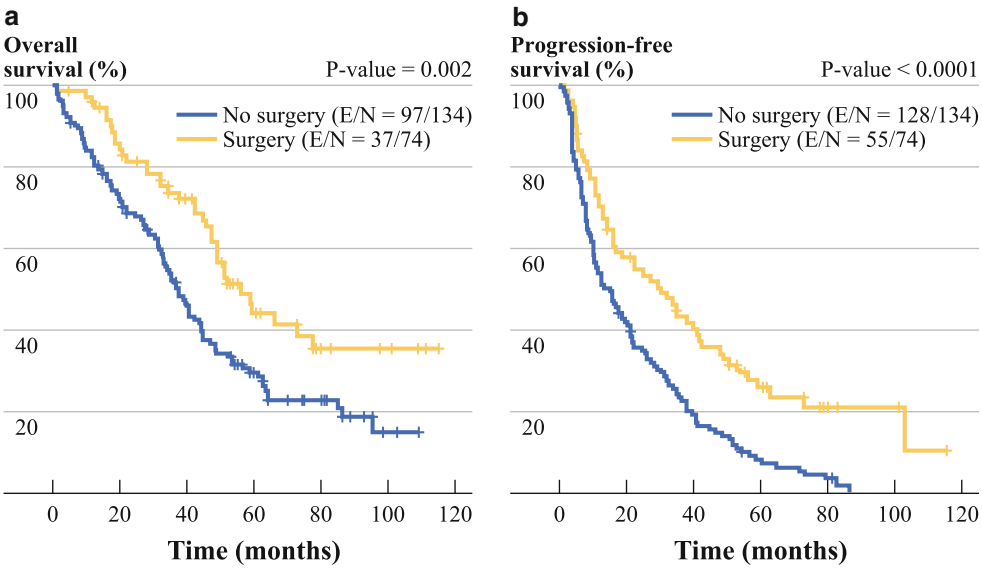

FIG. 1 **a** Overall and **b** progression-free survival, surgery versus no surgery; *E/N* events/number of patients per analysis

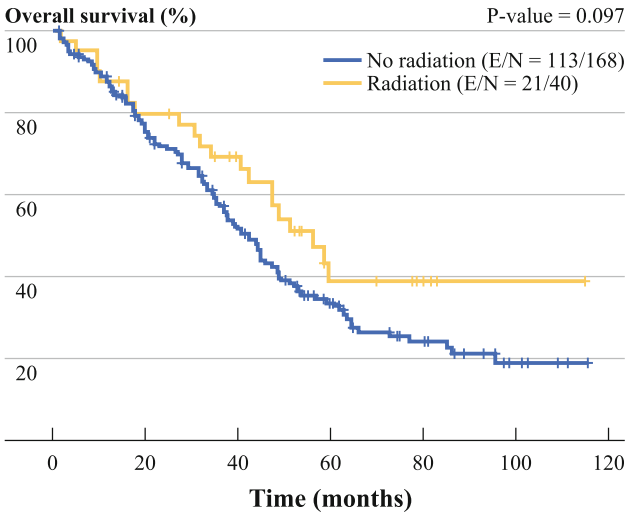

FIG. 2 Overall survival, radiation therapy versus no radiation therapy. *E/N* events/number of patients per analysis

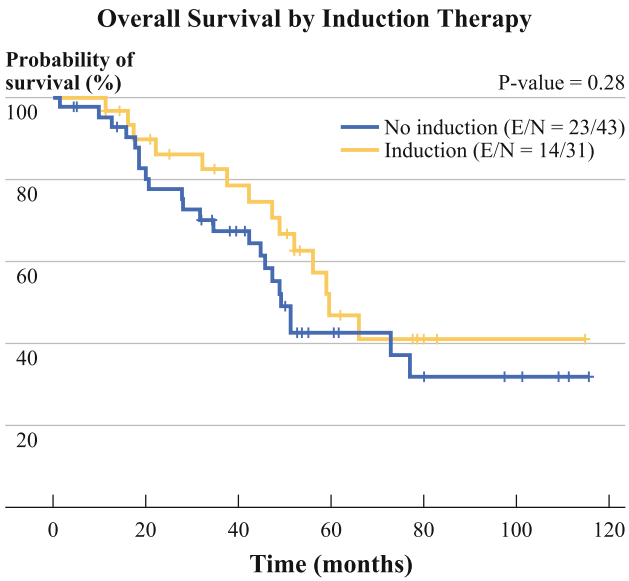

FIG. 3 Overall survival by use of induction therapy prior to surgery (surgery group). *E/N* events/number of patients per analysis

Use of RT did not correlate with positive margin status ($p = 0.76$).

DISCUSSION

This retrospective single-institutional experience, now with 74.2 months of median follow-up, demonstrates superior PFS and OS for patients with metastatic breast cancer who underwent surgical resection of the primary tumor. Superior OS was demonstrated on both univariate and multivariate analysis. This study differs from our previous report, which at 32.1 months follow-up demonstrated improved metastatic PFS but only a trend towards improved OS.[5]

Our study suggests a potential survival benefit for radiotherapy to the primary, based on an exploratory analysis using a multivariable model controlling for the effect of surgery. Our finding is concordant with the results of a retrospective single-institution analysis of locoregional radiotherapy (without surgery) in metastatic disease.[7] However, in our dataset most patients treated with RT also received surgery, and we were able to demonstrate a survival benefit only after adjusting for collinearity with surgery, a fact that limits the strength of this analysis.

Postoperative RT was selectively administered in a fashion that did not correspond to nonmetastatic standard practice (i.e., postlumpectomy RT for all patients,

TABLE 2 Multivariate Cox proportional hazards model of effect of surgery on overall survival ($n = 139$)

Variable	Reference group	*p* value	Hazard ratio	95 % hazard ratio confidence limits
Age	Continuous	0.52	1.01	0.99–1.02
Race	White	0.71	0.91	0.56–1.49
Prior cancer	No	0.05	0.51	0.26–1.0
T stage	T1 or T2	0.19	0.72	0.44–1.17
N stage	Node positive	0.04	0.55	0.31–0.97
Number of metastases	Single	0.06	0.62	0.38–1.01
ER	Positive	0.002	0.40	0.22–0.72
PR	Positive	0.72	0.91	0.54–1.54
HER2	Positive	0.38	0.80	0.48–1.32
Surgery	Yes	0.04	0.58	0.35–0.98

ER estrogen receptor, *PR* progesterone receptor, *HER2* human epidermal growth factor receptor 2

TABLE 3 Multivariate Cox proportional hazards model of effect of radiation therapy on overall survival ($n = 139$)

	Reference group	*p* value	Hazard ratio	95 % hazard ratio confidence limits
Age	Continuous	0.24	1.01	0.99–1.03
Race	White	0.30	0.76	0.46–1.27
Prior cancer	No	0.06	0.52	0.26–1.02
T stage	T1 or T2	0.15	0.69	0.43–1.14
N stage	Node positive	0.10	0.64	0.37–1.10
Number of metastases	Single	0.05	0.61	0.37–0.99
ER	Positive	0.008	0.45	0.25–0.81
PR	Positive	0.47	0.82	0.48–1.41
HER2	Positive	0.58	0.86	0.50–1.47
Radiation	Yes	0.015	0.47	0.25–0.87

ER estrogen receptor, *PR* progesterone receptor, *HER2* human epidermal growth factor receptor 2

postmastectomy RT for patients with clearly specified high risk factors), suggesting a selection bias in clinical decision-making for use of RT. On univariate analysis of the surgical cohort, we demonstrated an association with longer survival among patients receiving RT that was not borne out on multivariate analysis. These results are hypothesis-generating only and should be validated prospectively.

In our patient cohort, receipt of upfront chemotherapy or induction systemic therapy (either hormonal therapy or chemotherapy) was not associated with improved OS. This could reflect the wide variety of reasons for which UC or IT may be administered in patients with metastatic disease, for example, either excellent performance status or, in sharp contrast, highly symptomatic or rapidly progressive disease. Furthermore, virtually all patients in our dataset received some form of systemic therapy, and a majority (61 %) received chemotherapy. In contrast, radiotherapy and surgery were only used in a subset of our patient cohort, allowing a control group, albeit biased by selection, by which the effects of surgery and RT could be assessed. Finally, our finding that UC/IT did not yield a survival benefit in metastatic patients is in keeping with outcomes among patients with primary breast cancer, where preoperative and postoperative chemotherapy have produced comparable OS in randomized trials. Our findings that upfront chemotherapy and induction systemic therapy did not yield a survival benefit should be tempered by these facts.

Certain differences between our surgical and nonsurgical cohorts may reflect evidence of selection bias, including fewer T4 tumors and more patients with solitary metastases in the surgical cohort. Chemotherapy was used in a greater proportion of the surgical patients, reflecting an aggressive multidisciplinary approach. Interestingly, patients with bone-only metastasis were not more likely to receive surgery than patients with liver metastases, possibly reflecting an institutional bias towards hepatic resections in the setting of metastatic breast cancer. This also may reflect inherent difficulties in assessing the number and progress of bone metastases during treatment. In our series, stage IV patients with nodal metastasis had improved OS; this counterintuitive finding may represent a lower burden of distant metastasis in the setting of tumor biology with a predilection for regional spread.

Our findings are consistent with other published series of metastatic patients undergoing surgical resection of the IPT.[8,9] Other single-institution retrospective analyses have been less conclusive.[10–13] Notably, a systematic review of

10 retrospective studies evaluating the impact of breast surgery on survival in metastatic disease showed surgery was associated with improved OS on pooled multivariate analysis.[14]

Large database studies have generally supported the hypothesis that surgery to the IPT can improve survival in stage IV disease. An analysis from the National Cancer Data Base showed that surgery was associated with improved OS.[15] An analysis of the Surveillance, Epidemiology, and End Results (SEER) database also showed that surgical excision of the IPT was associated with significantly improved survival on multivariate analysis.[16] The apparent benefit of local surgery in metastatic patients may reflect a selection bias toward escalated local therapy in patients with good performance status and good response to upfront chemotherapy. Cady et al. performed a retrospective matched-pair analysis, concluding that selection bias—including a bias toward performing surgery in patients with excellent response to upfront systemic therapy—may explain most, if not all, of the apparent survival advantage of surgery in metastatic patients.[17]

The classical view of the biology of metastasis contends that tumors progressively acquire a series of mutations, enabling certain tumorigenic clones to metastasize and establish disease in specific organs.[18] This viewpoint has been challenged by accumulating evidence that the gene expression profile of the primary tumor is an inherent feature that predicts metastasis and is not related to clonal selection.[19–22] Norton and Massagué proposed that cells shed from the primary tumor and metastatic sites may travel back to the site of the primary tumor, effectively reseeding the primary tumor.[23] Therefore, both a rational scientific basis and growing clinical evidence support rigorous evaluation of the role of resection of the primary tumor in patients with stage IV disease.

The Translational Breast Cancer Research Consortium has recently initiated a multi-institutional prospective analysis of surgery for patients presenting with metastatic breast cancer. However, this study is not randomized, and decisions on surgery and RT are at the discretion of the physician and patient.

A phase III randomized controlled trial assessing the impact of locoregional treatment of the primary tumor on OS is currently open in Turkey.[24] It is unclear if this study will have statistical power to reach its primary objective, given its accrual target of 271 patients.[24]

Badwe and Parmar have presented two updates of a prospective randomized controlled trial ongoing in India, with discordant results at 6 months (PFS benefit for surgery) versus 18 months (no OS benefit for surgery).[25,26] As demonstrated by our institutional experience, sufficient follow-up time is necessary to detect a potential association with survival in patients receiving surgical resection. Badwe and Parmar's findings are also complicated by the fact that nearly half of the patients included in the analysis were treated off protocol because they did not meet eligibility criteria.[25,26] Well-designed trials are necessary to define optimal local treatment for patients with stage IV breast cancer.

The Eastern Cooperative Oncology Group initiated a randomized trial for patients presenting with metastatic disease and an IPT. The trial's primary objective is to determine whether early local therapy improves OS; secondary endpoints include control of chest wall disease and quality of life.

In conclusion, this study provides additional evidence that resection of the primary tumor may be beneficial for selected stage IV breast cancer patients, and suggests consideration of surgical resection for selected stage IV patients. The results may be influenced by selection bias, and only by completion of prospective randomized trials will these important questions be answered.

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