Review

Primary Breast Cancer with Synchronous Metastatic Disease – Indications for Local Radiotherapy to the Breast and Chest Wall

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Abstract. *Aim: To review literature on local therapy in patients with primary metastatic breast cancer with focus on local radiotherapy (RT). Patients and Methods: A Medline search using the key words "metastatic breast cancer", "primary resection/radiotherapy", "local therapy", "local radiotherapy" was carried out. All original studies in the English language were included in the present review. Results: A total of 27 original studies including more than 33,000 patients with metastatic breast cancer were identified, including two large database analyses (n=25,757). All studies were retrospective in nature. Most studies showed a survival benefit with the addition of local therapy in a metastatic situation. The majority of studies focused on the role of surgery. Fourteen studies (52%) mentioned radiotherapy (RT) in 0.3% to 100% of patients. Six of these studies analyzed the effect of RT separately and five found an additional benefit of RT. Two studies showed best outcomes when RT and surgery were combined. Conclusion: Most retrospective studies showed a survival benefit for local therapy in patients with breast cancer with distant metastases. The role of RT remains unclear. Some reports showed improved outcome with the combination of surgery and RT. This approach should be considered in patients with good survival prognosis in whom local control is important. There are several prognostic factors to aid decision-making. Results of prospective randomized studies are pending.*

Patients with breast cancer diagnosed with distant metastases are usually treated with systemic therapy (1). Local treatment such as surgery or radiotherapy (RT) is generally limited to the control of symptoms, including pain, ulceration and bleeding. However, several retrospective studies have been published over recent years demonstrating a survival benefit when local therapy was added despite the presence of metastatic disease. Most studies focused on surgery. Since RT is known to reduce the risk of local recurrence in breast cancer without distant metastases, it may be questioned whether patients will also benefit in a metastatic situation. The present study focused on the role of local RT. Additionally, prognostic factors were summarized to facilitate decision-making for or against RT of the breast or chest wall in patients with metastatic breast cancer.

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Materials and Methods

A literature review was carried out searching Medline using the following terms: "metastatic breast cancer", "primary resection/ radiotherapy", "local therapy", "local radiotherapy". All original articles providing new data on local therapy of patients with *de novo* metastatic breast cancer were included in the review.

Results

Retrospective studies. Twenty-five retrospective studies with a median of 304 patients (range=75-728) dealing with local therapy to the breast/chest wall in metastatic breast cancer were found (Table I). Additionally, two database analyses were included (25,757 patients) (2, 3). In 22/27 studies, a survival benefit was described (81%), whereas no difference from adding local therapy was shown in 3/27 studies (11%) (Table I). Two studies reported on progression-free survival (PFS) and showed a benefit for local therapy (4, 10). However, most analyses focused on surgery. Only 52% provided information on RT added to surgery or RT alone. In these studies, RT was administered in 0.3-100%. Some study groups did not differentiate between local RT and RT to metastatatic sites. Rhu *et al*. (5) and Ruitenkamp *et al*.

(6) showed a benefit for surgery but not for local RT, while four other study groups found RT to be of benefit (7-10). Two studies showed improved results for the combination of surgery and RT (8, 9). The most frequent prognostic factors associated with improved survival were single sites of metastasis, bone metastases, young age (*e.g.* <51 years or <65 years), negative resection margins and human epidermal growth factor receptor 2 (HER2) positivity (Table I). Triple-negative tumors were negatively associated with survival.

Prospective studies. There are six ongoing or closed randomized trials with preliminary results on patients with synchronous metastatic breast cancer. However, no final results have been published yet: (i) Indian trial (n=350): Preliminary results: After complete or partial response to chemotherapy, patients were randomized to arm A: locoregional treatment (breast-conserving surgery or mastectomy, axilla dissection and RT) or arm B: no locoregional treatment; no statistical significant difference in overall survival at 5 years (20.5% *vs*. 19.2%), improved local progression-free survival in the surgical arm (80% *vs*. 20% at 5 years), distant disease-free survival was shorter in the surgical group (11). (ii) Turkish trial (MF07-01, n=278): Preliminary results: Arm A: locoregional treatment (breast-conserving therapy with RT or mastectomy without RT) followed by systemic therapy *vs*. arm B: systemic therapy without local treatment; overall survival improved in arm A in sub-groups of hormone receptor-positive disease, <50 years and patients with solitary bone metastases. Survival was worse for those with triple-negative disease (12, 13). (iii) Japanese trial (JCOG1017): No, results yet: after 3 months of systemic therapy, patients who had no progression were randomized to arm A: tumor resection with systemic therapy (no RT) *vs*. arm B: systemic therapy alone (14). (iv) Dutch trial (SUBMIT): No results yet: Arm A: Surgery (RT optional if margins are positive) plus systemic therapy *vs*. arm B: systemic therapy only. RT option in systemic only arm in cases of progression; hypofractionated regimes mandatory in both arms (15). (v) ECOG group: No results yet: after induction chemotherapy, patients without progression were randomized to arm A: surgery and RT *vs*. arm B: systemic therapy (NCT01242800). (vi) Austrian trial: No results yet: arm A: mastectomy or lumpectomy with/without RT *vs*. arm B: no local treatment (NCT01015625).

Discussion

Several retrospective trials including two large database analyses have shown a survival benefit for local therapy in metastatic breast cancer (Table I). Only few studies with a small number of patients showed diverging results without benefit of local therapy (16-18). The main limitation of all studies was their retrospective design with the risk of potential selection biases. Patients with better prognostic features are more likely to receive surgery. In the near future, fully published results of several randomized trials are awaited. Until that time, individual based decision making is mandatory considering the results of retrospective studies and preliminary results of prospective studies.

Prognostic factors. Additional local therapy may cause additional side-effects in a potentially palliative setting. Against this background, patients have to be carefully selected for additional local therapy.

Several prognostic factors were identified in the above-mentioned retrospective studies (Table I). The most common prognostic factors positively associated with superior outcomes included younger age, small tumor burden and limited number of metastatic sites. These findings were confirmed in a sub-group analysis of preliminary results of the Turkish MF07-01 trial, where improved survival was seen in sub-groups of patients with hormone receptor-positive disease, younger patients and patients with single bone metastasis, while patients with triple-negative disease had worse outcomes (12). In addition, there are survival-predicting models published in the literature also highlighting the importance of receptor status, number and type of metastatic sites, and performance status in patients with metastatic breast cancer. For instance, one could use the simple prognostic score presented by Regierer *et al*. to identify patients who might benefit from local therapy (19). The authors classified patients with metastatic breast cancer into high-, intermediate- and low-risk groups according to the prognostic parameters: metastasis-free survival, hormone receptor status and localization of metastatic sites.

Locoregional treatment. The majority of available retrospective studies showed a benefit for locoregional treatment in metastatic breast cancer (Table I). For instance, two database studies with large cohorts of patients showed improved survival [36 *vs*. 21 months, $p<0.001$ (3), with a hazard ratio (HR) of 0.61 for those with negative margins (2)]. In contrast, there exist three retrospective studies showing controversial results: Leung *et al*. only found a survival benefit for additional chemotherapy (18) but their sample size was low, with only 52 patients in the surgical group. In the studies of Dominici *et al*. (16) and Shibasaki *et al*. (17), also showing no benefit for locoregional therapy, the group of patients with locoregional treatment only included 54 and 36 patients, respectively (16, 17).

Preliminary results of two randomized prospective studies did not suggest a clear overall survival benefit for locoregional treatment in metastatic breast cancer either. In the Indian study comparing locoregional *vs*. no locoregional treatment, median overall survival was similar in both arms

(18.8 *vs.* 20.5 months, HR=1.07 after 17 months, p=0.60) (11). Additionally, in the Turkish study, no benefit with respect to overall survival was seen between patients who received locoregional treatment and those who did not (35% *vs.* 31% overall survival after 54 months, p=0.24) (13). On the other hand, a clear benefit in progression-free survival was detected in the locoregional treatment arm in the Indian study (locoregional progression at two years: 52% in those without locoregional treatment *vs.* 11% in those with, p<0.001) (11). In the Turkish trial, overall survival was significantly improved in the sub-group of patients with hormone receptor positivity, younger age (<50 years) and solitary bone metastases (p=0.03) (13). Taking preliminary results of prospective studies and the great majority of retrospective studies into account, at least a sub-group of patients with metastatic breast cancer appeared to benefit from locoregional treatment.

Local radiotherapy. As most studies focused on the role of local surgery in metastatic breast cancer, the role of additional RT or RT alone remains unclear. The study groups of Rhu *et al.* (5) and Ruiterkamp *et al.* (6) analyzed locoregional RT separately, showing no statistically significant additional benefit compared to surgery alone. However, only a minority of patients received RT in those series. In contrast, in the study of Gnerlich *et al.*, local RT was associated with a decreased risk of death (3). Moreover, LeScodan *et al.* showed local RT alone to be an alternative option with a survival benefit when compared to no local treatment (8). Among 581 patients with metastatic breast cancer, 249 patients received locoregional RT alone, 41 patients adjuvant RT after surgery and 30 patients surgery alone (considered group A with locoregional treatment); no locoregional treatment was administered to 261 patients (group B). After a median follow-up of 39 months, the 3-year overall survival rates were 43.4% and 26.7% in group A and B, respectively (p=0.00002). Bourgier *et al.* retrospectively categorized patients with metastatic breast cancer in their institution into two groups: those with locoregional RT alone (group A, n=147) and those treated with surgery followed by RT (group B, n=92). The overall survival rates after 3 years were 39% in group A and 57% in group B. However, no significant differences were observed between the two groups when adjusted for prognostic factors. The authors concluded that RT alone provides long-standing local control and yields overall survival rates equivalent to those obtained when RT is combined with surgery (10).

However, two studies showed superior results when surgery was combined with RT (9, 12). In the study of Akay *et al.*, surgery plus RT was associated with better survival compared to treatment with surgery or RT alone (50% *vs.* 25% *vs.* 14%, respectively; p≤0.0001). LeScodan *et al.* described a trend towards better outcome of combined therapy (p=0.07). Consequently, if there is an indication for surgery in the metastatic setting, one should always consider additional RT as being benefical in the non-metastatic setting (20).

In those studies investigating the impact of axillary surgery, no benefit was found (2, 6). In cases of extensive lymph node involvement, there is also the option of delivering RT to the axilla, which has shown equivalent results with less toxicity in patients without distant metastases (21).

No information on RT techniques was provided in any of the above mentioned studies. To spare precious remaining lifetime, hypofractionated regimes are preferable if possible. In this setting, hypofractionated regimes are mandatory in the Dutch prospective SUBMIT trial (15). In the above mentioned randomized trials, RT was planned in the locoregional treatment arm for all patients (11), after breast-conserving therapy only (12), if margins were positive (15), or was optional (Austrian trial, ECOG trial) or not administered at all (14). No prospective trial has yet analyzed surgery *vs.* surgery with RT or RT alone.

Timing of locoregional therapy. Not all retrospective studies provided data regarding the timing of locoregional therapy. Surgery with/without RT can either be performed prior to or following systemic therapy. This is also reflected by the design of the above mentioned prospective trials. In the Indian trial, only patients with complete or partial response to initial systemic therapy were randomized, The Japanese group and the ECOG group excluded patients with progressive disease after induction chemotherapy. The Turkish group and Dutch group started randomization prior to systemic therapy. According to Khan *et al.*, upfront systemic therapy appears reasonable, since response to systemic treatment will have a major impact on subsequent procedures. In cases of progression of metastatic sites after systemic treatment, locoregional therapy would not make sense (22). On the other hand, local treatment could provide a benefit to patients in cases of a response of metastatic sites and persisting local disease after induction chemotherapy (22, 23).

In the absence of fully published results of randomized trials one should not rule-out local therapy for patients with metastatic breast cancer in general. Prognostic tools enable treating physicians to identify patients who would likely benefit from additional local therapy. In particular younger patients, with receptor-positive disease with low tumor burden and only one metastatic site should be considered for addition of local treatment. As bi-modal treatment (surgery with RT) has shown superior results to surgery alone, one should always consider delivering postoperative RT analogous to indications for adjuvant RT for non-metastatic breast cancer.

Table I. *Original articles focusing on local therapy in patients with metastatic breast cancer.*

Study, year (Ref)	No. of patients (entire group)	Local surgery (%)	RT in local treatment group (%)	Benefit of local therapy	Prognostic parameters
Khan *et al.* 2002* (2)	16,023	57.2%	n.r. in the database	Improved OS when free margins, HR=0.61	Number of metatases, type of metastatic burden, extent of resection
Babiera *et al.* 2006 (24)	224	37%	n.r.	Improved OS, p=0.12 improved PFS, p=0.0007	Only one metastatic site, lack of *HER2* amplification
Rapiti *et al.* 2006 (25)	300	42%	89% Including RT to metastatic sites), 27% local RT after BCT	Improved OS=40% reduced risk of death (HR=0.6)	Bone metastases only, negative margins
Gnerlich *et al.* 2007* (3)	9,734	47%	Local RT not reported separately	Improved OS, 36 *vs.* 21 months, $p\leq0.001$	-
Fields *et al.* 2007 (26)	409	45.7%	n.r.	RT decreased risk of death improved OS, 31.9 *vs.* 15.4 months, $p\leq0.0001$	Bone metastases only
Rao *et al.* 2008 (4)	75	100%	n.r.	PFS improved for negative margins (HR=2.3), single metastatic site (HR=2.6), Caucasian race (HR=2.7)	Single metastatic side, negative margins, Caucasion race
Blanchard *et al.* 2008 (27)	395	61.3%	0.3%	Improved OS, 27.1 *vs.* 16.8 months ($p\leq0.0001$)	In multivariate analysis, no prognostic factor besides surgery
Cady *et al.* 2008 (28)	622	37.6%	n.r.	Improved OS, $p\leq0.0001$, case matching reduced survival advantage	
Hazard *et al.* 2008 (29)	111	42%	67% Postoperatively, 29% RT only	Improved OS, HR=0.783	None
LeScodan *et al.* 2009 (8)	581	12%	78% RT only, post-operatively: 13%, mean dose: 48.7Gy+Boost	Improved OS at 3 years (43.4% *vs.* 26.7%), $p\leq0.0002$; trend for improved OS with RT+ surgery	Visceral metastases
Shien *et al.* 2009 (30)	344	47%	Not used postoperatively, some patients without local surgery underwent local RT (not analyzed)	Improved OS (27 *vs.* 22 months, p=0.049)	Young age (<51 years), bone and soft tissue metatases
Ruiterkamp *et al.* 2009 (6)	728	40%	34% Postoperatively, 10% RT only	Improved OS (31 *vs.* 14 months, $p\leq0.0001$)	None
McGuire *et al.* 2009 (31)	566	27%	59% After mastectomy, 61% after lumpectomy	Improved OS (37% *vs.* 20%, p=0.04)	Mastectomy
Bafford *et al.* 2009 (32)	147	41%		OS improved, 4.13 *vs.* 2.36 years, p=0.003	HER2 positivity
Leung *et al.* 2010 (18)	157	33	37%	No improved OS	Chemotherapy
Bourgier *et al.* 2010 (10)	308	30%	48% RT only, 30% surgery and RT	Long LC and PFS after local RT alone and surgery+RT	ER status, number of metastatic sites
Neumann *et al.* 2010 (33)	186	37%	n.r.	Improved OS, HR=0.71 (not in triple negative patients)	Hormone receptor-positive, HER2 amplified
Dominici *et al.* 2011 (16)	551	9.8%	Local RT not reported separately	No improved OS	-
Shibasaki *et al.* 2011 (17)	92	39.1%	22% Postoperatively, 13% RT only	No improved OS (25 *vs.* 24.8 months p=0.352), improved QOL in selected patients	Triple negative, more than three sites=negative prognostic parameters
Perez-Fidalgo *et al.* 2011 (34)	208	59%	Not analyzed seperately	Improved OS (40.4 *vs.* 24.3 months, $p\leq0.001$)	Visceral metastases, no bone metastases, ER-positive
Rashaan *et al.* 2011 (35)	171	34.5%	n.r.	Improved OS for young patients, HR=0.5	Younger age, no comorbidities in multivariate analysis
Pathy *et al.* 2011 (36)	375	37.1%	33.9% Including to metastatic sites (local RT not reported separately)	Improved OS, 28% lower risk for death	Few metastatic sites, age <65 years

Table I. *Continued*

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Study, year (Ref)	No. of patients (entire group)	Local surgery (%)	RT in local treatment group (%)	Benefit of local therapy	Prognostic parameters
Botteri *et al*. 2013 (37)	187**	70%	33.3% Postoperatively, no RT only	Improved OS, HR=0.64	Single metastatic sites
Lang *et al*. 2013 (7)	208	35.6%	32.4% Postoperatively, 11.9% RT only	Improved OS, p=0.04	ER positivity, single metastatic focus
Akay *et al*. 2014 (9)	172	46%	40% Postoperatively, 10% RT only	Improved OS, best outcome for surgery plus RT $p \leq 0.0001$	Combination RT/surgery, response to chemotherapy
Bertraut 2015 (38)	232			Improved OS, HR=0.43	Luminal tumors, HER2 positive
Rhu 2015 (5)	262	15.3%	20% To breast tumor, 52.7% including metastatic sites also	Improved OS for surgery, HR=0.51, not for RT	Single-organ metastases, especially bone metastases

HER2: Human epidermal growth factor receptor 2, HR: hazard ratio, LC: local control; n.r.: not reported, OS: overall survival, PFS: progression-free survival, QOL: quality of life, RT: radiotherapy. *Database analysis, **bone metastases only.

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