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ORIGINAL ARTICLE – BREAST ONCOLOGY

Radiological Staging for Distant Metastases in Breast Cancer Patients with Confirmed Local and/or Locoregional Recurrence: How Useful are Current Guideline Recommendations?

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ABSTRACT

Background. Breast cancer patients with local and/or locoregional recurrence (LR) are at higher risk of developing distant metastases (DM) at a later time. Once LR has been confirmed, some international interdisciplinary guidelines recommend performing radiological examinations for DM to determine the course of further therapy (curative or palliative approach). This study analyzed the metastatic patterns of patients with LR with particular regard to the frequency of concurrent diagnosis of LR and DM; in other words: are radiological staging procedures actually justified for DM at the time of diagnosis of LR?

Methods. This study included all patients (n = 1368) who were diagnosed and treated for nonmetastatic breast cancer (Stage I–III) at the University Women's Hospital Basel, Switzerland between 1990 and 2009.

Results. In 137 patients, LR was diagnosed without a history of DM: in-breast/thoracic wall only, n = 90 (65.7%); involvement of axillary/supra-/infraclavicular lymph nodes, n = 47 (34.3%). DM was found at the time of diagnosis of LR in 44 patients (32.1%). Concurrent diagnosis of LR and DM occurred significantly more often in patients with lymph node recurrence compared with those with in-breast/chest wall recurrence (48.9% vs. 23.3%; p = 0.004).

Conclusions. Approximately one-third of patients with a LR had synchronous DM at the time of their local/locoregional event. For this reason, routine systemic staging imaging at the time of LR should be an absolute requirement for planning further therapy. Confirmation of DM may spare the patients radical surgical interventions with questionable impact on survival in the face of an incurable disease.

Depending on tumor type and characteristics, surgical margin, lymph node status, type of surgery, and adjuvant therapy, up to 6% of node-negative and up to 15% of limited volume node-positive breast cancer (BC) patients develop local and/or locoregional recurrence (LR).[1–4] These patients have a higher risk of developing distant metastases (DM) at a later point in time.[5,6] Obviously, diagnosis and therapy of LR stands as a grey area between the clearly distinguished management of early BC and distant metastatic disease. Even otherwise very detailed interdisciplinary guidelines omit this issue or only partially distinguish between LR and distant metastatic disease ("Stage IV metastatic or recurrent breast cancer").[7–10] Thus, it is not surprising that there are only a few recommendations with regard to staging evaluation of BC patients who present with LR.[7,11] These recommendations, however, are not substantiated by evidence-based data and do not report a level of evidence. The authors of the German "Interdisciplinary S3 Guidelines for the Diagnosis, Treatment and Follow-up Care of Breast Cancer" justify performing these studies to determine whether a curative or a palliative only approach is appropriate before starting the therapy.[11] However, it

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should be mentioned here in qualification that this justification not only applies to the situation after a diagnosis of LR but also for the adjuvant situation after the first diagnosis of primary disease. For this latter situation, however, recommendations exist for staging examinations that are based on a probabilistic assessment of the occurrence of DM, which considers factors, such as positive axillary nodes, large tumors, aggressive biology or clinical signs, symptoms, or laboratory values suggesting the presence of metastases.[7–11]

In retrospective series, between 15 and 37% of patients with LR had synchronous DM at the time of presentation.[3,4,12–18] Most of these studies, however, analyzed selected cohorts in respect of the type of previous surgery (mastectomy only,[4,17] breast-conserving therapy only[12,13,15]), or defined adjuvant study protocols,[3] and reported this data only as supplemental information with no aim of assessing the usefulness of radiological staging examinations. Two further studies reported DM of 16% and 32% at time of LR presentation.[14,16] The purpose of these studies, however, was to assess the capacity of radiological procedures, namely positron emission tomography (PET) and computed tomography of the chest, abdomen, and pelvis (CTCAP).[14,16]

Most recently, Neumann et al. presented data on 445 patients with a LR in which 27% had synchronous DM identified within 30 days after the diagnosis of LR. This analysis, however, was restricted on BC patients with advanced stages at initial diagnosis.[18]

The present study analyzed the metastatic patterns of patients with LR in an unselected (i.e., including different kinds of previous surgery and all nonmetastatic stages at diagnosis), large cohort and focused particularly on the frequency of concurrent diagnosis of LR and DM. In other words, are radiological staging procedures actually justified for DM at the time of diagnosis of LR?

PATIENTS AND METHODS

Data from the prospective, relational Basel Breast Cancer Database (BBCD), which includes all newly diagnosed primary invasive BC cases treated at the University Women's Hospital Basel, Switzerland since 1990, provided the basis for this study. Structure and content of the database has been described previously.[19]

For this study, data from all female patients who were initially diagnosed with nonmetastatic BC (Stage I-III) up to and including 2009 was analyzed (n = 1368). In 2011, with the exception of 2.5% of the entire cohort (n = 37) who were lost to follow-up, outcome information was available for all patients recorded in the BBCD.

Follow-up: Every visit included history taking, eliciting of symptoms and physical examination. Ipsilateral (after breast-conserving surgery) and contralateral clinical mammography and sonography was recommended yearly.

As of March 2011, 325 patients (23.8% of all patients who had stage I–III disease at initial BC diagnosis) had developed recurrent BC. Recurrence was classified as local (in-breast in case of primary breast-conserving surgery, operation scar, or chest wall), regional (in the axillary, infra- and/or supraclavicular lymph nodes), or distant. Local recurrences appeared at clinical and/or radiological examination. The staging procedure for DM included the following: clinical examination, serum CA 15-3 levels, chest x-ray/liver sonography/bone scan, CT chest and abdomen/bone scan, or PET/CT.

From the above-mentioned 325 patients, 280 patients (20.5% of the entire cohort) had secondary distant metastatic disease, and in 145 cases (10.6%), the patients were diagnosed with locoregional recurrence (Table 1). The cohort was followed until death or January 2014 (median follow-up time: 77 months, range 5–286 months; for patients with LR only: 152 months, range 29–286 months).

The study design and data collection methods were approved by the institutional review board.

Statistical Analysis

Comparisons between nominal parameters were made with the Fisher exact test. Survival times were depicted by means of Kaplan–Meier curves, and those were compared with log-rank test. The odds ratios (OR) of synchronous presence of DM at the time of diagnosis of LR were calculated using univariate and multivariable logistic regression analyses (multivariable analysis adjusted for LR site [local vs. locoregional lymph nodes], age at diagnosis of LR, positive lymph node status at initial diagnosis, and hormonal receptor status [positive vs. negative). Results

TABLE 1 Types of recurrences in 325 patients

Entire cohort of the BBCD, n = 1368	n (%)
(1) LR only	45 (3.3)
(2) DM and LR diagnosed simultaneously	44 (3.2)
(3) First LR, subsequent DM	48 (3.5)
(4) DM only	180 (13.2)
(5) First DM, subsequent LR	8 (0.6)

BBCD Basel Breast Cancer Database; *DM* distant metastases; *LR* local recurrence

The study cohort, including 137 patients who had LR without previous DM, is shown in the subheadings (1), (2) and (3)

are presented with corresponding 95% confidence intervals (CI) and p values. The level of significance was $p < 0.05$. The data were analyzed by using the Statistical Package Software R (Version 3.3.0, www.r-project.org).

RESULTS

Local Recurrences and Distant Metastases

To verify the recommendation for radiological staging examinations on DM, the subgroup of patients with an LR but in whom no previous DMs were diagnosed is of interest. In accordance with international guidelines, history taking, clinical breast examination, yearly ipsilateral (after breast-conserving surgery), and contralateral mammography and sonography were cornerstones of aftercare in our study cohort. Once LR had been diagnosed, staging examinations on DM were routinely performed as the next step. A total of 137 patients met this criterion and formed the basis of this analysis (Table 1, subgroups 1–3). In these cases, LR appeared in the course of the patient's self-examination, clinical examination, and/or radiological examination.

Table 2 shows the patterns of LR in this group. The majority were local only ($n = 90$, 65.7%), occurring on the chest wall ($n = 42$, 30.7%), or in the breast ($n = 48$, 35.0%); in 47 patients (34.3%), LR also occurred in the regional lymph nodes.

Of the 137 patients who were diagnosed with LR without previous DM, 92 patients (67.1%) had or developed DM: in 44 patients (32.1%), DM was diagnosed simultaneously at the time of LR diagnosis; in 48 patients (35.0%), LR was diagnosed as a first isolated event and DM developed later in the course of the disease (Table 3). In 45 patients (32.9%), LR remained the only event during the observation period.

The local recurrence-free survival time was 38.5 months. In the 48 cases with metachronous DM, distant failure was diagnosed in median 24.5 months after the LR.

Site of LR

Table 3 also shows that DM occurred more often and after a shorter local recurrence-free survival time (in median 25 months vs. 43.5, $p = 0.258$) in patients with axillary/supraclavicular/infraclavicular lymph nodes than in those with in-breast/chest wall recurrence only (60.0% vs. 80.6%, $p = 0.021$). Furthermore, patients who presented with locoregional lymph nodes had more often a concurrent diagnosis of LR and DM (48.9% vs. 23.3%; $p = 0.004$)—an association that remained statistically significant in the multivariable analysis ($p = 0.006$; Table 4).

Disease Stage at Diagnosis

The nodal-positive status at initial diagnosis was found to be a significant factor for the development of subsequent DM (76.5% vs. 50.0% in patients with LR and initially node-negative disease, $p = 0.002$; Table 5). At the time of diagnosis of LR, DM was found more often in 81 patients who had nodal-positive disease at initial diagnosis compared with those with nodal-negativity ($n = 56$), although without reaching statistical significance (35.8% vs. 23.2%, univariate analysis: $p = 0.134$; multivariable analysis: 0.587). In the 30 patients who had Stage I (T1 N0) disease at initial diagnosis, 7 (23.3%) had synchronous diagnosis of LR and DM.

Clinicopathologic Characteristics

From the 44 patients who had synchronous diagnosis of LR and DM, the percentage of those who had a hormonal receptor-negative carcinoma was significantly higher compared with the 93 patients of the control group (patients who had LR alone and LR and subsequent DM) (40.5% vs. 19.8%, univariate analysis: $p = 0.019$); however, this association was not consistent in the multivariable analysis ($p = 0.259$; Table 4). Other clinicopathologic characteristics, such age at first diagnosis, age at diagnosis of LR, histologic subtype, grading, and types of previous therapy were not significantly associated with the synchronous detection of LR and DM.

Of the patients who had hormonal receptor-negative tumors ($n = 34$), 17 patients (50%) had synchronous LR and DM. But even in the low-risk situation of patients with hormonal receptor-positive disease, the frequency of the occurrence of DM was, at 26.6%, still very high.

DISCUSSION

Local Recurrence and Synchronous Diagnosis of Distant Metastases: How Often?

Two studies, namely the present and one by Neuman et al. provide data on this particular issue. Both studies found in patients with LR a comparably high percentage of synchronous DM (present study: 32%; Neuman et al.[18]: 27%). The strongest associated factor to synchronous DM was lymph node recurrence (presented study: 49%; Neuman et al.[18]: 35%). Furthermore, Neuman et al. reported a higher rate of synchronous DM in patients with postmastectomy chest wall recurrence compared with patients with

TABLE 2 Local recurrence without previous distant metastases

Entire study group, n = 137	n (%)
Sites of recurrence	
(1) In-breast following breast-conserving surgery	48 (35.0)
(2) Thoracic wall following mastectomy	42 (30.7)
(4) Axillary lymph nodes	27 (19.7)
(5) Supra-infraclavicular lymph nodes	5 (3.7)
(6) 1 + 4	7 (5.1)
(7) 1 + 4 + 5	1 (0.7)
(8) 2 + 4	4 (2.9)
(9) 2 + 4 + 5[a]	2 (1.5)
(10) 4 + 5	1 (0.7)
AJCC/UICC TNM Stage at initial diagnosis[b]	
Stage I	30 (21.9)
Stage IIA	37 (27.0)
Stage IIB	28 (20.4)
Stage III A-C	42 (30.7)
Nodal-negative disease (Stages I, IIA, IIIA)	56 (40.9)
Median age at initial diagnosis (range)	58 (26–92)
Median age at diagnosis of LR (range)	64 (28–94)
Histologic subtype	
Ductal invasive	104 (75.9)
Lobular invasive	24 (17.5)
Rare types	9 (6.6)
Grading	
G1/G2	52 (41.6)
G3	73 (58.4)
Not available	12
Hormonal receptor status	
Positive	94 (73.4)
Negative	34 (26.6)
Not available	9
Her2-status (2002–2009, n = 32)[c]	
Positive	8 (25.0)
Therapy at initial diagnosis	
Surgery: breast-conserving therapy	68 (49.6)
Surgery: mastectomy	69 (50.4)
Radiotherapy	61 (44.5)
No systemic therapy	30 (21.9)
Endocrine therapy (ET) alone	61 (44.5)
Chemotherapy (CT) alone[d]	20 (14.6)
CT + ET	26 (19.0)

Sites of local recurrence, stage, clinicopathologic characteristics, and therapy at initial diagnosis

AJCC American Joint Committee on Cancer; *UICC* International Union Against Cancer; *DM* distant metastases; *LR* local recurrence

[a]In one case, there also was internal mammary lymph node metastases

[b]In 20 cases, in which neoadjuvant systemic therapy was performed, cTNM classification at diagnosis was reported

[c]Because HER-2 status has been routinely assessed for all patients since 2002, we included data from 2002 to 2009 only in the analysis of this particular characteristic

[d]Including Her2-directed therapy with trastuzumab

TABLE 3 Distant metastases with regard to local recurrence site

	Entire group, $n = 137$	A. Breast/chest wall, $n = 90$	B. Locoregional lymph nodes[b], $n = 47$	p value, A versus B
Further course: LR only (%)	45 (32.9)	36 (40.0)	9 (19.2)	**0.021**
Simultaneous or subsequent DM (%)	92 (67.1)	54 (60.0)	38 (80.6)	
Simultaneous diagnosis of LR and DM (%)[a]	44 (32.1)	21 (23.3)	23 (48.9)	**0.004**
Metachronous course: LR → DM (%)	48 (35.0)	33 (36.7)	15 (31.9)	0.706
Time between LR and DM (months, range)	24.5 (2–115)	29.5 (2–115)	20.5 (3–62)	0.274
Local recurrence-free survival (months, range)	38.5 (2–215)	43.5 (2–208)	25 (2–215)	0.258

Bold values indicate statistical significance ($p < 0.05$)

LR local/locoregional recurrence; *DM* distant metastases

[a]Distribution of DM was as follows: bone metastases were the most frequent metastatic location (56.8%), followed by metastases of lymph nodes (40.9%), the lung (29.5%), liver (15.9%), brain (2.3%), and other sites (11.4%). Thirty-five patients (79.5%) had visceral metastases, and 17 patients (38.5%) had multiple metastatic sites

[b]In 14 cases, the patients had both local and locoregional lymph node recurrence; we placed these patients in the "locoregional lymph nodes" category

TABLE 4 Multivariable analysis: association between four clinicopathologic variables and the risk of synchronous detection of local recurrence and distant distant metastases

	OR (95% CI)	p value
Local recurrence site: locoregional lymph nodes	2.99 (1.38–6.50)	**0.006**
Age at diagnosis of local recurrence	0.99 (0.97–1.02)	0.697
Positive lymph node status at initial diagnosis	1.25 (0.56–2.82)	0.587
Positive hormonal receptor status	0.82 (0.58–1.16)	0.259

Bold value indicates statistical significance ($p < 0.05$)

OR odds ratio; *CI* confidence interval

TABLE 5 Local recurrence and distant metastases with regard to nodal status at initial diagnosis

	A. Node-negative, $n = 56$	B. Node-positive, $n = 81$	p value, A versus B
Further course: LR only (%)	28 (50.0)	19 (23.5)	**0.002**
Simultaneous or subsequent DM (%)	28 (50.0)	62 (76.5)	
Concurrent diagnosis of LR and DM (%)	13 (23.2)	29 (35.8)	0.134
Metachronous course: LR → DM (%)	15 (26.8)	33 (40.7)	

Bold value indicates statistical significance ($p < 0.05$)

LR local/locoregional recurrence; *DM* distant metastases

an in-breast recurrence (30% vs. 15%; this data corresponds to ours with a rate of 23% for both recurrence types). Additionally, disease stage at initial diagnosis was found to be a significant predictor for LR and synchronous DM (stage III: 37% vs. stage II: 20%).[18] Our data show that even in patients who presented with early-stage disease at initial diagnosis, namely stage I or nodal-negative disease (patients who had stage I disease were not included in the cohort analyzed by Neuman et al., and nodal-negative disease was not separately analyzed, respectively), the rate of synchronous DM was at 23% still relatively high for both groups.

Neuman et al. concluded that patients with LR have "a moderate risk for synchronous distant metastases".[18] However, we take issue with this assessment. We think that the reported risk for synchronous DM is not moderate but rather high. This can best be illustrated by the data analysis of the impact of staging procedures to detect asymptomatic DM in the management of women with operable invasive BC. The incidence of detectable metastatic disease at the time of BC diagnosis was just 13.5% even in the highest nonmetastatic disease stage (stage IIIC, i.e., patients who had ≥ 10 positive lymph nodes).[20] In contrast, the detection rate in patients

with LR is at best (in-breast recurrence) 5–10% higher than in this group; in many cases (those in which the patients had lymph node recurrence), the detection rate increased three- to fourfold. In conclusion, these data clearly support the consideration of systemic staging imaging at the time of LR.

Surgical Management of Local/Locoregional Recurrence: The Impact of Staging Examinations

The therapy of isolated LR depends on the management of the initial primary BC therapy (e.g., breast-conserving surgery vs. mastectomy, with or without radiotherapy). The standard approach is surgery [overview in:[21,22]]:

- For patients who developed an isolated in-breast LR after breast-conserving surgery plus adjuvant radiotherapy, mastectomy is the surgical standard of care in most cases.
- For patients who developed axillary lymph node metastases, recurrent disease should be resected; for patients who initially had sentinel lymph node biopsy, a complete axillary lymph node dissection is recommended. For patients with axillary recurrence after a prior axillary lymph node dissection, tumor debulking should be performed.

These types of radical surgery, however, are clearly indicated only with curative intention, i.e., exclusion of distant metastatic disease is essential to allow appropriate therapy planning. Once DM occur, the disease is generally considered to be treatable but no longer curable.[10] In this situation, surgical procedures might be offered with palliative intention, and the primary goals of treatment include prevention and palliation of symptoms, maintenance or improvement of quality of life, and potentially the prolongation of survival.[19] However, the real impact of breast surgery on survival remains controversial. Retrospective studies that indicated that patients who present with primary DM might benefit from the surgical excision of the primary breast lesion in terms of survival may be biased by one crucial confounder, namely the selection for or against surgery [overview in:[23,24]]. In this context, it must be emphasized that numerous studies have looked at the impact of surgical removal of the primary breast tumor in patients with metastatic disease (stage IV at initial diagnosis) [overview in:[23,24]]. To our knowledge, there is no evidence-based data regarding the impact of surgical removal of a LR with synchronous secondary metastatic disease. In the future, we might develop an approach that considers that the more modern target therapies may lead to mixed responses in the metastatic and local sites. Consequently, local treatment may be a good option in selected situations.

The following limitations of our study must be considered in the interpretation of the results. First, our study originates from a single region of a small country with a high socioeconomic status. Second, it is a retrospective analysis. Nevertheless, our study has one important strength: the almost complete data documentation of the entire cohort in a prospectively maintained database with a very low lost-to-follow-up rate of $< 3\%$. Hence, our data provide a comprehensive picture of recurrent disease with very few events potentially missed. To our knowledge, this is the only study that analyzed an unselected cohort of patients who developed LR and DM (Neuman et al.[18] restricted their analysis to patients with advanced stages at initial diagnosis).

CONCLUSIONS

Approximately one-third of patients with a LR had synchronous DM at the time of their local/locoregional event. Even in low-risk subgroups, DM must be expected in at least 20–25% of cases. Thus, routine systemic staging imaging at the time of LR should be an absolute requirement for planning a further therapy course. Confirmation of DM may spare the patients radical surgical interventions with questionable impact on survival in the face of an incurable disease.

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