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# Primary and secondary distant metastatic breast cancer: Two sides of the same coin

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ABSTRACT

*Objectives:* This study evaluated the differences between breast cancer (BC) patients who present with primary distant metastatic disease (PMD) and those who develop distant metastases during the course of their illness (secondary metastatic disease [SMD]) with regard to clinicopathological characteristics, patterns of metastatic sites, palliative therapy and survival.
*Patients & methods:* Based on a cohort of patients with newly diagnosed BC ($n = 1459$), we analyzed all patients who had PMD ($n = 92$, 6.3%) and those who developed SMD ($n = 277$, 20.3%).
*Results:* There were no significant differences with regard to the patient's age in which metastatic disease had been diagnosed (PMD/SMD: 64 years/66 years, $p = 0.19$). The SMD group had more often triple-negative carcinomas (25.5%/7.3%, $p = 0.019$); there were no significant differences with regard to grading ($p = 0.61$), HER2 status ($p = 0.67$) and hormonal receptor status ($p = 1.00$). The mean number of metastatic locations was similar (2.3/2.3, $p = 0.91$). While patients with PMD usually initiated systemic therapy, patients with SMD received systemic therapy after diagnosis of metastatic disease less often (16.4%/2.6%, $p < 0.001$). Both groups received palliative chemotherapy similarly often (PMD/SMD: 62.8%/63.3%, $p = 1.00$). The mean number of palliative therapy lines was similar (PMD/SMD: 2.8/3.2, $p = 0.39$). Compared to patients with SMD, patients who had PMD had a significantly improved metastatic disease survival ($p < 0.001$). The one-year, two-year and five-year survival rates were as follows: 76.9%/60.3%, 58.2%/43.0%, 23.1%/10.6%. The median survival times were 18.5 months and 32 months.
*Conclusion:* The poorer prognosis of patients with SMD may be explained by differences in clinicopathological features of the tumor, metastatic patterns, the use palliative therapy and drug resistance of the tumor cells which occurs in therapy-naïve PMD patients at a later phase of the disease course.


## Introduction

In Western countries, approximately 5–10% of all breast cancer (BC) patients present with distant metastases at initial diagnosis (primary metastatic disease). Depending on prognostic factors, up to 30% of node-negative and up to 70% of node-positive BC patients develop distant metastases during the course of their illness (secondary metastatic disease) [1]. The prognoses and clinical courses of patients with distant metastatic BC vary considerably depending on host and tumor characteristics. Once distant metastases occur, BC remains a treatable condition but is no longer considered curable [1–3].

This study evaluates to what extent both forms of distant metastatic disease (DMD), primary and secondary metastatic BC, differ in terms of clinicopathological characteristics, patterns of metastatic sites, palliative therapy and survival. To our knowledge, our study is the first comprehensive description of and systematic comparison between these particular subgroups of metastatic BC.

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## 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. This institution comprises the largest breast center in the canton of Basel and represents the population of the region. For this study, data from all cases which were diagnosed with BC up to and including 2009 was analyzed ($n = 1495$, 1460 patients).

During this 20-year period, 92 patients (6.3%) had DMD at initial diagnosis, or in other words, had primary metastatic disease (PMD). In 2011, with the exception of 37 patients who were lost to follow-up (2.5% of the entire study group), outcome information was available for all patients. As of March 2011, 277 patients (20.3% of all patients who had stages I–III disease at initial BC diagnosis) had developed distant metastases over time, i.e. had secondary metastatic disease (SMD).

Out of 369 patients with confirmed distant metastatic BC, we were able to obtain information regarding the time of diagnosis of metastatic disease and date of death but we did not have complete information about the disease course and palliative therapy details for six patients (PMD, $n = 1$; SMD, $n = 5$). Thus, these patients were not considered for analysis, and ultimately 363 patients were included in the study:

A: patients who had PMD, $n = 91$ (25.1%)
B: patients who had SMD, $n = 272$ (74.9%); in these cases, the metastatic disease free interval was a median of 38 months (range 2–215 months).

The patients in this study cohort were followed until death. Patients who remained alive were followed until January 2013 (i.e. patients who are still alive had a minimum follow-up time of 24 months).

In order to analyze metastatic patterns and clinical outcomes with respect to palliative therapy, we analyzed only the 340 patients who ultimately died of their metastatic disease (PMD, $n = 78$; SMD, $n = 262$). In other words, we analyzed only completed disease and treatment courses.

### *Clinicopathological data*

The following data was available for all patients: age at initial diagnosis, histological subtype, grading, hormonal receptor (HR) status and tumor stage according to the American Joint Committee on Cancer (AJCC)/International Union Against Cancer (UICC) TNM Classification [4,5]. Because HER2 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.

### *Metastatic pattern*

For this part of the data analysis, we evaluated six metastatic sites: 1) bone, 2) liver, 3) lung, 4) brain, 5) lymph nodes (not including ipsilateral BC-related locoregional lymph nodes), and 6) other anatomical sites.

For each case, the location of the metastatic lesion and the number of metastatic sites were recorded. In all cases, this constellation was described at the initial diagnosis of DMD (first DMD event). When additional metastatic lesions developed at other locations subsequently, the new metastatic site was described as the "second DMD event". Therefore, this second event is not only representative of the number of metastatic sites but also has temporal significance. For example, a patient was diagnosed with DMD in June 2005. Bone and liver metastases were found. This was recorded as two metastatic sites at the "first DMD event". Palliative therapy was initiated. In August 2007, the disease progressed and additional lung metastases were found. This was recorded as one site at the "second DMD event". For this particular case, we recorded two DMD events, a total number of three metastatic sites and a time of 13 months between first and second DMD event.

Usually, the lesions of the first and second DMD events determine disease course and the palliative therapy administered, and reliably reflect the course of DMD (i.e. no palliative radiotherapy or surgery administered to sites which were not reported in either of both DMD events). Additional development of metastatic lesions might occur in some late palliative stages but since palliative care and diagnostic work-up in this situation vary considerably depending on the individual situation, the recording of a third DMD event would not be expected to provide clinically meaningful information.

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

**Table 1**
Comparison of clinicopathologic characteristics between a cohort of 363 breast cancer patients with distant metastatic disease. A. Patients with primary metastatic disease (PMD), B. Patients with secondary metastatic disease (SMD).

| Variable | PMD $n = 91$ | SMD $n = 272$ | $p$-Value |
|---|---|---|---|
| Age when DMD was diagnosed (years) | | | |
| Mean/median (range) | 65.3/66 (32–92) | 62.8/64 (28–94) | 0.19 |
| AJCC/UICC TNM stage at initial diagnosis | | | |
| Stage I | – | 37 (13.6) | |
| Stage II | – | 121 (44.5) | |
| Stage III | – | 114 (41.9) | |
| Stage IV | 91 (100) | – | |
| Bilateral synchronous carcinoma | 2 (2.2) | 11 (4.0) | 0.53 |
| Histologic subtype[a] | | | |
| Ductal invasive | 67 (76.1) | 210 (77.5) | 0.77 |
| Lobular invasive | 17 (19.3) | 47 (17.3) | |
| Rare types | 4 (4.6) | 14 (5.2) | |
| Not available | 3 | 1 | |
| Grading[a] | | | |
| G1/2 | 34 (41.0) | 86 (33.6) | |
| G3 | 49 (59.0) | 170 (66.4) | 0.61 |
| Not available | 8 | 16 | |
| Hormonal receptor status[a] | | | |
| Positive | 61 (75.3) | 197 (75.2) | 1.00 |
| Negative | 20 (24.7) | 65 (24.8) | |
| Not available | 10 | 10 | |
| HER2 status, 2002–2009[a] | $n = 55$ (%) | $n = 55$ (%) | |
| Positive | 13 (23.6) | 16 (29.1) | 0.67 |
| "Triple-negative" carcinoma | 4 (7.3) | 14 (25.5) | **0.019** |
| Not available | – | – | |

DMD: distant metastatic disease.
[a] Histologic subtype, grading, hormonal receptor status and HER2 status were measured in primary breast tumor.

### *Statistical analysis*

Using the Kaplan–Meier method, metastatic disease survival (MDS) was calculated from the date of diagnosis of distant metastases to the date of death, or for patients who survived, to the date of last follow-up. Statistical differences between groups in terms of survival curves were analyzed using the log rank test.

To compare ordinal variables between two groups, the nonparametric Wilcoxon-Test was performed. Comparisons between nominal parameters were made with the Fisher exact test.

To identify factors associated with survival time, we created a multivariable Cox regression which included the variables kind of metastatic disease (PMD vs. SMD), patient's age, HR status, presence of visceral metastases and number of metastatic sites, both at