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Short Communication

# Clinicopathological differences between breast cancer in patients with primary metastatic disease and those without: A multicentre study

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**Abstract** ***Objective:*** Approximately 6% of breast cancer (BC) patients present with primary metastatic disease (pmBC) at first diagnosis. The clinicopathological differences between tumours from patients who have metastatic disease and those who do not are unclear.
***Methods:*** This study was an exploratory analysis of patients with pmBC treated in 8 German breast cancer centres between 1998 and 2010. Phenotypes were defined using the following immunohistochemical markers: oestrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (Her2). The control arm included the group of patients who had neither local recurrence nor distant metastases at a follow-up of at least 30 months after initial diagnosis.
***Results:*** A total of 2214 patients were included. Of these, 1642 had non metastatic BC, and 572 had pmBC. Eighty-five patients (15%) with pmBC were diagnosed at stage T1. On multivariate analysis, factors associated with pmBC were as follows: positive lymph node status, grade 3, lobular histology and Luminal B phenotype (Her 2 positive). Of the sample, 197 patients (34%) with pmBC were diagnosed as stage T2, 90 patients (16%) were diagnosed as

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stage T3, and 200 patients (35%) were diagnosed as stage T4. Only positive lymph node status and grade 3 were reported as risk factors for distant metastases in patients with stage T3 and T4 cancer.

***Conclusion:*** There are differences in the clinicopathological features among breast cancer patients with primary metastases and those without. Receptor expression and histological type play a minor role in the risk for metastasis in patients with stage T3 and T4 disease when compared to patients with T1 pmBC tumours. On initial diagnosis, lobular histology and Luminal B positivity (Her 2 positive) in T1 pmBC were determined to be risk factors for primary metastatic disease.



## 1. Introduction

There are approximately 58,000 patients with newly diagnosed breast cancer registered in Germany per year.[1] In 2006, 429,000 cases of breast cancer were reported in Europe.[2] Approximately one in five of these patients develops metastatic disease.[3–5] Risk factors for metastases are as follows: tumour size and lymph node status, grade, invasion of vessels and hormone receptor status.[6] Once metastatic disease is detected, it is incurable, and therapeutic options are palliative. The 5-year overall survival rate is approximately 20%,[7] and the average post-diagnosis survival time is 2–3 years.[8]

Patients with primary metastatic breast cancer are a subgroup of patients who are of particular interest. Approximately 6% of all breast cancer patients are diagnosed with metastatic disease at the time of their initial diagnosis,[9] and the incidence of metastatic disease has not changed over the last 20 years worldwide.[10,11] Although these cases are also incurable and rely on the same palliative therapies, the survival rates of these patients tend to be longer than those of patients who develop metastases in the months or years following their initial diagnosis.[12–14] The clinico-pathological characteristics of these tumours and the risk factors for the development of primary metastatic breast cancer are not fully understood.

The aim of this exploratory analysis was to determine whether there are differences between tumour characteristics in patients with pmBC and those without, adjusted for loco-regional tumour spread.

## 2. Methods

This study was a retrospective exploratory analysis based on data from 8 accredited breast cancer centres. The observation period was 1998–2010.

The eligibility criteria were as follows: patients were required to have histologically confirmed breast carcinoma with documented TNM staging as well as known immunohistochemical parameters (ER, PR and Her2 receptors). All patients had to have at least one liver ultrasound, a chest X-ray and a bone scan at the time of primary diagnosis.

Breast cancer patients without distant metastases at the time of initial diagnosis and 30 months later were included in the control group. This sample was obtained from only one EUSOMA breast cancer centre in Wiesbaden. The patients who tested positive for distant metastases comprised the evaluation group, which was collected from all 8 breast cancer centres.

Clinical (c TNM) and pathological (pTNM) T- and N-stages as well as grading were documented. M status was defined using radiological findings. Hormone receptor status was analysed in 4 groups, which are as follows: ER positive/PR positive; ER positive/PR negative; ER negative/PR positive; and ER/PR negative. Hormone receptor status was used to approximate the following phenotypes: ER or PR positive and Her2 negative – luminal A phenotype; ER positive or PR positive and HER-2 positive – luminal B (Her2 positive); ER negative/PR negative and HER-2 positive – HER-2 phenotype; ER negative/PR negative and HER-2 negative (triple negative) – basal phenotype.[15] The oestrogen receptor (ER) and progesterone receptor (PR) were considered positive if $\geqslant 10\%$ of tumour cells were immunohistochemistry positive. The most commonly used assay was the 6F-11 antibody (Novocastra, Berlin, Germany) for ER and PR-312 antibody (Novocastra, Berlin, Germany) for PR detection. HER2 was considered negative if the immunohistochemistry was scored as 0 or 1+ (CB11 antibody, Novocastra, Berlin, Germany) or negative if the IHC score was 2+ by fluorescence in situ hybridisation test (FISH).

The two groups were compared using either analysis of variances (ANOVA) or $\chi^2$ test where appropriate. Multivariate logistic regression analyses were conducted to investigate the role of the ER/PR/Her2 combination.

The statistical analysis was performed using SPSS (version 18.0, SPSS Inc., 2010, Chicago, IL). All $p$ values were two sided, and the cut-off for statistical significance was 0.05.

## 3. Results

A total of 2214 patients with pathologically confirmed breast cancer were included in this analysis. Of these, 1642 patients were diagnosed with breast carcinoma without metastases (BC), and 572 patients tested