Abstract. Background: In consideration of increasing incidence by introduction of screening mammography, the prevalence of distant metastases and necessity of staging procedures in early breast cancer should be proved. Patients and Methods: A retrospective review was undertaken of 466 patients with newly diagnosed breast cancer in the period from 2003 to 2006. Results: Distant metastases were found in 22 (4.8%) patients at the time of primary diagnosis of breast cancer. None of these patients had a tumour ≤1 cm and the percentage of metastatic disease increased with local extension (pT1 1.4%; pT2 7.9%; pT3 14.3%; pT4 23.1%; p<0.001) and nodal status (pN0 1.7%; pN1 3.8%; pN2 21.7%; pN3 17.6%; p<0.001) Conclusion: Indication for bone scan, liver ultrasound and chest x-ray should be limited to patients with tumours >2 cm, or tumours >1 cm with lymph node involvement (N1-3).

Since January 2004, screening mammography was implemented in Germany for women aged between 50 and 69 years of age and can be repeated every two years, additionally for patients with familial risk between 40 and 49 years (1-3). While the incidence has been increasing since the introduction of early diagnostic methods, mortality from breast cancer has decreased in women aged between 50 and 69 years and the higher detection rate of small lesions without lymph node involvement or invasive growth can be attributed to screening methods (4). Fundamental risk factors arise as a result of the stage of the disease i.e. tumour size, lymph node status and the presence of distant metastases. Furthermore, it is known that tumour size and axillary involvement correlate, have prognostic value and can have an effect on individual prognosis when they are combined with other prognostic factors such as grading, hormone receptor status, blood and lymphatic vessel invasion and age (5-9). Staging procedures such as chest x-ray (CXR), bone scan (BS) and liver ultrasound (LUS) are recommended for patients with a new diagnosis of breast cancer before systemic therapy to provide information about distant metastases in lung, liver and bone (10-13). Suspicious findings should be further investigated by computer tomography (CT) or magnetic resonance imaging (MRI).

Stage-independent prevalence of distant metastases at the time of first diagnosis is declared in the literature as being between 3.9 and 6.4%, with the highest rate in bone at 35% followed by lung and liver (11, 13, 14). In consideration of increasing incidence and rising costs for routine testing of every tumour stage and in consideration of very low rates of distant metastases at initial diagnosis, the necessity of routine staging methods at every tumour stage must be reconsidered.

Patients and Methods

Patients. The data of 508 female primary breast cancer patients referred to our institution between January 2003 and December 2006 were analyzed. The following inclusion criterion was defined: women with the diagnosis of primary breast cancer. The following exclusion criteria were defined: secondary carcinoma; bilateral tumour and similar distant metastases; relapse of an earlier carcinoma of the breast. A total of 466 women were thus included in this study. For the statistical analysis of the prevalence of distant metastases and the value of routine staging methods, women with a neoadjuvant therapy were included but because of the uncertain characteristics of tumour size, lymphatic and blood vessel invasion and lymph node status they were excluded for the definition of risk factors. Metastatic screening including BS, LUS and CXR was recommended in 409 patients (87.8%); 50 patients (10.7%) had a carcinoma in situ and consequently no staging procedures; the remaining cases were not documented. The analysis included age, histological classification, pathological TNM, grading, lymphatic and blood vessel invasion, hormone receptor status, BS, CXR, LUS, further investigations in patients with suspect findings and localization of distant metastases.

Statistical analysis. All following analyses were carried out with the Statistical Package for the Social Sciences Version 14.0 and in all tests the significance level was set at p<0.05. Sensitivity (Sens.), specificity (Spec.), positive and negative predictive values were calculated for every staging procedure.

Cost analysis. Cost analysis followed the EBM (uniform assessment standard), a catalogue for medically performed services (15). Every service has its own EBM number and a monetary conversion factor whose calculatory price is defined at € 0.05. By multiplication of...
the EBM number and calculatory monetary conversion factor, the price for each test can be calculated. Costs for preparing and postprocessing were not considered.

Results

Among 466 patients with the diagnosis of a primary breast cancer at our institute, BS was documented in 409, CXR and LUS in 407 cases. The missing data result from 50 patients with noninvasive breast cancer without routine staging procedures and the retrospective nature of data collection. The tumour characteristics are shown in Table I.

After testing these patients with BS, LUS and CXR, 22 (4.7%) out of 466 patients were diagnosed as having distant metastases, 59% with bone metastases followed by 22.7% with liver metastases and 18.1% with lung metastases. Two of these patients showed more than only one localization of metastatic disease: one showed metastases in bone, bone marrow and brain, the other in liver and lung at the same time. Patients with pT1 tumours rarely had metastatic lesions. No metastases were found in patients with tumours ≤1 cm (pTmic, pT1a, pT1b) and only 3 (2.1%) out of 139 patients with pT1c tumours had distant metastases. The percentage of metastatic disease increased with the local extension (pT2 7.9%; pT3 14.3%; pT4 23.1%; \( p < 0.001 \)) and the same relation in correlation was found between distant metastases and lymph node status (pN0 1.7%; pN1 3.8%; pN2 21.7%; pN3 17.6%; \( p < 0.001 \)). Summarized data are given in Table II. Altogether we found only one case of metastatic disease in pT1N0 (0.6%). Sensitivity, specificity and positive predictive value of BS were 100%, 86% and 21%. Sensitivity, specificity and positive predictive value of LUS were 100%, 93% and 15% and sensitivity, specificity and positive predictive value of CXR were 100%, 97% and 25%. Summarized data are given in Table III.

In 115 (24.7%) cases a suspect finding was documented and further testing was carried out. Overall, 141 additional tests were ordered to confirm or to weaken suspect findings in every tumour stage and in 20 (17.4%) of these 115 cases, metastatic disease was confirmed. Hence, only 2 out of the 22 cases with metastases were picked up by routine BS, LUS or CXR; in 20 (98.9%) cases, additional tests were ordered to confirm the findings of routine staging procedures. These results show that almost every positive finding in staging was followed by further investigations to confirm the diagnosis. Summarized data are given in Table IV. The costs for routine staging procedures amount to 43,823.03 € including all further investigations, the total cost of screening was finally 52,969.37 €. Consequently, 17.3% of the total cost was spent on additional testing.

Discussion

In this retrospective study, it has been shown that tumour size and lymph node involvement were particularly important factors indicative of the occurrence of distant metastases. In patients with a tumour size up to 1 cm, no metastatic spread was found; the percentage of patients with a tumour size up to 2 cm was very low and increased with tumour growth (\( p < 0.001 \)) and lymph node involvement (\( p < 0.001 \)). The correlation between tumour size, lymph node involvement and survival has been known for many years and has already been described by Fisher et al. (16) in a large study of 2,578 patients. Carter et al. (6) analyzed data of 23,740 patients.
and confirmed the correlation between tumour size, lymph node involvement and survival of breast cancer patients. Any single factor was important for the prognosis but had additional effects in combination. In tumours smaller than 2 cm, the 5-year survival rate in patients without positive nodes, or only one to three positive nodes, was 77-99%, whereas those with four or more nodes involved had a maximum 64% survival and this trend was demonstrated in all T-stages.

The prevalence of distant metastases is very low in newly diagnosed breast cancer patients but metastases can develop only a few months after initial staging. In this study, 4.8% of 466 patients with primary breast cancer had distant metastases and this corresponds with that reported in other papers (13, 17-20). Bone is the most common location for distant metastases, with an overall rate between 1.4 and 6.8% in the literature, followed by liver with a rate between 0.6 and 2.6%, and lung with rates between 0.4 and 3.7% (11, 13, 17, 18, 21-25) (Table V). In a retrospective analysis of 266 patients with initial staging procedures, Berclaz et al. (18) reported 8.6% distant metastases at the time of diagnosis and the statistical analysis not only detected an exclusive occurrence of distant spread at the T2 stage but also an exclusive occurrence of distant metastases in cases having axillary lymph node involvement and so they announced that they would no longer perform BS and LUS in asymptomatic patients with negative axillary lymph nodes in conformity with Bares (26). In this study, such data could not be confirmed because four of our patients had distant metastases without positive axillary lymph nodes and distant metastases were found in T1c. These circumstances and the fact that 25% of patients without nodal involvement develop distant metastases in follow-up and even 30% of them die from metastatic disease force us to find a different solution.

Ravaioli et al. (14) tried to identify groups, from 406 patients, with a higher risk for metastatic disease. The low-risk group included pT1-3 and one to three involved axillary nodes with a comparative low rate of 1.5% detected metastases in contrast to 10.7% in a high-risk group including patients with more than three positive lymph nodes and pT4 tumour. They recommend staging tests in patients with more than three positive lymph nodes and T4 tumours.

Samant and Ganguly (12) reported that only 3% of all T1-2N0 patients had distant metastases at the time of diagnosis compared to 30% of all T3-4 or N2. Gerber et al. (19) reported a higher frequency of distant metastases in patients with increasing tumour size (pT≤2.0 cm: 1.6%, pT 2.1-5.0 cm: 3.0%, pT>5 cm: 15.1%) and lymph node involvement (pN0:1.9%, pN1-3:1.8%, pN4-9: 4.0%, pN≥10: 18.7%) and showed that node negative and patients with one to three involved lymph nodes had a similar risk for initial metastatic disease (1.9 vs. 1.8%). They recommend routinely staging tests in high-risk patients to reduce the number of unnecessary examinations and costs (19).

In common use of screening mammography, smaller and therewith prognostically favourable tumours are detected, while at the same time the incidence increases. For many years, the staging methods have been discussed controversially and various constructive suggestions have
been made (27). In our study, we found no distant metastases with a tumour size up to 1 cm and a low risk (0.6%) for patients with a tumour size between 1.1 to 2.0 cm and a lymph node status pN0.

Based on these results we recommend: staging procedures after breast surgery (exact tumour size); staging procedures not be performed in asymptomatic patients with tumours up to 2 cm and no lymph node involvement (pT1mic/a/b/c and N0); staging procedures in locally advanced breast cancer (>1 cm) and N1-3.

If our institute had performed staging according to the aforementioned recommendations between 2003 and 2006, 161 (34.5%) patients would have received no staging tests and further diagnostic and 37.8% (20,026.43 €) of the costs could have been saved. In the 45 further diagnostic tests (CT Abdomen and Thorax, Bone X-ray and MRI) carried out, only one case of metastatic disease was found in pT1N0.

References


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