Survival patients with pulmonary metastases in breast cancer neoplasia

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Abstract: - Breast cancer is one of the most frequent neoplasia in women (27% of the total types of cancer). It represents the second cause of death in the USA after pulmonary cancer.
We conducted a survey from January 2000 to December 2005 on 120 patients admitted in Cluj-Napoca Oncology Institute and "Leon Daniello" Pneumology Clinical Hospital. We introduced in the study patients diagnosed with breast carcinoma and pulmonary metastases, we analyzed risk factor and evolution of the diseases with survival function calculated since breast cancer diagnosis, and the other calculated since pulmonary metastases. Age of the patients over 60 years (p=0.01), urban areas (p=0.048), smoking (p=0.001), time between the first symptoms and the doctor' presentation (more than 1 year) was significant statistic in both survival (p=0.005 and p=0.003). Good performance status (p=0.03), the stage of the disease at presentation (p=0.004), type of metastasis, good risk class (p=0.0004), response at the treatment (only 5% had complete response) influence the survival calculated from the breast cancer diagnosis (69.15% at 1 year, 17.02% at 5 years, 4.26% at 10 years) and the survival calculated from the moment of pulmonary metastases (32.53% at 1 year, 4.82% at 5 years, 2.41% at 10 years).
Mathematics and statistic analysis were very important in evaluation and validation of prognostic factors of disease, because the doctor can choose the best treatment for each patient, can compare the therapeutic strategy in similar situation and can discover precocious recurrence of neoplasia.

Key-Words prognostic factor, survival, metastases, breast cancer

1 Introduction

Breast cancer is one of the most frequently occurring neoplasms in women (27% of all cancers) and the second cause of death in the United States of America after lung cancer [1, 2]. Ten percent of all cancer patients already have metastases, while 50% are going to develop them in the future [3].

2 Problem formulation

The high frequency of breast cancer (highest mortality rate-17.50% of all cancer-related deaths in women) as well as the variable clinical evolution of the disease led to the inclusion of breast cancer patients with lung metastases in our study [4]. The disease progresses rapidly in some patients who develop vital organ metastases and die within a few months. In other patients, the evolution of the disease is slow, with long periods of stability. Patient division into high or low risk categories according to prognostic factors may allow differential approaches, individualized follow-up for the early detection of recurrences and efficient treatments aimed at increasing the patients' quality of life and survival chances.

3 Material

A study was carried out on 120 patients admitted at the Cluj-Napoca Institute of Oncology between January 2000 and December 2005. The study included patients diagnosed with breast carcinoma and lung metastases.

Inclusion criteria: - patients with (hystopathologically or cytologically) confirmed breast cancer and lung metastases

1. Pleurisy with positive cytology
2. Exudative pleurisy of unknown etiology
3. Multiple lung nodules interpreted on X-ray or CT examination as having metastatic origin, confirmed or not by biopsies
4. X-ray or CT images showing carcinomatous lymphangitis.

Exclusion criteria: the patients with a single, not-histopathologically confirmed lesion were excluded because of the difficulty in differentiating between metastatic lesion and primary lung carcinoma.

4 Methods

The patients underwent the following investigations: clinical examination, complete blood and biochemical tests (plus kidney and liver function tests), chest X-rays, EKG, abdominal ultrasound, bone scintigraphy, chest CT, fibrobronchoscopy with brushing, bronchial and transbronchial biopsies, chest ultrasounds, pleural biopsies with fluid cytology and chest biopsies.

The following prognostic factors were investigated retrospectively: patient age, place of origin, smoker/non-smoker status and time elapsed from the onset of symptoms to diagnosis. Factors related to local invasion (size of the primary tumor, presence of axillary lymph node metastasis, TNM stage at diagnosis, staging, other metastases, localization of metastases) were also considered. The patients were divided into risk groups according to prognostic factors. The main treatment options (radical mastectomy, radiotherapy, hormone therapy, chemotherapy) as well as the patients' evolution and response to treatment: *complete response, partial response, stationary and progressive disease* were investigated.

Survival was calculated until the time of death or after the last follow-up (patients who failed to report for follow-up on the scheduled day or later). We evaluated recurrence patterns and calculated the survival rate related with prognostic factors. The data obtained were analyzed statistically.

Survival was calculated from the detection of the primary tumor until the last follow-up. Survival with metastasis was calculated from the moment lung metastases were diagnosed until the patient left the study (due to confirmed death or failure to report for check-up). The Kaplan Meier survival curves were used to compare two groups of patients. The median survival time was calculated in order to describe survival in a group of patients. The differences between survivals in two groups were evaluated with the logrank test. The Cox regression was used to predict survival time according to various characteristics. The hazard rate was calculated. The calculations were performed with SPSS 13.0.

5 Problem Solution

Between January 2000 and December 2005, 6772 patients newly diagnosed with breast cancer were recorded at the Cluj-Napoca Institute of Oncology. Out of these, 120 patients with lung metastases were included in our study. The lung metastases were either detected at their onset or were already developing.

The **mean age** of the patients included in the study group was of 57.03 years (between 24 and 78 years). **Age** was not a significant prognostic factor. Stage III patients over the age of 60 with metastasis survived longer (median (m_e)=14months) than patients under 60 years of age (m_e=7months) (p=0.01). Once metastasis occurred, there were no significant differences between the survival of stage IV patients under the age of 60 compared with patients above 60 (p=0.86).

The place of origin of breast cancer patients with lung metastases was predominantly urban. Stage III patients from the urban area (n=30, m_e=13months) survived significantly longer than the patients from the rural area (n=26, m_e=8months) (p=0.048). Stage IV patients from the rural area (n=10, m_e=12months) survived significantly longer than the patients from the urban area (n=21, m_e=6months) (p=0.03). Once metastases occurred, stage III patients from the urban area (m_e=10months) survived longer than the patients from the rural area (m_e=5months) (p=0.03) while stage IV patients from the urban area (m_e=5months) did not survive significantly longer than the patients from the rural area (m_e=7months) (p=0.97). Therefore, the place of origin was not a statistically significant prognostic factor in the advanced stages of the disease.

The time interval from the onset of symptoms to first reporting to a physician was a major prognostic factor reflected in the advanced stage of the disease at diagnosis. The mean interval from symptom onset to first reporting to a physician was of 12.47 months. The survival of breast cancer patients was strongly influenced by the time elapsed from the onset of symptoms until first reporting to a physician. If this interval exceeded 1 year (n=70, m_e=17months for time greater than 1 year and n=50, m_e=38months for time < 1 year), the survival chances decreased significantly HR=2.12 (C.I.95% 1.32-3.40) (p=0.005) (fig.1).

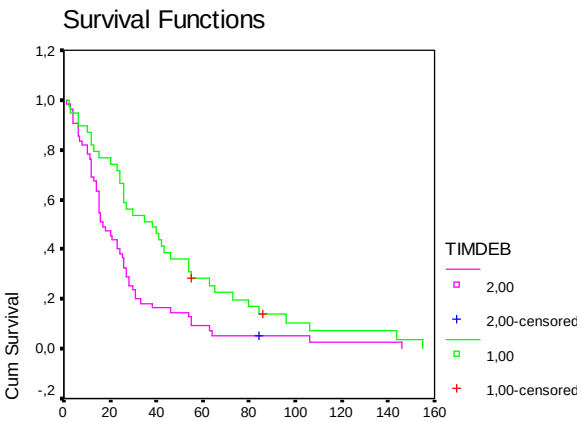

Fig.1. Survival curves for time from symptom debut (with green time <1 year, with mauve time ≥ 1 year)

Performance status. We divided our group of patients into two groups: one with low performance status (1-2, n=27) and another one with high performance status (3-4, n=11). The survival of patients with higher performance status (3-4) (m_e=9months) was significantly lower than that of patients with lower performance status (1-2) (m_e=19months) p=0.04 (fig.2).

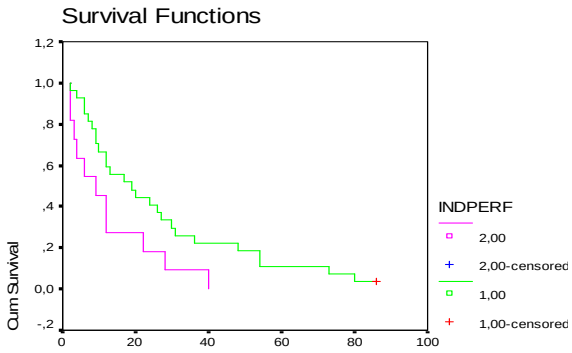

Fig.2. Survival curves for performance status (with green performance=1-2, with mauve performance=3-4)

Smoking. The survival with metastases was significantly lower at people who smoke (m_e=5months) than the people who don't (m_e=12months) (p=0.001). Smoking causes damage to the lungs and at a systemic level, which could contribute to the development of metastases in patients with breast carcinoma or other cancers.

The **TNM classification** is another system for dividing patients into risk groups. Sainsburg published survival data according to the stage of the disease at diagnosis [5]. Thus, **stages** I (n=2) and II (n=31) were related with increased survival rates compared with stages III (n=56) and IV (n=31). In our study, survival was significantly influenced by the advanced stages of the disease (p=0.004). The survival of stage IV patients (m_e=26months) was lower than that of early stage patients (m_e=9months) (fig.3).

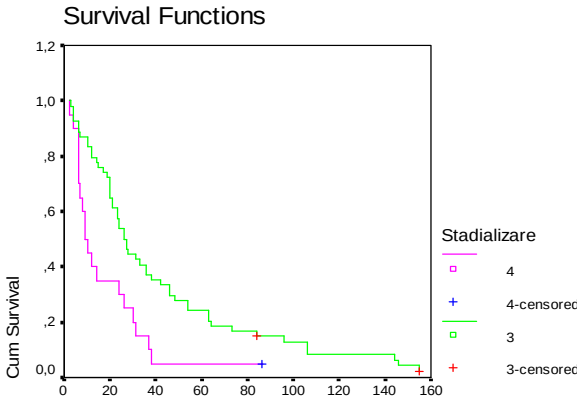

Fig.3. Survival curves for stages of the disease (with green stages ≤III, with mauve stages = IV)

Survival after the occurrence of metastases was also significantly influenced by the advanced stages of the disease (p=0.04). The survival of stage IV patients (m_e=7months) was below that of early stage patients (m_e=13months) (fig. 4). The advanced stage of the disease at diagnosis may suggest tumor aggressiveness. However, in some cases the advanced stage only indicates a long, slow evolution of the disease ignored by either patient or physician.

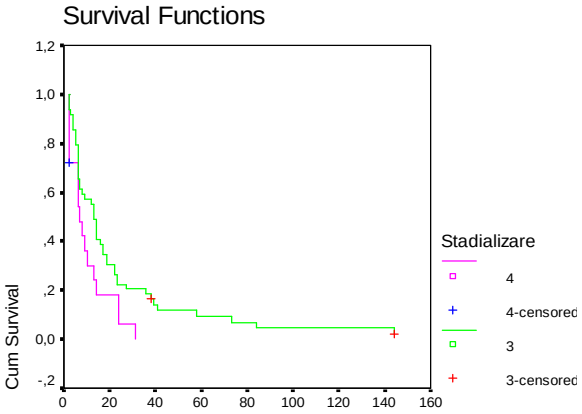

Fig.4. Survival with metastases curves for stages of the disease (with green stages ≤III, with mauve stages = IV)

The most important prognostic factor was the **disease-free interval** between the diagnosis of the primary tumor and the occurrence of distant recurrences. A short or inexistent disease-free interval between the diagnosis of the primary tumor and the occurrence of lung metastases represented an unfavorable risk factor that affected survival. The mean disease-free interval was of 15.66 months. Survival with metastases was significantly higher if the disease-free interval exceeded 2 years (n=34, m_e=12months) as compared with an interval below 2 years (n=86, m_e=8months) (p=0.02) (HR=0.51, C.I. 95% 0.26-1.01, p=0.052). The patients with metastases at diagnosis accounted for 29% of all patients. In other studies, this percentage was between 6 and 10 [6].

The **type of lung metastases** represented an unfavorable prognostic factor (Table 1). Patients with unilateral metastasis lived significantly longer than patients with bilateral localizations (p=0.01). The survival of patients with small opacities reduced significantly compared with that of patients with large opacities (p=0.002). The survival of patients with one or two types of metastases (lymphangitis, large opacities, small opacities, pleurisy, adenopathies) was significantly higher than that of patients with 3-4 types (p=0.0001). The survival of patients with lymphangitis was significantly lower than that of patients without it (p=0.006). The survival of patients with adenopathy was similar to that of patients without it (p=0.12).

Table 1. Metastasis pattern

Metastasis pattern	Number of patients	Procent	Survival (month)
Microopacities	11	36,00 %	10
Macroopacities	6	20,00 %	5
Pleuresy	12	40,00 %	22
Lymfangitis	1	3,33 %	6

Survival decreased as the **number of metastases localizations** increased (p=0.0001). The survival of patients with only lung metastases was significantly higher than that of patients with lung and other metastases (p=0.007)

The division of patients into various **risk groups** revealed that risk groups were a statistically significant prognostic factor in the survival of breast cancer patients (p=0.0004). *Low risk = 1; Intermediate risk = 2; High risk = 3.* Patients underwent treatment, once they were diagnosed, the extent of the disease as well as the main prognostic factors were evaluated.

Response to treatment. The heterogeneity of metastatic cancer as well as the large variations of the growth and response rate to systemic therapy explains the different clinical evolutions. Total remission was only registered in 5% of the patients with lung metastases while 6% of patients were stationary and 89% had developing disease. Although metastatic breast cancer is incurable, it is treatable with a relatively high success rate [7]. Only a small percentage of patients included in our study benefited from "potentially curative" treatment. Isolated metastases in the lung or pleural space developed in 15-25% of patients who benefited from surgical treatment (resection of lung metastases or pleurodesis with sclerosing agents), which proved to increase survival in comparative groups [8]. Godehard Friedel did not report statistical differences between single or multiple metastases when surgery was performed. The mean survival recorded in his study was of 20 – 30 months [9]. Soonmyung Paik showed that 6.8 out of 51% low risk patients developed distant recurrences after 10 years [10].

The survival rate varied (fig. 5, Table 2)**.**

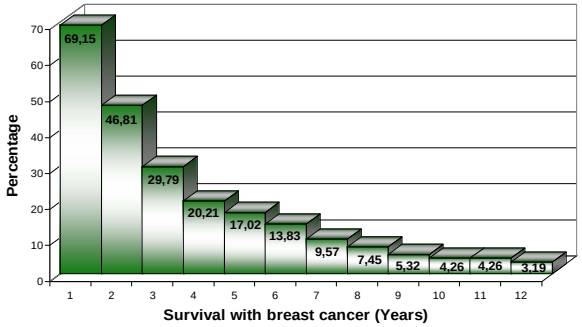

Fig.5. Survival rate with breast cancer (years)

Only a few patients with favorable evolution and complete remission after standard chemotherapy will not present signs of disease over a long period possibly exceeding 20 years.

Many patients, however, will develop local and distant recurrences with metastases [11].

Table 2. Survival with metastases

Median for survival with metastases: 10 (in months)			
Survival Time	Patients number	Death percentage	Survival cumulative percentage
0 Years	80	66.67	100.00
1 Year	21	17.50	33.33
2 Years	4	3.33	15.83
3 Years	7	5.83	12.50
4 Years	2	1.67	6.67
5 Years	0	0.00	5.00
6 Years	3	2.50	5.00
7 Years	0	0.00	2.50
8 Years	0	0.00	2.50
9 Years	0	0.00	2.50
10 Years	0	0.00	2.50
11 Years	3	2.50	2.50
	120	100.00	

The newly available drugs enable patients to live longer with minimum symptoms. Studies carried out on selected patient groups (1 - 3%) indicated that long-term survival was possible in young patients with good performance status and limited metastatic disease. Another small percentage (9 - 25%) with favorable prognosis includes patients with single isolated lesions (teguments, lungs, lymph nodes) that may benefit from local treatment (surgery and radiotherapy). The discovery of additional predictive factors would help identify the patients able to undergo treatment with curative intent. However, in most cases conservative treatment with reduced cytotoxicity is preferred over treatment with curative intent. Patient quality of life is difficult to measure since survival is the main target. Quality of life involves multidimensional physical concepts (symptoms caused by cancer or drug toxicity) as well as often-subjective psychological and social elements (family or work relations, friendships). Metastases are incurable despite the currently available advanced therapies. Consequently, conventional or endocrine chemotherapy still constitute palliative treatment aimed at reducing symptoms, improving quality of life and prolonging survival. Studies carried out on large series of patients demonstrated that the survival of metastatic patients was of only 3% at 5 years (complete remission) and that only half of these patients

were alive at 10 years. Yanamata noted that a large number of patients with good performance status, reduced number of metastases and no associated diseases did not benefit from early detection. The early detection may have emotional value for the patient. Clinical trials of future therapies will have to treat the patients with asymptomatic recurrences since immediate palliative measures are not available. The American Society of Clinical Oncology (ASCO) introduced breast cancer guidelines and established strategies for detecting and treating recurrent cancer. These guidelines ensure access to better healthcare and reduce the medical costs involved. New knowledge of breast cancer biology and new clinically-available therapeutic agents (such as Her2, aromatase inhibitors) allow the selection of individual breast cancer treatments according to prognostic and predictive factors, response to previous treatment, risk, toxicity, patient preferences and options [12]. Despite these developments, not all metastatic breast cancer patients can be cured. However, toxic and costly treatments could be avoided in patients with resistant tumors. The identification of clinical patterns of recurrence may prove to be predictive. Cancer treatment strategies are becoming more and more complex, healthcare standards are improving while the use of a standardized algorithm remains controversial. The disease, the patients and the treatments must be fully understood in order for the best available treatment to be applied with maximum benefits.

5 Conclusions

We achieve the objective of our study. We divided the patients in tree risk groups according to predictive factors for survival. Breast cancer continues to be a significant cause of morbidity and mortality in women throughout the world. The natural history of breast cancer varies despite screening methods and early surgery associated with systemic chemotherapy. The identification and validation of prognostic factors with predictive role in the evolution of neoplasis disease allows patients to be assigned to risk groups according to their probability of developing the disease. Such patients may benefit from more aggressive therapies (with optimum efficiency-toxicity ratio) aimed at improving quality of life and prolonging survival. The identification of prognostic factors is valuable due to the following three reasons:

1. Optimum treatment may be selected for each patient
2. Various therapeutic strategies could be compared among groups of patients with similar recurrence risks and treatments
3. The knowledge that allows the identification of recurrence patterns may be improved and new treatment strategies established. Why spend money on inefficient therapies that are sub-optimally dosed in high-risk patients or excessive in low risk patients? The selection of the optimum therapy is a challenge for each team involved in the treatment of cancer patients with lung metastases.

The early detection of metastases proved to be beneficial. However, metastases may be treated more efficiently if detected early rather than late, thus improving survival and quality of life.

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