Prognostic Factors in the Evaluation of Metastatic Breast Cancer

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Abstract: - Breast cancer continues to be a major cause of morbidity and mortality in women worldwide , one of the most frequent neoplasia in female. The evaluation of prognostic factors and the follow-up of metastases are major research areas that enable cancer patients to have maximum therapeutic benefits, increased quality of life and survival .

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). Tumor localization (p=0,95), primary tumor size (p=0,000), number of metastatic ipsilateral axillary lymph node (p=0,0212) as prognostic factor in breast cancer. 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). Since classical prognostic factors could not be predictive for all the patients in our studied group, we aimed to identify other prognostic factors . We examined the status of **estrogen and progesterone receptors** as unfavorable predictive factors of treatment response and found that patients with hormone receptors had a significantly higher survival than those without the receptors (**p=0.0409** for estrogen and **p=0.0355 for progesteron**). In order to evaluate tumor aggressiveness we carried out immunohistochemical studies to detect P53 protein(p=0,012), bcl-2 gene(p=o,678) and PDGF (p=0,637) in the attempt to demonstrate that these could have been useful in assessing the future development of breast tumors

The identification of prognostic factors (with mathematics methods) 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

Key-Words prognostic factor, survival, metastases, breast cancer, metastases treatment, risk factors

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] Breast cancer continues to be a major cause of morbidity and mortality in women worldwide. In 2002, breast carcinoma accounted for 31% of all carcinoma cases in women in the United States of America (203.500 new cases and 39.000 deaths) [3]. Despite

the modern screening, diagnostic and treatment methods available, breast cancer mortality is still high in Romania, where every year 2900 deaths are registered, representing 17.50% of all cancer deaths in women [4,5]. Most patients die as a result of disease spread and metastases.

Breast cancer mortality decreased significantly in the last 10 years due to the early detection and treatment of the disease [4,2]. According to classical studies, the mean survival age of untreated patients was of 2.7 years. In treated patients, most cancers recurred within 2-3 years from the diagnosis of the primary tumor while recurrences within years or even decades were usually registered in only 3-5% of patients [6]. Ten percent of all cancer patients already have metastases, while 50% are going to develop them in the future [7].

Only 20% of metastatic patients survive the relapse. Metastatic patients cannot be cured with conventional therapy. The proportion of metastases is not influenced by aggressive local therapy, which indicates that most patients already have micrometastases. Although recurrences and metastatic cancer cannot be treated, the early detection of metastases and palliative treatment improve patient quality of life and survival. Treatment choice in advanced cancer cases may offer patients maximum palliative benefits.

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. The evaluation of prognostic factors and the follow-up of lung metastases are major research areas that enable cancer patients to have maximum therapeutic benefits, increased quality of life and survival.

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.

There are three categories of prognostic factors:
1.Spread due to local invasion (metastatic lymph nodes-including:
→ size of the primary tumo

→ number of invaded lymph nodes

2.Indicators of aggressive biological features – histological grade

3.Host-related factors:

I.age

II. menstrual status

Several prognostic factors were evaluated retrospectively:

- host-related factors: age, socioeconomic status, place of origin, exposure to noxious chemicals (smoker status), time elapsed from the onset of symptoms to first reporting to a physician for diagnosis.
- factors related with local invasion: size of the primary tumor, presence of axillary lymph node metastases, TNM stage at diagnosis, staging, other metastases, localization of metastases.
- factors related with tumor aggressiveness – tumor histology, size and hormonal status; the identification of c-erbB-2, bcl2 and P53 indicate tumor aggressiveness. Hormone receptor status may predict treatment response.

The **p53** gene, located on chromosome 17q, is the most frequent genetic anomaly involved in various neoplasias, tumor development and metastases.

The **Bcl2** gene, which belongs to the Bcl family, regulates apoptosis. An increase in this gene favors the survival of neoplastic cells.

PDGF was detected in numerous tumor lines such as breast and colon cancer or melanoma. PDGF contributes to angiogenesis via proliferation of endothelial cells and tube formation, induction of VEGF and other angiogenic factors or stable neovascularization by recruitment of pericytes and lyse muscle cells. PDGF released by endothelial cells induces the VEGF expression, which is a survival factor for young endothelial cells.

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.(fig 1)

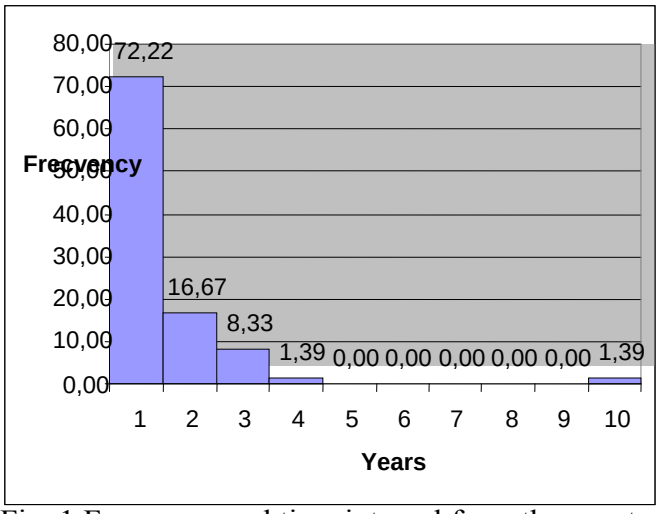

Fig. 1 Frecvency and time interval from the onset of symptoms to first reporting to a physician

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.2).

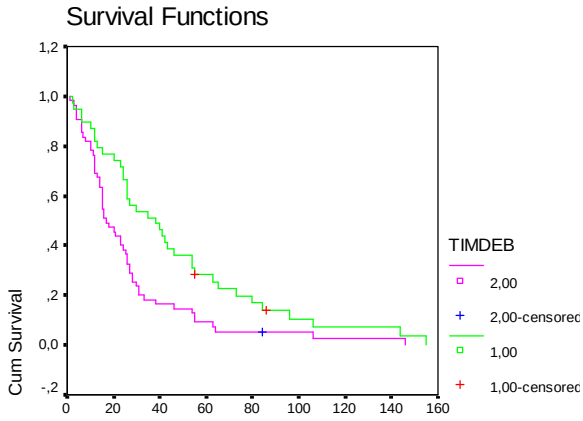

Fig.2. Survival curves for time from symptom debut (with green time <1 year, with mauve time ≥ 1 year)

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.3).

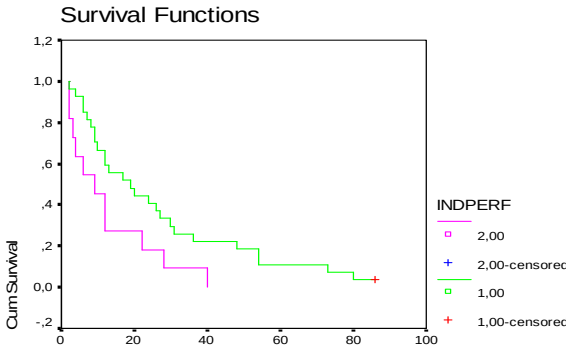

Fig.3. Survival curves for performance status (with green performance=1-2, with mauve performance=3-4)

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 [8]. 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.4).

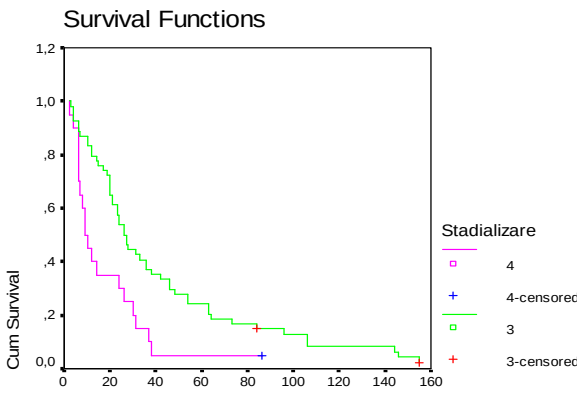

Fig.4. Survival curves for stages of the disease (with green stages ≤III, with mauve stages = IV)

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. 5). 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.

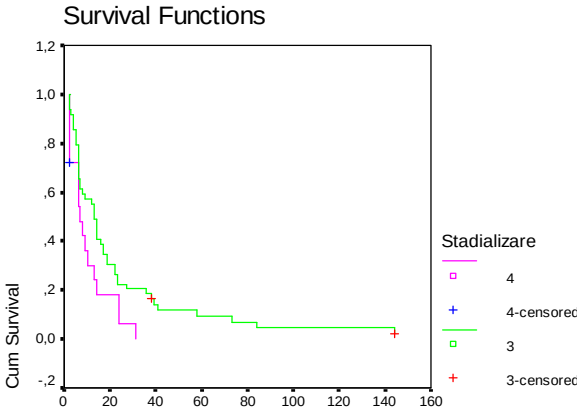

Fig.5. Survival with metastases curves for stages of the disease (with green stages ≤III, with mauve stages = IV)

Primary tumor localization. In our group of patients the primary tumor was mainly located in the left breast (55%). No survival differences were observed between cancers located in the left or right breast. No significant differences according to localization were recorded **(p=0.95).**

Tumor localization in breast quadrants: *upper-inner (8%), upper-outer (70.67%), lower-inner (0%), lower-outer (4%), central (4%), plurifocal (10.67%), diffuse (0%), bilateral (0%), lateral-outer (2.67%).* These figures are explained by the increased quantity of glandular tissue present in the upper quadrants. No survival differences according to tumor localization were noted (**p=0,9845**).

Primary tumor size as prognostic factor in breast cancer .The size of the primary tumor as unfavorable prognostic factor was evaluated and divided into 3 categories: *under 2 cm, between 2 and 5 cm, over 5 cm (between 5 and 10 cm, over 10 cm). (fig 6)*

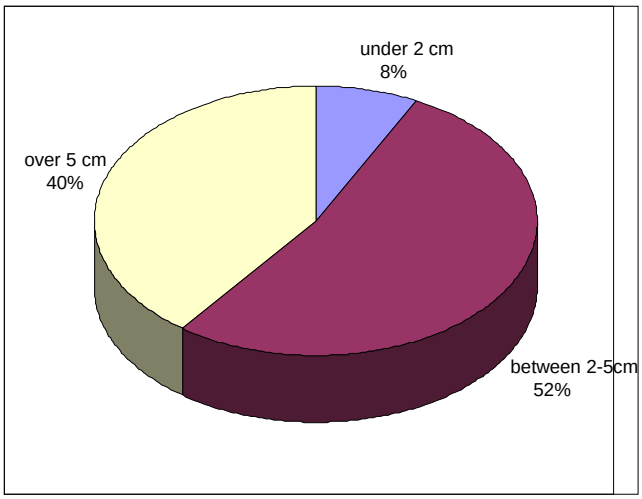

Fig. 6 The size of the primary tumor

A univariate analysis revealed that tumors exceeding 5 cm were unfavorable prognostic factors compared with tumors under 5 cm.

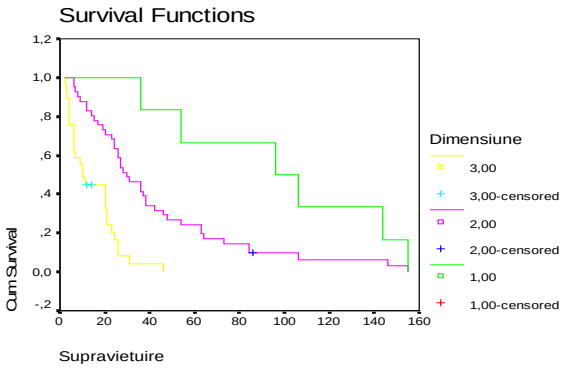

Fig 7 Survival curves for size of primary tumor

Breast cancer survival has statistical significance according to tumor size (p=0,000).(Fig

7) Survival in metastatic breast cancer has statistical significance according to tumor size (p=0,000).(fig 8)

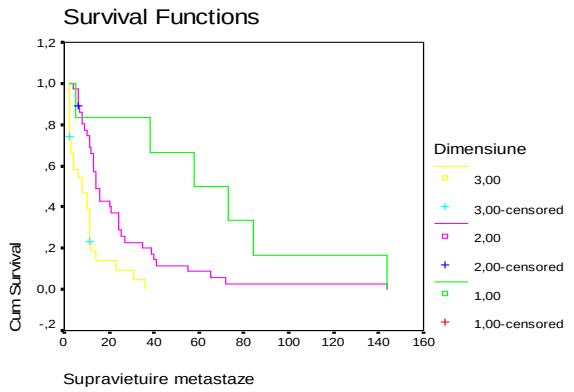

Fig 8.Survival with metastases curves for size of primary tumor

Tumor invasion is also evaluated in connection with lymph node metastases. The **number of metastatic ipsilateral axillary lymph nodes** is regarded as the most powerful prognostic indicator in breast cancer patients**.**

Diagnostic errors may occur when the extent of the invasion is assessed by clinical examination only. In order for invaded lymph nodes to be evaluated as prognostic factors, axillary lymph nodes were grouped as follows: 1-3 metastatic lymph nodes (group 1), 4-10 lymph nodes (group 2), not invaded or negative lymph nodes (group 3). Patients with adenopathy type 2 (over 4 lymph nodes) have a significantly lower survival compared with type 1 patients (there are too few patients with type 3). A multivariate analysis revealed that invaded lymph nodes influenced survival (**p=0,0212).**(fig 9)

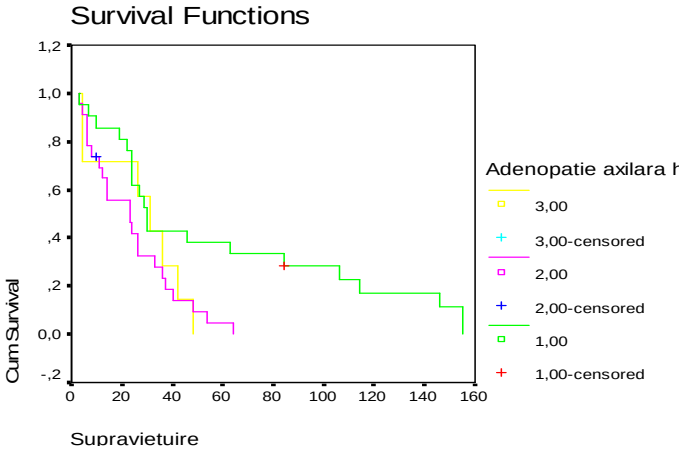

Fig 9. Survival curves for number of metastatic ipsilateral axillary lymph nodes

Evaluation of tumor aggressiveness – immunohistochemical studies

Since classical prognostic factors could not be predictive for all the patients in our studied group, we aimed to identify other prognostic factors. In order to evaluate tumor aggressiveness we carried out immunohistochemical studies to detect P53, bcl-2 and PDGF in the attempt to demonstrate that these could have been useful in assessing the future development of breast tumors. Numerous clinical studies showed that **protein p53** accumulation, which reflects the excessive presence of the p53 gene, could be an unfavorable prognostic indicator in breast cancer patients. The determination of this gene in patients with lung metastases may indicate whether such patients could have been assigned to unfavorable risk groups upon diagnosis and benefitted from other treatment types. The p53 gene is frequently mutated in breast cancer and protein p53 accumulation is used as a surrogate marker of p53 activity.
The accumulation of p53 is associated with unfavorable prognosis. Patients with a p53 factor < 20 (i.e. 0 or 10) have a statistically significant lower survival (p=**0,0120).** (fig 10) and survival after metastases (p=0,047)(fig 11**)**

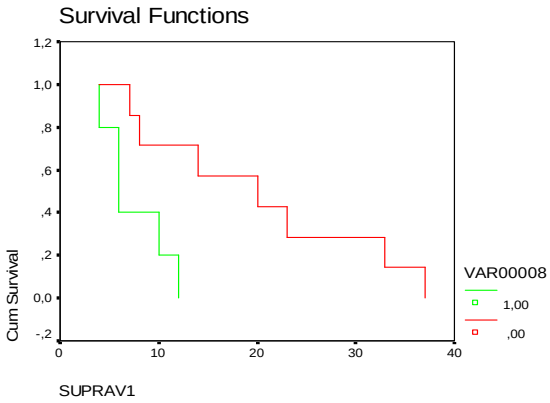

Fig 10 . Survival curves for p53 protein

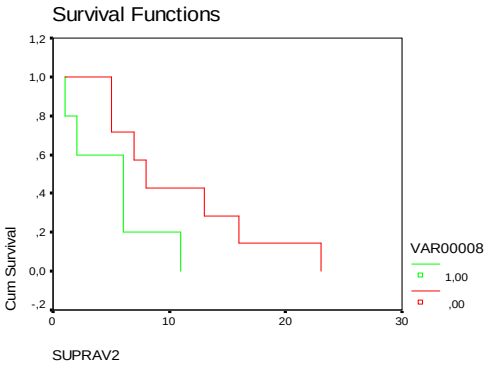

Fig 11. Survival with metastases curves for p53 protein

We used Spearman's correlation coefficient to evaluate whether tumor aggressiveness, expressed by the presence of the p53 protein, correlated with the time elapsed from the onset of symptoms to diagnosis. A statistically significant p was not obtained (p=0.8037).
P53 did not correlate with: the number and presence of other metastases **p=0.789**, the number of hormone receptors **p=0.184,** tumor stage **p=0.333**, disease stage **p=0.575** (Pearson's correlation coefficient was used). A significant inverse correlation between survival (both 1 and 2) and P53 was observed. In breast cancer the expression of the bcl2 oncoprotein has proved to correlate with the accumulation of the p53 protein.
Bcl2 gene did not correlate with survival 1 **p=0.678**, (fig 12) survival 2, after metastases **p=0.681**..

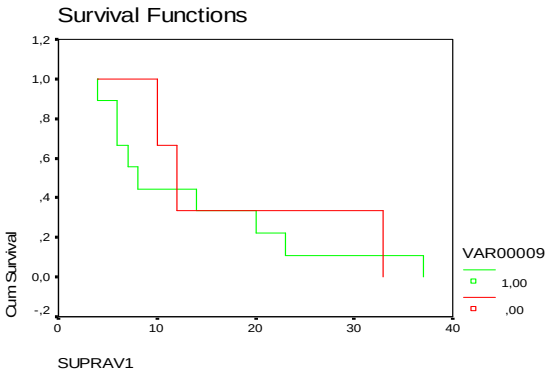

Fig 12. Survival curves for Bcl2 gene

It also failed to correlate with the time elapsed from the onset of symptoms to diagnosis **p=0812**, with the number of hormone receptors **p=0.184** or with the presence of other metastases **p=0.355**. A correlation coefficient was used for the PDGF (platelet-derived growth factor). PDGF did not correlate with survival 1 or 2 (1=from the detection of the primary tumor; 2=from the detection of metastases). PDGF did not correlate with survival p=0.637 or with the presence of other metastases (p=0.699).

We examined the status of **estrogen and progesterone receptors** as unfavorable predictive factors of treatment response and found that patients with hormone receptors had a significantly higher survival than those without the receptors (**p=0.0409**).Fig 13

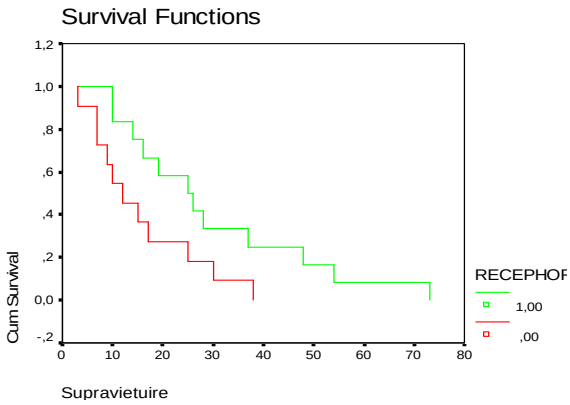

Fig 13 Survival curves for estrogen receptors

Patients with progesterone receptors had a significantly higher survival that those without the receptors (**p=0.0355**). (Fig 14)

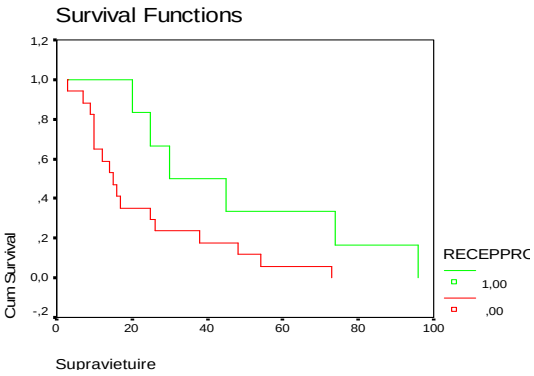

Fig 14 Survival curves for progesterone receptors

The significantly higher survival of cancer patients with positive estrogen and progesterone receptors is explained by their favorable response to associated hormone therapy.

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 [9].

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 [10]. 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 [11]. 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 [12]. Soonmyung Paik showed that 6.8 out of 51% low risk patients developed distant recurrences after 10 years [13].

The survival rate varied (fig. 15, Table 2)**.**

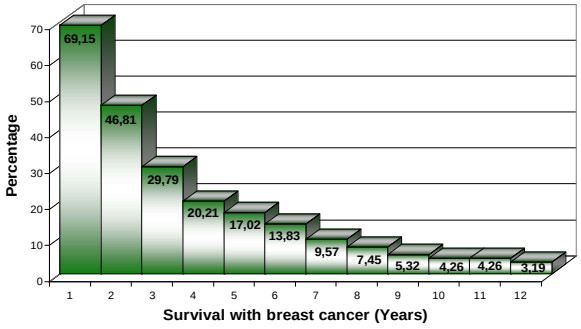

Fig.15. Survival rate with breast cancer (years)

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 [14].

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**	

6 Discussion

Some studies revealed that patients under 50 years of age have an increased recurrence rate at 10 years compared with elderly patients, 21.1 % vs. 12.3 % [13]. Patients under 35 years of age treated conservatively may present a 3-fold relative risk compared with patients aged over 35 [8]. Fisch also reported decreased survival in patients from the rural area and increased survival in the urban area [15]. Soonyung Paih noted that patients with tumors under 2 cm had decreased risk of recurrences and metastases compared with patients with larger tumors (13.3 % vs. 17.5 %) [13] . The number of metastatic ipsilateral axillary lymph nodes is the strongest prognostic indicator in breast cancer patients.

In order to evaluate invaded lymph nodes as prognostic factor, the following were established [16]: ***non invaded lymph nodes*** showed ***reduced risk of metastases; 1-3 metastatic lymph nodes (without other obvious distal metastases)*** signaled an ***intermediate degree of dissemination*** while ***>4 lymph nodes*** indicated ***unfavorable prognosis.***

Guo Jun Zhang reported a 20% risk of recurrence in group I, 14% in group II and 42% in group III ($p < 0.002$) as well as a 12% risk of death in group I, 18% in group II and 35% in group III ($p= 0.02$) [16].

The measurement of a large number of prognostic factors is not valuable in the routine management of breast cancer patients.

The use of independent prognostic factors identified groups of patients with different prognoses. Therefore, several prognostic factors were combined in an index that would assign patients to various risk groups with similar evolutions.

The survival of patients with favorable prognosis is similar with that of women without the disease. Patients with favorable prognosis will not undergo aggressive forms of adjuvant treatment. In contrast, patients with unfavorable prognosis have a 13% survival rate at 15 years and should benefit from intensive systemic therapy [18].

Although breast cancer prognosis using various clinicopathological variables has proved useful, it still has imperfections [19].

The identification of the hormonal status of the tumor as well as of c–erbB-2, bcl2 and P 53 indicates tumor aggressiveness.

The changes in the genes and proteins present in tumor cells correlated statistically with the clinical results obtained.

The bcl 2 oncogene, originally thought to be involved in follicular lymphoma, was associated with the status of estrogen and progesterone receptors and inversely associated with the expression of the epidermal growth factor, the c–erb B2 protein and the nuclear accumulation of the p53 protein. Numerous immunohistochemical studies showed that 20-45% of breast cancers presented nuclear accumulations of mutant p53 and that the nuclear accumulations indicated unfavorable clinical evolution regardless of lymph node status. The p53 protein is first of all important for the prognosis offered by the protein status in the studied tumors (normal or mutant type). Tumors with mutant p53 are more aggressive and less responsive to classical therapy. Therefore, the determination of gene p53 mutations becomes crucial for selecting the appropriate therapy in each patient. ***PDGF*** is a major mitogen and chemoattractant for fibroblasts, lyse muscle cells and glial cells. PDGF has three isoforms, each with different receptor affinity. It takes the form of a homodimer bound to a disulphide bridge or a heterodimer made of chains A and B. Chain B of the PDGF was identified as a proto-oncogene (homologous to *v-sis*).Antiangiogenic therapy is a novel treatment approach for cancer [16]. The ***bcl-2 protein*** family is a central regulator of the intrinsic signaling pathways. The overexpression of genes bcl+2 or bcl+x occurs in more than 50% of cancers, rendering tumor cells resistant to apoptotic stimuli [13, 19].

The c-erbB-2 overexpression was reported to be an unfavorable prognostic indicator independent of lymph node status. The determination of this gene expression in the primary tumor could select the groups with unfavorable or good prognosis [13].

Status of progesterone receptors according to Kyoung (90 ***- positive – negative – unknown***

Despite the numerous newly available treatment options (chemotherapy, hormone therapy, immune therapy), only a slight decrease in mortality rate was registered between 1930 and 1998 (1.6% a

year from 1989 to 1995 and 3.4% in recent years). These statistics show that the new treatment strategies still have a low impact on survival [3]. Breast cancer mortality in young patients was explained by the incidence of the primary tumor in such patients.

The discovery of additional predictive factors would better identify the patients able to undergo treatment with curative intent. However, the "curative intent" is not the target in most patients, who usually receive conservative treatment with low toxicity.

Since survival is the primary aim, patient quality of life is measured with difficulty. It covers multidimensional physical (symptoms caused by cancer or drug toxicity), psychological and social (family or work relations, friendships) concepts, which are usually subjective elements [20].

The effort to detect patients with the highest probability of benefitting from life-prolonging treatment and to establish the most effective treatment in terms of efficiency and toxicity is a real challenge for the clinician. Metastases are incurable despite the advanced treatments available. Consequently, conventional or endocrine chemotherapy still constitute palliative treatment aimed at reducing symptoms, improving quality of life and prolonging survival. The early detection of metastases has proved beneficial? Yanamata observed that early detection did not have any benefits for patients with good performance status, low number of metastases and no associated diseases. However, metastases may be treated more efficiently if detected early, thus prolonging patient survival and quality of life. People living in modern society are full of much pressure from all kinds of environment every day and with the great change of dining habit people easily have many chronic diseases. Most chronic diseases need special care from nursing staff to remind of when to have the correct medicine. Long survival of patients with breast cancer transform this diseas in a chronic disease. [21].

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 [19].

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. The analysis of sputum taken from patients can be an extremely valuable technique for an early detection diagnosis of lung cancer and may be for pulmonary metastases. [22] New studies can do more for this patients

7 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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