UNIVERSITY OF MEDICINE AND PHARMACY OF CRAIOVA
FACULTY OF GENERAL MEDICINE

DOCTOR’S DEGREE THESIS
ABSTRACT

CLINICAL, HISTOLOGICAL AND IMMUNOHISTOCHEMICAL STUDY IN A GROUP OF PATIENTS WITH BREAST CANCERS

SCIENTIFIC SUPERVISER
Prof.Univ.Dr. Laurentiu Mogoanta

Trainer for a doctor degree
Dragos Mihai  PLEȘAN

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SYNTESIS OF THE DOCTOR’S DEGREE THESIS MAIN PARTS

This thesis was structured on two parts: a general parts and a special one. As concerning the former, we registered and discussed information of the literature, which were brought up to date, and reported on subjects as: histology, immunohistology and the treatment of the breast cancers.

In the special part, we presented the motivation and objectives of the research, the results of personal observations, and we discussed them within some identical preoccupations in our country and abroad.

I. MOTIVATION, OBJECTIVES AND AIM OF THE RESEARCH

The study of the breast cancers was focussed on three directions, topics, such as:
- clinical study,
- histopathological study,
- immunohistochemical study.

Clinical study was performed in 562 pacients and the diagnosis of the breast cancers was established for all of them. We followed to distribute the tumors on such criteria as sex, age, residence place, tumor site, macroscopical aspect, signs and symptoms. We also studied the TNM staging, metastases, number of metastatic locations, synchronous metastases, overall survival at 5 year.

Histopathological study was performed in 562 pacients for a period of 10 years, from 1996 to 2005. Here we followed the site of the tumors, their macroscopic aspects, tumoral size, histologic type, histologic grade, invasion of the lymphnodes, pTNM classification.

Immunohistochemical study. This chapter comprised a correlative immunohistochemical study of cell proliferative activities and of oncogenes(p53), hormonal receptors, Her 2 neu from the breast carcinomas. We have studied 100 pacients of the 562 breast carcinomas. The aim of this study was to reveal some correlations between the cell proliferation markers Ki67, P53 and hormonal receptors, Her 2 neu and the histologic degree and the prognostic in the breast cancers.
II. PERSONAL RESEARCH PRESENTATION

A. CLINICAL AND STATISTICAL STUDY

*Breast cancer incidence* was 21, 91/100000 inhabitants, in Mehedinti county, from 1996 to 2005. It increased from 19, 95/100000 in 1995 to 30, 49/100000 in 2006. *Mortality* determined by breast cancer was of 11, 7/100000, in the same place and the same time mentioned above.

From all the cases hospitalized into the Clinical Hospital Drobeta Tr-Severin along a period of 10 years, 1996-2005, a number of 562 patients was diagnosed as having a breast cancer.

*Women/male rate* was 1,01/98.9 in patients with breast cancers. It were only 6 males out of 562 patients with breast cancers.

*Age incidence* of breast cancer was highest in the age group 50-59 years and included 158 patients (28.11%). Old age has a huge impact on the incidence of breast cancer. The age is more advanced with greater risk of breast cancer.

*Signs and symptoms* The most common signs and symptoms were: breast tumor 522 patients (93%), homolateral axillary adenopathy in 382 patients (68%), carcinomatous mastitis in 39 patients (6.9%), edema arm in 21 patients (3.7%), nipple discharge from nine patients (1.6%), bone metastases in 27 patients (4.8%), liver metastases in 18 patients (3.2%).

The most common *histological types* were: invasive ductal carcinoma in 138 patients representing 90%, invasive lobular carcinoma in 7 patients (4.6%), carcinoma in situ in one patient (0.8%), medullary carcinoma in 3 patients (2%) of cases, sarcoma in one patient (0.7%), squamous cell carcinoma in one patient (0.7%) and metastatic carcinoma in one patient (0.7%).

The distribution of *tumor histological grading* according to the histological grading was as follows: histological grading G1 in 35 patients (22%), G2 histological grading in 76 patients (50%), histological grading G3 in 41 patients (23%).

*TNM staging* was possible in 532 patients representing 94.66% of cases and in 30 patients (5.93%) of patients status was unknown. Distribution by TNM stage was as follows: stage I was determined in 18 cases (3.2%), stage II in 177 cases (31.49%), stage III in 275 cases (48.93%), stage IV was diagnosed in 62 cases (11.03%), the stage was unknown in 30 patients (5.93%).
Metastases were present in 110 patients, either initially as stage IV disease, 62 patients (56.36%) or occurred later in the disease progression in 50 patients (45.45%). Headquarters metastases was: bone metataze 61 patients (55.45%), liver metastases in 28 patients (25.45%), pleural metastases in 20 patients (18.18%), lung metastases in 19 patients (17.27%), lymph node metastases in 14 patients (12.72%), metastases in 9 patients (8.18%), peritoneal metastases in 9 patients (8.18%), skin metastases in 6 patients (5.45%), percardice metastases in 3 patients (2.72%).

The number of metastatic locations: 56.36% 1 single metastatic site, 2 sites metastatic to 33.63%, 3 metastatic to 9.09% and 4 metastatic to 0.9% metastatic locations.

Synchronous metastases group of 562 breast cancer patients studied, 62 patients had synchronous metastases at diagnosis, representing 11.03%. The frequency of metastases was: 61.8% bone metastases, liver metastases 21.7%, 31.4% pleural metastases, pulmonare14, 2%, cerbrale 2.3%, 3.5% skin.

Overall survival at 5 years survival for all stages was 50.43%
Survival at 5 years in breast cancer assigned to the stages was: stage I was 90.90%, 75.28% for stage II to stage III of 43.42% for stage IV was 19 56%.
Survival at 5 years in the entire study group (353 cases) was 49.85%. The number of cases dead at 5 years from diagnosis was 176 representing 50.14%.

The number of deaths divided by years had the following developments: 1 year 65 cases died (36.7%) died at two years 61 cases (34.4%) died at 3 years 21 cases (11, 8%) died at 4 years 17 cases (9.6%) at 5 years died 6 cases (2.8%).

B. HISTOPATHOLOGIC STUDY OF THE BREAST CANCERS

Histopathological study allowed a first step, the classification of 562 invasive breast carcinomas, according to WHO classification, in one of the following types and subtypes: invasive ductal carcinoma NOS (not otherwise Specified - non-specific type invasive ductal carcinoma)-385 cases (68.51%), invasive lobular carcinoma-84 cases (14.94%), classical type-47 cases (55.95%), solid type-9 cases (10.71%), alveolar type-14 cases (16.66%), tubulo-lobular type-4 cases (4.76%), pleiomorf (including type histiocitoid pleiomorf and signet ring cells)-10 cases (10.90%), lobular carcinoma mixed-ducto-29 cases (5.16%), tubular carcinoma-18 cases
Invasive cribriform carcinoma-12 cases (2.13%), mucinous carcinoma-11 cases (1.96%), type hipocellular-8 cases, type hipercelular-3 cases, medullary carcinoma-6 cases (1.07%), invasive carcinoma micropapilar-7 cases (1.25%), glycogen-rich cell carcinoma-5 cases (0.89%), carcinoma metaplasia: pure squamous cell carcinoma-4 cases (0.71%), adenoid cystic carcinoma -1case(0.17%).

The degree of tumor differentiation (histologic grade of malignancy) was assessed by Nottingham grading system, tumors were classified as: G1: 96 invasive breast carcinoma cases (17.08%), G2: 265 invasive breast carcinoma cases (47.16%), G3: 201 invasive breast carcinoma cases (35.76%).

Invasive ductal carcinoma NOS (not otherwise specified, nonspecific type) was the highest proportion of breast carcinomas studied, was diagnosed in 385 patients and thus representing 68.51% of cases of infiltrating breast carcinoma.

Invasive lobular carcinomas were diagnosed in 84 patients, representing 14.94% of the cases included in the study group.

Lobular carcinoma classic type was diagnosed in 47 cases, representing 55.95% of invasive lobular carcinomas in this study.

Invasive lobular carcinoma of solid type was diagnosed in 9 patients, representing 10.71% of all infiltrating lobular carcinomas.

Invasive lobular carcinoma of alveolar type was found in 14 patients, representing 16.66% of all infiltrating lobular carcinomas.

Lobular carcinoma with signet ring cells was diagnosed in 2 cases.

Breast carcinoma lobular carcinoma-type mixed ducto-lobular was revealed in 29 cases that represented 5.16% of all invasive breast carcinomas studied.

Tubular carcinoma was found in this study in 18 cases, representing 3.2% of all invasive breast carcinomas studied.

Medullary carcinoma was diagnosed in 6 cases, representing 1.07% of carcinomas included in the study.

Mucinous carcinoma was diagnosed in 11 cases in patients over 55 years and represented 1.96% of the cases analyzed.

C. IMMUNOHISTOCHEMICAL STUDY OF THE COLORECTAL STUDY

All 100 cases of invasive breast carcinoma studied in the period between 1996-2005, were processed histopathologically and immunohistochemically. The cases analyzed were mammary tumors belonging to patients aged 28 and 78 years (37 patients under 50 years and
63 patients ≥ 50 years). Tumors were smaller or equal to 2 cm in 35 cases and more than 2 cm in 65 cases.

Assess the status of estrogen and progesterone receptors

Estrogen receptors (ER) were tested positive (Allred score ≥ 3) in 61% of cases and progesterone receptor (PR) in 64% of cases.

Reported the histological type, invasive ductal carcinomas expressed estrogen receptors in 53 cases (58.88%) and progesterone receptors in 57 cases (63.33%), invasive lobular carcinomas while estrogen receptor expressed in 8 cases (80%) and progesterone receptors in 7 cases (70%).

Depending on immunoreaction, hormone receptor breast carcinomas are classified into four subtypes or phenotypes. Thus, to describe mammary carcinomas expressing both hormone receptor (ER phenotype positive / PR positive) breast carcinomas negative for both hormone receptors (ER phenotype negative / PR negative) and mammary carcinomas expressing only one hormone receptors (heterogeneous phenotypes: ER negative / PR positive and ER positive / PR negative).

Most cases (57%) had both types of receptors with a phenotype positive ER / PR positive. 32% of cases were completely devoid of hormone receptor phenotype with a negative ER / PR negative. The remaining cases (11%) had a heterogeneous phenotype. Thus, 7% of cases were ER negative / PR positive and 4% of cases were ER positive / PR negative (Table 6).

The phenotype of ER positive / PR positive was found in 55.55% (50 cases) of invasive ductal carcinomas vs. 70% (7 cases) of invasive lobular carcinomas and phenotype negative ER / PR negative was present in 33.33% (30 cases) of ductal carcinomas vs. 20% (2 cases) of lobular carcinomas. A particular phenotype of anti-hormonal therapy results, evolution and prognosis is positive ER / PR negative, therefore we analyzed the phenotype compared to the classic phenotype of ER positive / PR positive by some morphological and clinical parameters: age patients, tumor size, histological type and grade of tumors.

Thus, the phenotype of ER positive / PR negative was most common in patients over 50 years, compared with the phenotype of ER positive / PR positive (75% of cases vs. 68.42%). Tumors positive ER / PR negative were higher (more than 2 cm) tumors than ER positive / PR positive (50% of cases vs. 42.11%). The majority of tumors positive ER / PR negative were invasive ductal carcinoma type, they more frequently expressing phenotype ER + / PR-than lobular carcinomas (75% cases vs 25% case). He noted that all cases positive ER / PR negative values were quite low estrogen Allred score, this score is below 6.

Analysis of the HER2 staining revealed the 15 cases (15% of the cases studied) of invasive breast carcinoma in HER2-positive. Of these 10 cases
(representing 66.66%) were weakly positive (score 2 +), and 5 cases (representing 33.34%) were interpreted to score 3 + (positive) ASCO-CAP criteria. After correlating morphological parameters imunomarcajului clinics HER2 was observed that HER2 positive tumors belonged slightly more frequently in patients under 50 years (8 cases, ie 53.33%) than those over 50 years (7 cases, and 46, 67%). HER2 positive tumors were more common tumors over 2 cm in size. Thus, eight tumor size over 2 cm (representing 53.33%) were HER2 positive, whereas 7 tumors smaller than 2 cm (representing 46.67%) were HER2 negative. Correlating of HER2 staining tumors with their histological type was observed that one case of lobular type carcinoma (10% of lobular carcinomas were HER2 positive) was moderate HER2 positive (score 2 +). All other 14 cases were HER2-positive ductal type (9 cases with score 2 + and 5 cases with score 3 +). Thus, 15.55% of ductal carcinomas were HER2 positive inavzive. Similarly, tumors were HER2 positive type in the percentage of 6.66% lobular and ductal type in a percentage of 93.34% of cases.

With regard to histological grade, HER2 mostly positive (12 cases and 80%) were high grade (G3) and only 3 cases (20%) had low histological grade (G1 and G2). Thus, all 14 cases, histological grade G1 were HER2-negative, histological grade G2 cases were positive rate of only 6.52% (3 cases), while histological grade G3 tumors were positive in proportion 30% of cases (12 cases).

Ki-67 imunostaining analysis revealed the presence of the Ki-67 positivity of this marker in all cases studied. Most cases had a nuclear marker Ki 67, but two cases (2% of cases) had marked cytoplasmic / membrane. Specific marker Ki 67 is nuclear and was found in 98 cases. Thus, we found that patients younger than 50 years had more frequently a high Ki67 index (over 15% of tumor cells is positive to Ki 67) compared with patients over 50 years (60% of cases vs. 55.55% ). The patients with tumors larger than 2 cm were more often Ki 67 index high compared to those with tumors less than 2 cm (71.42% vs. 51.43%).

Regarding the histological type of carcinoma lobular type analysis, the Ki 67 index had decreased in all cases, while invasive ductal type Ki 67 index had dropped 43.87% of cases and high-index 56.12% of cases. Compared to histological grade, high grade tumors (G3) have always had a high index Ki 67, compared with low grade tumors (G1/G2) who had a proliferation index increased only 8.62% of cases. An increased proliferative activity (Ki 67 index level) were observed more frequently in tumors without estrogen receptors compared with those who were ER positive (48.72% vs. 27.11% of cases had a high proliferation
index). Also, progesterone negative tumors had a proliferative activity determined by Ki 67, higher than progesterone positive tumors (38.88% vs. 30.64% of cases had a high index Ki 67). A proliferative index was increased in most tumors with HER2 score 2+ and 3+. Thus, 93.34% of HER2-positive tumors had proliferative activity of over 15%, compared with only 6.66% tumor proliferative activity below 15%. Differences were less significant in the HER2-negative tumors, in which 79.52% had Ki 67 index and 20.48% had high Ki 67 index declined. As a result, a high index Ki 67 was observed more frequently in HER2-positive tumors compared with HER2-negative (93.34% vs. 79.52%). Ki-67 index was correlated in this study and immunoperoxidase oncoprotein p53 (see below).

*Imunostaining for p53* identified the presence of p53 protein overexpression (over 10% tumor cells labeled with this antibody) in 42 cases (42% of the cases studied). Tumors with p53 overexpression were more frequent in patients under 50 years (23 cases, 54.76% respectively) than those over 50 years (19 cases, 45.24% respectively). P53 positive tumors were more common in tumor size over 2 cm. Thus, 28 tumors of p53 positive tumors (representing 66.64% of the p53 overexpression group) had size over 2 cm, while only 14 of p53 positive tumors (representing 33.33% of the p53 overexpression group) have was smaller than 2 cm.

Invasive ductal carcinoma type p53 were positive in 40 cases, representing 44.44% of all cases of ductal invasive and lobular invasive type the only two cases, representing 20% of all cases of invasive lobular breast carcinoma type. Thus, p53 overexpression was interested much less invasive lobular carcinoma type (4.76%) than the invasive ductal type (95.24%).

With regard to histological grade, p53 protein overexpression most cases (30 cases, 71.43% respectively) were high grade (G3) and only 12 cases (28.57%) had low histological grade (G1 and G2). Thus, 75% of high-grade carcinomas were overexpressed p53 protein, while only 20% of low grade (G2/G3) had this feature. Association between overexpression p53 (p53 over 10%) with HER2 overexpression (score 2+ or 3+) was present in 7 patients. Thus, p53 and HER 2 coexpression was found in 7% of cases of invasive breast carcinoma included in this study. Therefore 16.66% of cases showed p53 positivity associated positive for HER2. Of these cases coexpression p53 and HER 2, most (5 cases representing 71.42%) had an index of cell proliferation by 30%.
Immunohistochemical overexpression of p53 was found in 46.66% as of the 15 cases HER2 positive (score 2 + and 3 +) and only in 35 cases (41.17%) of the 85 HER2-negative cases (score 0 and 1 +). Overexpression of p53 (corresponding to increased amounts of p53 protein determined by IHC) was more frequent in HER2 positive breast carcinomas compared to HER2 negative (46.66% vs. 41.17%). Most cases were p53 positive had a higher proliferative activity determined by Ki 67. Thus, 76.19% (32 cases) of p53 positive cases had a proliferation index above 15%, and only 54.76% of cases (23 cases) had a proliferation index of over 30%.

III. DISCUSSIONS OF THE RESULTS

In the “Discussion of the results” chapter we compared our results to the literature from our country and abroad.

VI. CONCLUSIONS

**Statistical and clinical study** was conducted for a period of 10 years, 1996-2005 and included 562 patients with breast cancer. **Male / female ratio** was 1.01 / 98.9, breast cancer is present in only 6 patients in the group of 562 male patients. **Age incidence** of breast cancer was highest in the age group 50-59 years and included 158 patients (28.11%). **Location** of left breast cancer was present in 286 cases (50.88%), the right breast was 271 cases (48.22%) and bilateral breast cancer was present in 5 cases (0.88%). Most common **histological types** were ductal invasive carcinoma 90% of patients, invasive lobular carcinoma 4.6%, 0.8% carcinoma in situ, medullary carcinoma in 2% of cases, sarcoma in 0.7%, squamous cell carcinoma and carcinoma metastatic to 0.7% to 0.7%.

The distribution of **tumor histological grading** according to the histological grading was as follows: histological grading G1 to 22%, histological grading in 50% of G2 and G3 histological grading in 23% of cases. **TNM staging** was possible in 94.66% of cases, and to 5.93% of the patients status was unknown. **Distribution by TNM stage** was: stage I was determined in 18 cases (3.2%), stage II in 177 cases (31.49%), stage III in 275 cases (48.93%), stage IV was diagnosed in 62 cases (11.03%), the stage was unknown to 5.93% of patients. **Metastases** were diagnosed in 62 cases (11.03%). Headquarters metastases was: 55.45% metataze bone, liver metastases from 25.45% to 18.18% of pleural metastases, lung metastases from 17.27% to 12.72% lymph node.
metastases, metastases in 8, 18%, peritoneal metastases from 8.18% to 2.72% metataze percardice. 
The number of metastatic locations were: a single site metastatic to 56.36%, 2 sites metastatic to 33.63%, 3 offices and 4 metastatic to 9.09% to 0.9% metastatic locations. 
Overall survival at 5 years for all stages was 50.43%. 
Survival at 5 years breast cancer has been assigned the following stages: stage I was 90.90%, 75.28% for stage II to stage III of 43.42% and for stage IV was 19.56%.

Histopathologic study of invasive breast carcinomas revealed the wide variety of histological types between dominating type invasive ductal carcinoma classic type NOS with 68.51% of cases. Net morphological separation of mammary carcinomas in various histological types was crucial, it provides clear data on the subsequent development of disease and by identifying particular types of breast carcinoma with a poor prognosis: metaplasia (4 cases), micropapilar (7 cases ) pleiomorfe lobular (10 cases) and those with favorable prognosis, survival and recurrence rate than low: tubular, mucinous, adenoid-cystic, cribriform invasive bone marrow.

Study on a group of patients allowed detection of extremely rare histological forms of breast carcinoma such as adenoid cystic carcinoma, squamous cell carcinoma pure medullary carcinoma cells and rich in glycogen. Invasive lobular carcinomas were most common (14.94% of cases) type of breast carcinoma as invasive ductal carcinoma NOS type and presented in a wide range of variants (classic, solid, alveolar, tubulo-lobular, pleiomorf, histiocitoid and signet ring cells). Identification of non-classical lobular carcinomas (37 cases) allowed selection of patients at risk of developing distant metastases and reduced disease-free survival.

Histological grading of breast carcinomas is hardly reproducible and difficult, but allowed the prognosis of patients included in the study. It was identified a large number of patients (201 patients reprezentând 35.76%) who had a high histologic grade (G3) correlate with a poor prognosis compared with patients whose tumors were well differentiated (G1, 91 cases, representing 17.08%).

Immunohistochemical study of invasive breast carcinomas have studied 100 patients with breast carcinoma. Hormone receptor immunohistochemical detection method allowed pecientelor receptor positive selection, the only subgroup receiving tamoxifen therapy. Corelated assessment related to estrogen and progesterone receptor imunoexpresion improve their predictive value in
identifying tumors with heterogeneous phenotype. Compared with phenotype classic ER + / PR +, a subgroup distinct breast carcinomas invasive is the phenotype ER + / PR -, which is more common in patients over 50 who had tumors larger than 2 cm, type ductal carcinoma invasive.

Detectarea patients with ER + /PR- phenotype enabled the selection of cases with clinical and biological features aggressive, which will have a decreased response to hormone therapy, these cases with a constant low level of ER receptors(score below 6).

Patients with age under 50 presented twice as often HER2 positive. Lobular carcinoma of the study group could be as aggressive as the ductal since invasive lobular breast carcinomas subgroup of HER2-overexpressed in a relatively similar to invasive ductal breast carcinomas subgroup. Constant presence to unite HER2 score higher in situ component of invasive carcinomas analyzed compared to the component suggested that HER2 plays an important role in the early stages of mammary tumorigenesis. Overexpression of HER2 protein intensity is frequently associated with poorly differentiated tumors and those without hormone reptiles. Identification of cases with HER2 and ER coexpression allowed the selection of patients who develop resistance to hormonal therapy and have a poor outcome.

Ki67 immunostaining done in a very small proportion of cases an unusual pattern membrane / cytoplasmic type of reactivity, appears to be associated with a poor prognosis(2% of the cases study). Increased cell proliferative activity correlated well with high histological grade (G3) of carcinomas, being more common in poorly differentiated tumors compared with well / moderately differentiated (100% vs. 8.62%). Cell proliferative activity and hormone receptor status were often in an inverse relationship.

P53 overexpression is more frequent in patients under age 50 with tumors over 2 cm, invasive ductal type with high histological grade. High rate of p53 oncoprotein overexpression in patients with heterogeneous phenotype hormonal receptors and those with hormone receptor-absent, compared with patients with double-positive phenotype, may explain the unfavorable prognosis of tumors lacking one or both hormone receptors. Coexpression p53 protein with HER2 was associated always a very high proliferative activity of these tumors, giving them an increased malignancy. Identifying cases with mutations of the p53 protein can select a group of patients with higher risk of recurrence and death, and p53 expression testing in patients HER2 positive tumors identified subset will benefit from aggressive treatment more aggressive.
V. KEYWORDS
Breast cancer, histopathology type, estrogen and progesterone receptors, Her2 neu, p53, ki 67 protein.

VI. CURRICULUM VITAE

First Name PLEȘAN DRAGOS MICHAEL
Address: Str. No. V. Babes. 4, Rev. 3, Sc. 2, BI-Tr TN19 Dr Severin, Mehedinti, Romania
Mobile Phone: 0744836391
E-Mail: dragomax2000s@yahoo.com
Born: 16 August 1980, Dr Tr Severin
Language: ROMANIAN
Languages: English French
Reading skills: Very Good Good
Writing skills: Very Good Good
Talking skills: Very Good Good

Use computer skills and competences (European license
Computer technical management-2005)
-Driver, Class B

Education and Training
1995-1999: Ministry of Education, School Trajan (No. theory. 1) Dr Tr Severin-formal education courses at Day
1999-2005: Ministry of Education, University of Craiova, Faculty of Medicine, Craiova-formal education courses at Day
2005: PhD Pharmacy Craiova, discipline normal and pathological physiology
2005: European Computer Driving Licence (ECDL Certificate)
2005-2008: Resident, Family Medicine specialist, Severin County Hospital
2008: Assistant professor UMF Craiova, discipline Gynecology
2008-present: Resident in Obstetrics and Gynecology, Hospital NR2 philanthropic Craiova.
2008: Test of English as a foreign langue (TOEFL) (B2)
2009: Certificate of Proficiency in English (CPE) (B2)
2011: Diploma of Medical Francais (B2)
Title of qualification: Doctor Doctor / Master's Degree
Main subjects: curative medicine
Classification level of education: Higher Medical Education

VII. PAPERWORKS

Scientific papers worked out by the author, presented in different national manifestation and/or published in journals of speciality.


