DOCTORAL DISSERTATION

Therapeutical options in breast cancer. Critical evaluation.

Results

Scientifical manager
Prof. Dr. Nemeș Răducu Nicolae

Doctorand
Dr. Milena Georgescu

Craiova
2011
CONTENTS

Surgical anatomy of the mammary gland
Cancer of the mammary gland
Epidemiology and risk factors
Pathologic anatomy
Morphologic criteria of prognosis
Natural history
Evolution of cancer of mammary gland
Diagnosis of breast cancer
Screening
Clinical examination
Paraclinical investigations
Peculiar clinical forms
Differential diagnosis
Staging
Treatment
Surgery
Radiotherapy
Chemotherapy and hormonotherapy
Categories and therapeutic indications
Personal research. Motivation for the study. Material and method

4. EPIDEMIOLOGIE. FACTORI DE RISC

Epidemiology. Risk factors
Occurrence (incidence)
Risk factors
Age
Background. Occupation. Education level
Significant Personal and family antecedents
Diagnosis. Staging
Clinical diagnosis
The beginning of subjective clinical signs
Objective examination. Semiologic characteristics of the tumor useful to staging
Image diagnosis
Morphopathologic diagnosis
Presurgery Morphopathologic diagnosis
Postsurgery Morphopathologic diagnosis
Staging
Clinical TNM staging (pretherapeutic, presurgery)
Ptnm anatomopathologic staging
Treatment
Surgical treatment
Conservative surgery
Radical surgery
Presurgery Neoadjuvant treatment
Postsurgery Adjuvant treatment
Adjuvant treatment following conservative surgery
Adjuvant treatment following radical surgery
Results
Evolution. Postsurgery complications
Relapse and long distance survival
Posttherapeutic relapse
Rate of long distance/long term survival in patients with breast cancer
Introduction

Mammary cancer represents an important public health issue, having a high occurrence worldwide (20-25% of the total of breast cancers with women), with an obvious increasing tendency; thus, in 2006, the annual occurrence adjusted depending on age of patients with breast cancer in the European Union (data collected from 25 countries) was of 110.3/100,000 women, and the annual death rate due to breast cancer was of 25/100,000 women. The increase of occurrence of breast cancer can be justified by the introduction of screening by mammography and to the increase of life expectancy amongst the population. The death rate has significantly decreased especially in the subgroup of young patients, due to early discovery of breast cancer and due to the improvement of therapeutic options. In spite of all this, with European women breast cancer is still the main cause of death by cancer, the death rate reaching 15-20%.

The past few decades were marked by important conceptual changes in the treatment of breast cancer, changes regarding the ratio and sequentially of each of the therapeutic means found today in the therapeutic arsenal of breast cancer. A first remark is that, even though mammary cancer benefits by important discoveries made in the domain of chemotherapy, surgery remains the main element in the therapeutic algorithm of mammary cancer. There is a significant tendency for restraining the extension of the surgical gesture, which has lead to the emergence of two different attitudes: radical surgery and conservative surgery, towards which there still are in our country a number of doubts.

Prospective and retrospective studies have shown that at 20 years old, both the conservative and the radical therapy have the same survival rate and free interval of disease, at least for mammary cancers in stages I and II, the only real counter-argument in disfavor of conservative surgery being that this is characterized by a higher rate of local relapses, obstacle which can be overcome by post-surgery radiotherapy. The rate of long-distance survival is the main parameter of evaluation in the evaluation of the efficiency of treatment of breast cancer, as in any other form of cancer. This complex parameter reflects, besides the efficiency of medical gestures, the efficiency of a coherent national program which must include the mass discovery of breast cancer by screening methods, the constant improvement of the population’s level of health education, the registration of new cases and the monitoring of previous cases, which supposes the existence of a national register of cancer and the active involvement of all stakeholders and execution factors. Unfortunately, in our country all these elements, which should contribute to the improvement of disease diagnosis, face serious conceptual and organizational deficiencies.

Valuing the experience of two prestigious clinics from Craiova, Clinic I Surgery and Clinic Surgery IV CFR, interpreted in the light of conceptual ethiopathogenic changes and therapeutic changes mentioned in specialty literature of the past few years and entered now in the current practice, we have undertaken in the current thesis a clinical comparative retrospective study, whose aim was the evaluation of two therapeutic surgery options in the treatment of breast cancer.

I thank to all those who have helped me to accomplish this research, the two clinic managers Professor PhD Ion Georgescu and Professor PhD Dan Mogoş, who put at my disposal the clinical material for this study, as well as to my PhD coordinator Professor PhD
PERSONAL RESEARCH. MOTIVATION OF THE STUDY.

MATERIAL AND METHOD

Starting from the current status of the issue, synthesized in the information mentioned above, we have carried out a clinical comparative retrospective study, whose aim was the evaluation of the weight of this two therapeutic surgery options in the treatment of breast cancer. We have included in our study a number of 377 case of patients with breast cancer who have been hospitalized in the previous 5 years (2005-2009) in the clinics Surgery I and surgery IV, divided into two groups (picture no 1) Group A- 171 female patients suffering from this disease, belonging to Clinic I Surgery Craiova and Group B- 206 female patients with breast cancer, pertaining to Clinic IV Surgery Craiova.

We have excluded from our group of study male patients due to the small number of cases (3), which would not have allowed any significant conclusions. The data necessary for the study were collected from the clinical observation factsheets, the surgery protocols, the results of biologic and/or bacteriologic examinations (biopsy puncture, extemporaneous histopathological exam, the examination of resected pieces after inclusion in paraffin), the reports and/or protocols of imaging examinations and necropsy protocols.

For each studied case there was drawn a factsheet, which included personal data, epidemiological data (incidence, age, gender, background, occupation), ethiopathogenic data, data referring to the biological status of female patients (co-morbidities without ethiopathogenic implications), elements of clinical diagnosis, paraclinical biological and imaging investigations, elements of morphopathological diagnosis (biopsy puncture, extemporaneous histopathological exam, the examination of resected pieces after inclusion in paraffin), histochemical exam for establishing the hormonal profile, postsurgery and presurgery staging (pTNM), ways of solving through surgery (radical or conservative surgery) and the type of used surgeries, adjuvant therapy and neoadjuvant therapy, evolution and complications (local and/or general, immediate or at distance, local or systemic relapse, survival rate, death rate). The obtained date were centralized and statistically processed with the help of Excel.

RESULTS DISCUSSION

In the study there were included 377 female patients with breast cancer who were hospitalized and subject to surgery during 2005-2009 in the clinics Surgery I (Group A 171 patients) and Surgery IV CFR (group B 206 patients).

The epidemiological study focused on two main axes: disease occurrence/incidence and risk factors.

According to specialty literature [88, 89, 90], we have noticed a strong tendency of annual increase of incidence of mammary cancers with the two groups, as well as the fact that the report cancer/benign mammary cancer was of 1.17/1, mammary cancer representing 53.94% of the total of mammary gland diseases of patients hospitalized in the two surgery clinics. The age represented one of the main risk factors [91, 92, 93, 94]; the data of our study, even though they mainly confirm the specialty literature data, have offered us the possibility to notice some peculiarities that differentiate it:

- the average age at the moment of establishing the diagnosis is higher than the average age mentioned in specialty literature: 61.97 years old for group A (Surgery I) and 59.42 years old for female patients in group B (Surgery IV CFR), with extremes between 23 years old
and 85 years old for the first group and between 31 years old and 82 years old for the second group;

-most of the cases are distributed in the decades VI and VII (55.5% for group A and 60.1% for group B) while specialty literature situates the maximum incidence of the disease in the decades IV-VI.

- the existence of an important number of breast cancer with female patients over 70 years old (46=26.9% in the group A, respectively 40=19.41 % in group B), age group subject to important co-morbidities, which can limit or contradict some of the therapeutic sequences.

Background, occupation and educational level are not considered risk factors directly involved in the emergence of mammary cancer. However, the social-economic status must be taken into account, since mammary gland cancer is more often encountered in all studies with women from social strata with high economic and educational status, probably due to the conjugation of factors linked to diet, age at first birth, use of estrogen hormones, coffee, alcohol, tobacco consumption and so on [95, 96, 97, 98].

From this point of view, our study has shown us some interesting data; thus, if in group A (Surgery I) there is a close distribution of female patients from the urban area and of female patients from the rural area (52% as compared to 48%), with a rate of 1.52/1, for group B, the prevalence of female patients from the urban area is more evident (63% as compared to 37%), with a rate of 2.21/1 in favor of the urban area.

As far as occupation and educational level are regarded, we have discovered that there is an obvious predominance of female patients from the intellectual background for group B as compared to group A (32/10), but also the fact that most of the female patients have retired 61.40% for group A, respectively 61.16% for group B), which can be explained taking into account that the average age is situated around 60 years old for both studied groups.

Analyzing the personal and family records and antecedents of female patients, we have grouped all the physiological and/or pathological circumstances that literature includes amongst the risk factors involved in the carcinogenesis of malignant mammary tumors [99, 100, 101, 102, 103].

A series of endogenous endocrine factors (age of first menstruation, age of beginning of menopause, parity, age of first term pregnancy) represents a prolonged stimulation of the mammary gland under the action of estrogens and increase the risk of emergence and development of mammary cancer; thus, precocious menarche, especially before 12 years old significantly increases the risk of emergence of mammary cancer, while late menopause (after 54 years old) doubles the risk of emergence of mammary cancer, as compared to natural menopause (round the age of 45 years old) [104, 105, 106, 107]. Early natural menopause of the menopause induced surgically decreases this risk. The parity was included amongst the risk factors of mammary cancer; thus, nulliparity or first birth after 30 years old increases the risk of emergence of mammary cancer 4 to 5 times, while the first pregnancy before 18 years old reduces it. Our study has revealed significant data from this point of view, the involvement of endogenous endocrine factors at more than 50% of cases being of: 51.46% (88 cases) in group A and 67.47% (139 cases) in group B, early menarche being the most often encountered endocrine disfunction, followed by late menopause, first birth after the age of 30 years old and nulliparity [108, 109, 110, 111]. In this category of risk factors we have included the use of birth control pills for more than 10 years, more frequently observed in group B. The explanation could be the fact that patients in group B mainly come from the urban environment and have a higher level of education than those in the first group [112, 113, 114, 115, 116].

Another category of risk factors on which we have focused was: family risk, which reflects an association of genetic influences and environmental influences. Any neoplasia of the mammary gland increases the risk that first grade relatives develop mammary cancer [117, 118, 119, 120]. On the studied clinical material we have discovered the presence of mammary of ovarian cancer at 5.89% of female patients belonging to group A and at 16.99% of patients belonging to group B.

Amongst the pathological antecedents at the level of the mammary gland we have noticed the presence of benign mammary tumors, considered pre-cancerous states,
encountered at 20% (19.41%) in group B and under 5% (3.50%) in group A, significant difference which we cannot explain.

Alcohol, coffee and tobacco consumption – uncertain risk factors – were noticed in variable proportions in our study, and the prolonged exposure to radiations in only one case. [121, 122, 123, 124, 125, 126].

Besides the pathological circumstances which can be frameworked in the category of risk factors, our study highlighted, in antecedents of female patients with mammary cancer, a significant number of co-morbidities, especially cardio-vascular and breathing co-morbidities. Taking into account the fact that the average age of female patients at the moment of establishing the diagnosis in the studied groups was about the average age of 60 years old, as well as the fact that almost 25% of the patients pertained to the age group 70 years old, the presence of co-morbidities has significant therapeutic implications, since it can limit or contradict some therapeutic sequences [127, 128, 129].

The clinical expression of breast cancer is poorer in subjective signs and/or functional signs. That is why, in most cases the first sign is the presence of the mammary tumor, discovered by chance by the patient. Our study registered this way of diagnosis in almost equal percentages (73.68% group A and 73.30% group B), within the limits of scientific literature data (65-80%).

Unilateral, constant, located pain, persisting after menstruation or at menopause, estimated in literature at 8% of less advanced cancers and 15% as associated symptom, was present on the case records studied by us in almost identical proportions (22.2% group I, respectively 22.3% group II) [130, 131, 132].

Abnormal mammary leaks were encountered in a small number of cases, with almost identical proportion for the two studied groups (4.09% group I and 4.85% group II) [133, 134, 135, 136].

We have not met the debut of the disease by axillary adenopathy without mammary tumor or the debut of the disease by systemic manifestations belonging to long term metastasis: bone aches, abdominal aches, chest pains, cough and neurological manifestations.

Taking into account the fact that in breast cancer, as in all cancers, the prognosis depends firstly on the precocity of the diagnosis, we have researched the lapse of time from the debut of the first signs of the disease till the moment of the first medical examination and the establishment of diagnosis and on the cumulated statistics of the two groups we have discovered that, even though breast cancer belongs to a superficially situated anatomical area, which can be seen and thus accessible to both selfexamination and to clinical examination, in less than 25% of cases the diagnosis was established in the first three months after the apparent beginning of the disease, most of the cases being situated in the interval 4-6 months (21.48%) and 7-12 months (25.19%), and in 15.69% of the cases the diagnosis was established at more than one year after the beginning of the disease, in advanced disease stages.

The local clinical exam, carried out by trained professionals can lead to this method close to the value of mammography and can be accepted as screening method. The clinical breast examination must be carried out in the premenstrual period, when gland density decreases, the investigation/inspection and palpation being the two essential steps of this examination.

The bilateral inspection, as compared to the controlateral breast in different postures which can allow the emphasis of otherwise unapparent changes, is able to identify: changes in volume, asymmetries, tegumental anomalies (retractions, erythema, oedema, ulcerations, eczematiform lesions, ecchymoses, scars), changes of areola and of the nipple (asymmetries, axis deviation, retraction or umbilication of the nipple, erythema, erosions or nipple crusts) [137, 138, 139, 140].

Palpation has emphasized the presence of the tumor and after identifying and isolating it there have been searched its semiologic characteristics, especially those which define the malignant characteristic. The topography of the primary tumor was one of the main studied
parameters; our study has revealed an almost equal proportion of mammary cancer at the two breasts, with a minimum prevalence for the left breast in group B (51/49%) and more expressed in group A (53/47%). As far as the distribution at the level of the mammary gland is regarded, we have noticed that the most frequent location of breast cancer is the supero-external dial (43.9% in group A and 41.7% in group B), followed by the supero-internal dials, infero-internal dials and central dials and in 13.5% cases the primary tumor was located at the limit between the dials.

The dimension (largest diameter) represents one of the most important parameters in the appreciation and staging framework of mammary cancer. That is why, it must be determined with accuracy, measured with a sliding instrument and we must pay attention to the fact that the stromal reaction and the oedema always increase the tumor’s real dimensions, which must be also measured on the mammographic or echographic image [141, 142, 143]. The tumor’s dimensions on the investigated group varied between 0.5 cm (the smallest tumor identifiable by palpation) and 20 cm in diameter. Using the standard dimensions in staging classification TNM for category T, we have discovered that most of the tumors (52.66% group A and 59.40% group B) were recorded in category T2, with a maximum diameter between 2 and 5 centimeters. For all the other categories, the tumors’ dimensions were different for the two groups; thus, in group A the ratio T3/T1 was of 33/24 cases, while in group B the tumors in category T1 were prevalent (T1/T3=54/28), fact which will be also reflected in the therapeutic approach, that will be analyzed later.

The tumor’s dimensions do not represent the only parameter used for definition of T category in TNM classification, since it is completed by the form and the limits/margins of the tumors, its consistency, its sensitivity and the mobility of the tumor as related to the tissues and subjacent plans. The clinical characteristics of the malignant tumor defined in literature and recorded by us were: the irregular form, with diffuse limits, firm consistency (83% group A, 71% group B), uneven, adherence to teguments (38% group A respectively 24% group B) and/or profound plans (25% group A and 8% group B), not causing pain. Most of the times, some of the malignancy characteristics lack, especially in the beginning phases of the disease or sometimes, benign tumors can present some of the above mentioned signs, which renders the differential diagnosis between malignant tumors and benign tumors difficult to achieve only through clinical criteria.

The second semilogic parameter essential to pretherapeutic staging is the evaluation of adenopathy (N category) which must establish whether or not the adenopathy is malignant and in which N category can be framed, clinical elements which increase the suspicion of ganglionary invasion being: dimension exceeding 1 cm, hard consistency, irregularity, multiple or grouped lymph nodes, fixed in the adjacent tissues. The clinical study carried out by us revealed the lack of adenopathy in 14.03% in group A and 9.66% in group B, adenopathy N0 (uninvaded ganglions) in 29.23% of the cases belonging to group A and 24.63% of the cases in group B, adenopathy N1 in almost equal proportions in the two groups (38.01% group A, respectively 39.61% group B) and a higher incidence for adenopathy N2 for group B (26.08% as compared to group A (18.71%).

Medical imaging is an essential step in the diagnosis and staging of breast cancer, image investigations being necessary for the positive diagnosis (identification of primary tumor and evaluation of malignancy criteria), as well as for the evaluation of systemic resound and for the identification of long distance metastases [144, 145]. Alongside the development of imaging techniques and of mammography, the oldest imaging technique aimed at diagnosing mammary cancer, other techniques such as echography, Doppler echography, tridimensional Doppler echography, skin thermography, transillumination, magnetic resolution, computer tomography have also been developed as well as other techniques, each with its indications, contraindications, advantages and disadvantages, of which most refer to cost [146, 147, 148, 149, 150].

Of all specific imaging investigation, mammography and mammary echography were the routine investigations used by the studied patients, their proportion being different in the two groups, expressing the preference of the two groups whose experience is comparatively
analyzed in this research. With an almost equal proportion between the two types of targeted imaging investigation (49% mammographies versus 45% echographies) for group A (Surgery I), the group of Surgery Clinic IV CFR (group B) favored mammary echography, probably due to the non-invasive trait of the method, even though scientific literature mentions the fact that echography is never the first choice imaging investigation, since it rather completes mammography, each of the two methods being more efficient there where the other is less efficient.

Mammography, the oldest method of paraclinical investigation (1913), remains the most useful method of diagnosis in mammary diseases in general and in especially in breast cancer [152, 153, 154]. Ranked with a sensitivity (ability to discover cancer in the female patient who suffers from it) of 76-94% and a specificity (ability to accurately identify a patients who does not suffer from the disease) higher than 90%, it was used in 84 cases (49.12%) in group A and at 64 patients (31.06%) in group B and it emphasized the following mammographic aspects, considered pathognomic for mammary cancer:
- dense opacity, non-homogenous, with irregular margins, blurred, with spicule prolongations in the mammary tissue, rendering a star-like image, image which in 99% of the cases betrays a case of cancer.
- microcalcifications as only mammographic change or accompanying an opacity; there are present in approximately 60% of the cancers discovered by mammographic techniques, histologically representing intraductal calcifications in the areas of tumoral necrosis.
- the thickening, the oedema and retraction of the tegument, which can be highlighted radiologically before having a clinical expression;
- architectural disorganizations of the structure of fibrous bays.

Echography, the examination complementary to clinical and mammographic exam, was practiced in 77 (45.02%) cases in group A and in 126 (60.86%) of the cases in group B and it emphasized the following malignancy aspects:
- the gaping area of irregular form, which is not precisely delimited, with a heterogenous ecostructure and the great axis perpendicular on the tegumental surface
- - the thickening of teguments;
- - a fixed image which is not distorted under the probe’s pressure [155, 156, 157, 158].

- Simple lung radiography was the main imaging investigation carried out for the evaluation of systemic resound and for the identification of long-distance metastases; it was practiced in 147 (85.96%) cases in group B and it led to the identification of lung metastases in 4, respectively 3 cases and to the identification of pleural liquid collections in other 4 cases.
- Systemic computer tomography was used as method of systemic evaluation especially in local relapses and/or in systemic relapses and it led to the identification of pleural-pulmonary metastases in 3 cases and bone metastases in 2 cases [159].

The morphologic diagnosis represented an important stage in the diagnostic and therapeutic algorithm of mammary cancer; it confirms the suspicion of mammary cancer and it represents an important criterion in the choice of the type of surgery as well as in establishing the indications of neoadjuvant therapy and adjuvant therapy complementary to surgery.

Morphologic investigation of breast cancer unfolds in two steps such as follows:
- - presurgery morphologic examination, which includes the cytological examination and the extemporaneous histopathological examination;
- - postsurgery histopathological examination of the resection piece;

Pre-surgery cytological examination supposes the examination of smears obtained from the pathologic mammary secretions or by aspiration puncture with a fine needle. The main flaw of the method consists in the difficulties of interpreting the results, determined by the lack of normal relationships between cells, depending mainly on the experience of the cytologist [160, 161].

Cytological examination base on the examination of pathologic mammary secretions was carried out in 17 cases (7 in group A= 4.09% and 10 in group B=4.85%) and it was positive
in 12 cases and negative or inconclusive in 5 cases. In accordance with the data from scientific literature, we have considered the positive smear as having orienting value, which imposes the continuation of clinical, imaging and morphologic investigations.

The aspiration puncture with a fine needle, mentioned in scientific literature in the evaluation of all mammary tumors in which surgery is not the first therapeutic sequence was carried out in 130 (76.02%) cases in group A and in 129 (62.62%) cases in group B; it was positive in 95% of cases in both groups and negative or inconclusive in the rest. We can conclude that as far as the value of the cytological examination is regarded, negative cytology does not exclude cancer, while positive results impose surgery with extemporaneous histopathological examination.

Histopathological examination is the only one capable of asserting the malignancy or benignity of a mammary tumor, starting from the supposition that any breast cancer must be considered cancer till the diagnosis is invalidated histopathologically; it is part of the surgical treatment and it must not be carried out without knowing the therapeutic surgery options in the context of the complex protocol of treatment of mammary cancer. The extemporaneous histopathological examination can establish the final diagnosis in 85-90% of cases. The accuracy of the method is high in the case of well-delimited formations, and its limits are directly linked to the capacity to interpret the margin lesions [162, 163, 164].

Two peculiar situations with therapeutic implications must be taken into account in interpreting biopsy:

- the surgical margin of excisional biopsy can contain cancer;
- the multicentricity of malignant lesions (the presence of carcinoma in another dial than the one in which the primary tumor is found) – 44% of cases and 6-8 % of cases with extension at the opposite breast;

Extemporaneous histopathological examination was carried out in 54 (31.57%) cases j group A and in 166 (80.52%) cases in group B and it highlighted the invasive ductal carcinoma as the main histological type of mammary cancer. The comparative analysis of the two groups showed essential differences in the value and proportion granted to the extemporaneous histopathological examination as compared to cytological examination by puncture with fine needle. Thus, with patients in group A, with whom radical surgery was the main therapeutic option, the extemporaneous histopathological examination was carried out only for stages in which surgery is the first therapeutic sequence (stages 0, I and IIA) and less in more advanced stages (IIB, IIIA and IIIB), confirmed by puncture-biopsy and cytological examination and which - by the moment of the intervention – were submitted to neoadjuvant therapy.

With patients in group B, for whom conservative surgery was the main therapeutic option, the cytological examination of pathologic material collected by puncture with fine needle was doubled by the extemporaneous histopathological examination, which aimed at the histological confirming of the malignant lesion and the exam of the margins of the limited resection.

The two options regarding the indications of the extemporaneous histopathological examination are correct from a theoretical point of view, but we must take into account the case of falsely positive punctures. Consequently, we consider the reconfirming of malignancy diagnosis by extemporaneous histopathological examination the most cautious even for the confirmed cases by puncture which benefited by neoadjuvant therapy.

The post-surgery anatomopathological examination of the resection piece has an important role in the therapeutic algorithm of mammary cancer. It establishes the necessary parameters for post-therapeutic staging (pTNM): histological type of tumor, the degree of cellular differentiation and the number of invaded ganglions, parameters according to which we will decide the opportunity and type of adjuvant therapy for each female patient [165, 166, 167, 168].

The study of histological forms has shown that the main prevailing histopathological form of mammary cancer was invasive ductal carcinoma. In both groups (101 cases=80.15% group A and 165 cases=80.88% group B), followed by the invasive lobular carcinoma and
colloid carcinoma, the rest of histological forms of mammary cancer were encountered exceptionally in our case records. Regarding the degree of cellular differentiation, most of the tumors in group A were weakly differentiated, pertaining to G3 category (62 cases=57.40%), while in group B the tumors presented a medium differentiation, pertaining to G2 category (106=51.45%).

As far as the number of invaded ganglions is regarded, there were considered for the study only the cases in which the examined resection piece included minimum 10 ganglions and we discovered an almost equal distribution of ganglionary invasion for group A (1-3 invaded ganglions-37.73%, 3-6 invaded ganglions– 28.30% and more than 6 invaded ganglions in 34.4%), while in group B most of the cases (70.37%) presented between 4 and 7 invaded ganglions, 25% of cases between 1 and 3 invaded ganglions and only 4.63% presented more than 6 invaded ganglions.

The staging of malignant mammary tumors allows the frameworking of female patients on groups with prognostic characteristics and similar therapeutic conduct. We have used the staging classification TNM for breast cancerm established in 1987 by UICC and AJCC, changed in 2002.

Clinical staging was based upon the clinical examination, the mammographic examination and the cytological/biopsy examination, to which, for a complete pre-therapeutic survey, there were added lung radiography, liver radiography and biological exams. When the initiation of a presurgery systemic treatment is foreseen, we must exclude the presence of the disease with metastases, by supplementary investigations such as chest radiography, abdominal radiography, bone scan, computer chest, abdominal and cranial tomography. These investigations are recommended for patients in clinically advanced stages (large tumors or lymphatic ganglions discovered at palpation) or when the values of analyzes or the symptomatology indicates the presence of metastases even when the neoadjuvant treatment is not foreseen [III, B].

Pre-surgery staging includes besides the clinical classification TNM the anatomopathological examination of biopsy, which furnishes data regarding the histopathological type and it must comprise sufficient tissue so that it might allow determining the estrogen receptors (ER), the progesterone receptors (PgR) and the status HER2 by IHC or FISH/CISH [III, B].

In the cases where surgery represents the first therapeutic sequence, the information brought by the histopathological examination of the excision complete the clinical staging, and the histopathological staging (pTNM) becomes the basis for the therapeutic decision. The anatomopathological staging (pTNM) is determined by the histopathological examination of the resection piece and it should include the primary resected breast tissue and at least six removed ipsilateral axillary lymph nodes. The anatomopathological examination of the resection piece must state the number of tumors detected in the resected breast tissue, the largest diameter of the biggest tumor (category T), the histological type and grade of the tumor, and it should consider the resection margins, including the minimum edge expressed in millimeters and its anatomical direction. The pathological examination should also assess the number of positive lymph nodes and the expansion of the node invasion – ITC, micrometastases, metastases (N category). The pathological examination should also include the immunohistochemical assessment of ER and PgR and the determination of the expression HER2 by immunohistochemistry. All the obtained data will enable the postoperative stage classification of each case and will be used as criteria to determine the appropriateness and type of the postsurgical treatment sequences.

Our study allowed the following findings concerning the staging of breast cancer:
- the distribution of cases according to the preoperative staging revealed some differences between the two study groups, differences which justify, at least to a certain degree, the option for radical surgery in group A and for conservative surgery in group B. Thus, if for both groups on the whole, there are two incidence curve peaks of the cases in stages II and III, the detailed analysis reveals a peak shift of the curve towards stage IIA for group B, and towards stage IIB for group A; in stage IIIB, which is suitable for radical surgery, where the
The second peak of the curve is found, the incidence is clearly in favor of group A (29.05% vs. 22.84%).

- the comparative study of preoperative and postoperative staging shows an almost perfect symmetry of the incidence curves, including maintaining the placement of peaks in the three stages, IIB and IIIB for group A and IIA and IIIB for group B, which shows that the pretherapeutic assessment of the classification stage was correct in both groups.

Nowadays, the treatment of breast cancer is a pluridisciplinary complex treatment, which underwent an impressive evolution along the time, partly because of the progress made in understanding the biology of the disease, and secondly due to the increasingly frequent detection of the disease in earlier and earlier stages, and also due to the diversification of therapeutic methods, including surgery, radiotherapy, chemotherapy, hormone therapy and immunotherapy, the indications and sequence of these therapeutic procedures varying according to the disease stage, the histological type and tumor grading, the patient's age and general condition [169, 170, 171].

Surgery, the only therapeutic option for a long time, still remains the mainstay in the treatment algorithm for breast cancer, but the time and type of the surgical operation employed have undergone conceptual changes along the time, in keeping with the evolution of conceptual knowledge on the biology and natural history of breast cancer. Thus, we had in turn the prehalstedian stage, characterized by the lack of a natural history pattern and of a well-codified surgical technique; the halstedian stage, dominated by the Halsted operation and its variants; and the posthalstedian stage, which was theoretically established by Bernard Fisher (1979), based on the "systemic" behavior pattern of breast cancer, according to which the operable breast cancer is a systemic disease whose survival is less influenced by aggressive local treatment, which allows the replacement of the aggressive local therapy by smaller-scale operations, which do not mutilate, with similar results.

This development led to the definition of two distinct surgical options, conservative surgery and radical surgery, whose indications and limitations tend to be increasingly well defined, in keeping with the accumulated experience and the interpretation of results from a distance. Our comparative study also follows that line, valorizing the experience of two clinics, one (Surgical Clinic I - group A) that adopts radical surgery, and one (Surgical Clinic IV CFR) that is a promoter of conservative surgery; we tried to see to what extent our data correspond to those of the literature and to define the criteria that may lead to choosing the best therapeutic option.

According to the clinical material studied, 350 patients were operated out of 377 (92.83% operability index), 147 (85.96%) group A and 203 (98.54%) group B. 27 patients were not operated (24 group A and 3 group B): 4 patients refused surgery, the rest being hospitalized in stage III B and C; they were transferred to the oncology clinic for neoadjuvant radiochemotherapy and did not return to service until the end of the study.

The conservative treatment of breast cancer represents a therapeutic alternative to radical surgery and it comprises at least two treatment sequences: a minimal surgical intervention (sectorectomie or cadranectomie with negative resection margins) followed by postoperative adjuvant radiotherapy to eradicate any residual disease, with or without chemotherapy and hormonal therapy [172, 173, 174].

The conservative treatment of mammary gland cancer has elective indication and curative visa in the early stages (I and II), but it can be used, with limited indications and palliative character also in advanced stages (IIIA and IIIB), especially in the case of elderly, sick patients.

Conservative mammary gland cancer surgery includes:
- Primary tumor surgery - lifting of the primary tumor through a conservative mammectomy, defined as a bloc excision of the primary tumor with 1.5 cm healthy peritumoral breast tissue, by extemporaneously histopathology verification of the absence of tumor invasion into the remaining wall cavity. The term conservative mammectomy replaced the other terms used in the mammary gland cancer conservative surgery (tylectomy, lumpectomy, sectorectomy, quadranectomy), over which there is controversy.
- Surgery of axillary lymph nodes - axillary lymphadenectomy, now considered by many authors as having a more prognostic significance, and as an important parameter to determine whether adjuvant chemotherapy is appropriate. The radical, axillary lymphadenectomy visa is questioned by the circumvention of a main lymph node station – the internal mammary lymph nodes. The magnitude of the mammary gland excision depends on: the morphology of the primary tumor (size, location and the histopathological type of the primary tumor), breast size and the associated breast lesions. In determining the indication of conservative surgery, in the end there are two important parameters, ensuring the achievement of both objectives proposed by this type of surgery: the local control of the disease and a satisfactory aesthetic result; these are the ratio tumor / breast, and the existence of negative edges in the remaining cavity walls [175, 176, 177].

Following the stated purpose of this paper, to evaluate the indications, the advantages and limitations of various therapeutic procedures, the present study has used the collective experience of two surgery teams – Craiova Surgery Clinic I (group A), who have an eclectic therapeutic attitude, and CFR Surgical Clinic IV (group B), who uses conservative surgery for breast cancer. In these circumstances, it was natural for the weight of conservative surgery to vary in the two groups. Thus, if for group A the conservative surgery (24 cases) represented only 16.32%, being reserved exclusively for patients in the early stages (5 stage I, 14 stage IIA, 4 stage IIB and 1 stage IIIA), in group B the share of conservative surgery (50.97%) was almost equal to that of radical surgery (49.03%), restricted in most cases to the early stages (stage I 11 cases, 48 cases stage IIA), but with the tendency of widening the indications of the conservative surgery area towards more advanced stages (IIB 31 cases, 8 cases IIIA, IIB 2 cases and IIIC 1 case).

We also mention that the contraindications of conservative surgery were respected: multicentric tumors, relatively large tumors (> 3-4 cm) in women with small breasts, especially when the patient did not have neoadjuvant chemotherapy, positive margins after resection or recovery, breast cancer inflammatory phenomena, and the patient’s choice for radical mastectomy.

Introduced by Halsted in 1894, based on the concept of loco-regional disease that he also postulated, radical mammectomy bearing his name gave the chance for a better local control of the disease and led to a significant reduction in the rate of local recurrence; it become the standard treatment for breast cancer for more than half a century, but despite improvements in the local control of the disease, the curative potential of surgery has remained limited. In addition, the too large scale and its somewhat disfiguring character and also some late complications with disabling character such as lymphedema, have given rise to technical variations of the Halsted operation, which are less extensive, better tolerated by patients, and burdened by fewer disabling complications, but based on the same pathogenic halstedian concept. These processes - the Patey and Maden operations - have completely replaced the Halsted operation and today they make up the standard radical surgery of breast cancer [178, 179].

Notable progress made in recent decades in the field of adjuvant and neoadjuvant therapy, and the appearance of the "systemic" pattern in the behavior of breast cancer have led to the gradual restriction of radical surgery indications, as the test of time defeated conservatism and the surgeons’ distrust in conservative surgery.

The analysis of the material considered in our study revealed several findings on which we believe several comments are needed:

- Although the standards relating to the indications of radical surgery were met, the weight of this type of surgery was different in the two groups. Thus, in group A (Surgery I), radical operations with curative visa were performed in 71, 92% of cases (117), while in group B (CFR Surgery IV), they represented only 49.03% (97) of cases, the remainder being resolved by conservative surgery. Without thinking strictly about another therapeutic design, we believe that the first explanation of this difference lies in the lot structure. Thus, starting from the assumption that radical surgery is reserved primarily to locally advanced stages (stage IIB and
IIIA), stages when surgery with curative intentionality is theoretically possible, we found that the percentage of the cases that have been assessed in these stages was significantly higher in group A, especially in stage IIB (31.75% vs. 24.75%), while for stage IIIA the incidence is similar (10.13% group A vs. 13.10% group B); regarding stage IIIB, suitable for radical surgery, the incidence is still higher for the patients from group A (29.05% vs. 22.81%). On the other hand, even for stage IIA, which usually tends to be conservative surgery, and IIB to which conservatory surgery tends to expand the indications, the analysis of the semiological characters of tumors belonging to group A showed us that they were within the upper limit of this stage (tumors with a maximum diameter > 3-4 cm), which is rather a contraindication for conservative surgery, especially in the case of the patients with small breasts, where the large size of the tumor makes nearly impossible to meet and carry out safe resection margins. Finally, one last argument in favor of radical surgery was the large share of the invasive ductal carcinoma at the histopathological extemporaneous examination.

- The modified Maden radical mamectomia was the election process used in both groups: 96 cases for group A and 73 cases for group B.
- Simple mamectomia was used in few cases (three for group A and 1 for group B) and only at the patients' express request, referred to specifically and explicitly with their signature in the sheet of observations.
- "Toilet" mamectomia was practiced in 40 cases, 18 cases in group A and 22 cases group B, with the same indications in both groups; it was usually reserved for neglected cases, with bulky tumors, sores, infected, fixed on deep levels, with fixed ipsilateral lymph, which often makes true ganglion blocks, which are difficult or impossible to remove. The operation, though laborious and sometimes burdened by high risks, is still a necessity and cannot meet the criteria of radical surgery, especially in terms of cancer healing. Moreover, it mostly ends with important skin or parietal flaws, which may be covered by plastic processes that are carried out subsequently or during the same surgical session. In group A, the therapeutic approach consisted of performing both mamectomia and skin plasty during the same surgical session, in collaboration with the plastic surgeon.

Neoadjuvant (preoperative) chemotherapy aims at reducing tumor volume and reducing the risk of dissemination of malignant cells during the surgical act; is indicated for the treatment of breast cancer in its early developmental stages, and also in some stages of locally advanced disease (IIB and IIIA), stages when surgery is possible with the intention of cancer healing [180, 181, 182].

In our study, neoadjuvant chemotherapy was used in 85 cases (49.70%) in the patients in group A and in 74 cases (35.92%) in the patients in group B. We noted that in group A, neoadjuvant chemotherapy was used in 67.05% (57) of the cases of patients belonging to stages I, II and IIIA, i.e. those suitable for surgery with cancer healing visa, as opposed to group B, in which neoadjuvant chemotherapy was used only in 40.54% (30) of cases in similar stages. In stage IIB, stage where surgery is not the first therapeutic sequence, neoadjuvant chemotherapy was used in 26 (30.58%) cases in group A and in 36 (48.64%) cases in group B.

Neoadjuvant (preoperative) radiotherapy has few indications, which vary by stage; it can replace or allow the postponement of surgery at a stage when surgery is the first therapeutic sequence (stages I and II) in the patients with biological imbalance, or with comorbidities that do not allow surgery (4 cases in group A and 7 cases in group B), or it can complete neoadjuvant chemotherapy with no answer or uncertain treatment response in the patients with stage III (4 cases in group A and 17 cases in group B).

By comparing TNM clinical staging with the postsurgical anatomopathological staging (pTNM), we tried to evaluate the effectiveness and the place of neoadjuvant therapy in the therapeutic algorithm of breast cancer, by assessing tumor regression (downstaging) and we found that only a small percentage of cases have changed stage (13.96% group I and 5.0% group B), a change that may be wrong pretherapeutical staging rather than a genuine tumor regression, which confirms literature data; according to these, the initial stage of the disease
remains unchanged [183, 184]. However, neoadjuvant therapy maintains its value and the indications established and confirmed by randomized trials, according to which neoadjuvant therapy:

- increases the disease-free interval
- reduces the local recurrence rate
- increases the percentage of conservative surgery
- improves the overall survival rate

Adjuvant (postsurgical) treatment includes chemotherapy, radiotherapy, hormone therapy and targeted molecular therapy, each with specific guidelines that must take into account the following factors:

- the number of positive lymph nodes, which are defined according to risk groups:
  - group I – 0 positive nodes
  - group II - 0-3 positive nodes
  - group III - more than 3 positive nodes
- tumor size - less than 1 cm tumors with negative lymph nodes have a favorable prognosis
- the nuclear grade - well differentiated tumors have the best prognosis
- histology type - mucinous (colloid), tubular and medullar carcinoma have a good prognosis for tumors <3 cm
- the molecular profile and the hormonal status, determined by immunohistochemical examination
- other factors: lymphatic and vascular tumor invasion, the tumor proliferation rate, etc.

Adjuvant therapy after conservative surgery. Conservative surgery for breast cancer would not have been possible without the development and improvement in adjuvant treatment and mainly of radiotherapy. Nowadays, when most authors consider it unacceptable that conservatory surgery should lack from the therapeutic arsenal of breast cancer stage I and II, its failures are thought to be due more to incorrect or incomplete adjuvant radiotherapy, which thus becomes the main therapeutic approach along with surgery [185, 186].

The indications concerning the type of radiation, its duration and the areas to be irradiated have as main indicator the number of invaded lymph nodes, confirmed by the pathological examination of the resection piece, and identified in the pTNM postsurgical classification.

Based on these criteria, in establishing the type and fields of radiation we used the guidelines of the National Comprehensive Cancer Network (NCCN) for conservative treatment (conservative mammaectomy + axillary lymph nodes evidation) of breast cancer stages I, IIA, IIB and IIIC:

- ≥ 4 invaded axillary lymph nodes - whole breast irradiation with or without overload (photon radiotherapy, brachytherapy or electron beam radiotherapy), of the tumor bed (stage I), of the supra and infraclavicular region. One is to consider the internal mammary node irradiation in stage IIIA. Radiation therapy must be preceded by chemotherapy, when it is indicated.
- 1-3 positive axillary lymph nodes - whole breast irradiation with or without overload, and of the tumor bed (stage I), preceded by chemotherapy, when it is indicated. One should seriously consider the infraclavicular and supraclavicular irradiation in stage IIB and the irradiation of the internal mammary lymph nodes in stage IIIA. Radiation therapy must be preceded by chemotherapy, when indicated.
- non-invaded axillary lymph nodes - whole breast irradiation, with or without overload, and of the tumor bed, or one should consider partial breast irradiation in selected patients. Irradiation must be preceded by chemotherapy, when indicated.

Radiotherapy was performed as described above in all cases operated in group I (graph no. 23) and in 97 patients (91.50%) in group II (graph no. 23).

Chemotherapy preceded radiation therapy in all the 24 cases that underwent conservative surgery according to the scheme 6 cycles of Docetaxel + Epirubicin in 14 cases and FEC (5 Fluourouracil + Cyclophosphamide + Epirubicin) in 10 cases. The combination chemo-radiotherapy was performed only in 26 cases in group B.
In all the 24 cases that underwent conservative surgery in group I, the molecular profile was determined by immunohistochemical examination, and in 18 cases with positive estrogen receptors (RE+HER-) hormone therapy was associated with anastrozole in 7 cases, with letrozole in 5 cases, with tamoxifen in 5 cases, and with exemestane in 1 case. In group B, the molecular profile was established only in 46% of cases, and hormonal therapy was associated with other means of adjuvant therapy in 32 (30.18%) cases.

**Adjuvant therapy after radical surgery.** Adjuvant therapy after radical surgery has the same therapeutic possibilities as well as after conservative therapy, with the main criteria for determining the sequence of therapeutic indications the number of invaded axillary lymph nodes and the classification in risk groups according to the NCCN Guidelines.

The NCCN Guidelines [61] to determine the radiation fields after radical mamectomy with axillary lymphadenectomy were:

- ≥ 4 invaded lymph nodes - chest wall irradiation (stage I) + the irradiation of supra and subclavian areas preceded by chemotherapy; one should consider the internal mammary node irradiation for stage III
- 1-3 invaded lymph nodes - the irradiation of the chest wall and of the supra and subclavian areas preceded by chemotherapy, if it was performed, one should consider the internal mammary node irradiation for stage III
- non-invaded lymph nodes + tumor > 5 cm or positive margins - the chest wall irradiation + supra and subclavian areas. One should take into account the internal mammary lymph nodes irradiation for stage III
- non-invaded axillary lymph nodes and tumors ≤ 5 cm and resection margins <1mm - chest wall irradiation preceded by chemotherapy
- non-invaded axillary lymph nodes and tumor ≤ 5 cm with free margins ≥ 1 mm - no postoperative irradiation.

As indicated above, adjuvant postoperative radiotherapy was performed for 87.80% (108) patients in group I and for only 34.02% (33) of the patients belonging to group II.

Chemotherapy, in accordance with treatment guidelines, preceded radiation in all cases where it was indicated [187, 188, 189]. The chemotherapy performed in 91.05% (112) of cases belonging to group I consisted of six courses of chemotherapy regimens administered sequentially as follows: Docetaxel - Epirubicin 81 cases (72.32%) and FEC 31 cases (27.68%). In group II, adjuvant chemotherapy was associated with radiotherapy only in 72.16% (70) of cases using the same number of courses and the same regimens.

The immunohistochemical examination conducted in 112 (95.01%) patients in group I allowed to establish their molecular profile, noting the existence of endocrine-responsive tumors in 67.85% of them; they received adjuvant hormonal therapy with anastrozole in 26 cases, exemestane in 15 cases, letrozole in 26 cases and tamoxifen in 19 cases. In group II, 23 (30.92%) patients received hormone therapy, the indication being determined by the same immunohistochemical criteria.

Without being a type of surgery with major vital complications, breast surgery records, however, immediate and remote postoperative complications, some debilitating, specific to this type of surgery. There were a total of 55 such postoperative complications recorded, with a postoperative morbidity rate of 21.42%, in relatively similar proportions for the two groups: 20 (13.6%) cases in group I and 35 (16.9 %) in group II.

The difference between the two groups was given by 13 cases of postoperative edema of the breast, reported in the second group, late complications, specific to conservative surgery. It appears in the first three months in most cases and is usually triggered by radiotherapy. The volume increasing of the breast is discreet, but it may reach impressive dimensions, miming a carcinomatous mastitis, which can sometimes lead to an unexpected radical mamectomy, as a result of a misinterpreted puncture, like it happened in one of our cases. This particular complication of breast conservative surgery is a lymphatic disease, related to the interception in the lymphatic drainage of breast axillary lymphadenectomy; but the appearance of complications over 3 months after surgery, so after the start of radiotherapy, raises the question
whether this complication is rather a complication of radiotherapy than of the actual conservative intervention.

The axillary lymphocele, present in 7 cases, was usually the result of clogging or early removal of drain tubes, being resolved by puncture and compression bandages in all cases.

The postoperative hematoma present in four cases in both groups was rather the result of coagulation deficits that were unreported by the preoperative investigation of coagulation, because there was not any major source of bleeding identified in any of the reinterventions for hemostasis.

The wound discharge, found in almost identical proportions in both groups (3.40% group I and 3.39% group II) increased the number of hospitalization days and led to the emergence of vicious scars, unsightly, but not disabling.

Lymphedema or the thick arm syndrome, a complication specific to breast cancer surgery, was found in seven cases (5 group I and 2 group II), all after radical surgery, managed by postural and Detralex treatment [190, 191].

Post-treatment relapse in the mammary gland cancer is classified according to the anatomical seat:
- local recurrence, when it appears and develops at the remaining glandular parenchyma level or at chest wall level
- regional relapse when it occurs and develops at the axillary or supraclavicular lymph nodes or level
- "systemic relapse" or metastatic disease when it occurs in the patients without metastases that are clinically manifest or detected from images metastases before beginning treatment [192, 193, 194].

Relapse may also occur after conservative or radical surgery, most authors acknowledging the higher rate of recurrence after conservative surgery.

Local relapse after conservative surgery, found in 3 cases in group II (relapse rate = 2.83%) occurred postoperatively in 8, 12 and 15 months respectively in two patients who refused postoperative adjuvant radiotherapy or followed an incomplete treatment; in the third case, the extemporaneous histopathological examination showed a benign lesion, which is why the patient did not report to the paraffin outcome, returning in 8 months with a tumor in the central square, with characters

Local recurrence after radical surgery, also found in three cases belonging to group I (local recurrence rate = 2.29%) occurred after the Maden surgery, performed to pretreatment staged cancer, stage IIIB, in 12, 14 and 15 months respectively postoperatively, and it consisted of the appearance of nodules in the permeation of the postoperative scar (three cases) and of an axillary lymph block (1 case). Histopathology of the resection piece showed a G3 invasive ductal carcinoma in all cases, which persisted after the local recurrence treatment (excision of permeation lymph nodes = axillary iterative lymphadenectomy).

Regarding the "systemic relapse" or metastatic disease, defined for the purposes of the foregoing, it was found in 15 (10.20%) cases belonging to group I and in 9 cases (9.27%) belonging to group II. This particular type of recurrence occurred after the Maden operation in 19 cases and after toilet mamectomy in 5 cases, with patients staged before treatment IIIB (3 cases), IIIA (5 cases) and IIIB (16 cases) after a disease-free interval of between 4 and 25 months. The primary tumor histology was invasive ductal carcinoma in 20 cases and the invasive lobular carcinoma in 15 cases, 10 cases G2 and G3 in 15 cases. Chemotherapy was the treatment of choice and the survival rate for this type of relapse ranged from 18 to 31 months.

A special situation that we encountered during our study and that we wish to point out due to its special importance, is the problem of the so-called "false relapses". Less commonly encountered after radical surgery (3 cases in group I), usually under the form of false permeation nodules or of axillary lymph nodes, their character, usually inflammatory, is usually confirmed by histopathology of the resection piece after surgery (the excision of growths at the old scar level, or the level of axillary tumor formations interpreted as a tumor adenopathy). The problem is more serious when such false recurrences are common after breast conservative
surgery and may compromise the patients’ and even the surgeon’s trust in conservative surgery, leading to abusive radical mamectomy, usually requested by the patient. In our study, we also encountered such false recurrences in 7 patients in group II, manifested by the appearance of vaguely defined tumors at the level of the postsectorectomy scar (3 cases) or the axillary scar level (2 cases), postoperative blood nipple discharge (1 case), and breast pain + postoperative swelling of the breast (1 case). In the last two cases, there was radical mamectomy following the patients’ request, but the histopathology of the resection piece denied the presence of the tumor tissue.

Remote Survival is the main parameter for assessing the effectiveness of breast cancer treatment, like in any other form of cancer; it is a complex parameter, which reflects both the effectiveness of the actual medical gestures and the effectiveness of a coherent national program that should include mass localization by screening methods, the continuous improvement in the level of the population health education, the registration of new cases and the monitoring of old cases, which implies the existence of a national cancer registry and the active involvement of all stakeholders [195, 196, 197]. Unfortunately, in our country, all these elements which could help improve prognosis, are still burdened by serious conceptual and especially organizational shortcomings, so that the data on remote survival rates should be considered with reservation.

Regarding our study, its shortcomings are represented by the fact that, while evaluating a large number of cases (377), the considered period is relatively short, and a sufficient amount of time has not lapsed since the end of the study to allow assessment of survival over 5 years for all the interval, so that the data obtained could be charged with an error factor. Despite these obstacles, our findings revealed some elements that we want to mention (graphs 27 and 28):
- we have not recorded any death from cancer in the patients with breast cancer stage I and II who underwent conservative surgery (24 in group I and 106 in group II) during the studied period and we have not recorded any cases of metastatic disease in these patients
- after conservative surgery, the remote survival rate was significantly higher for the patients in group I (Surgery I) compared to group II: 32/27 after 2 years, 33/14 after 3 years, 29/6 after 4 years and 14/7 after 5 years. The explanation could be found in the fact that, although the beneficiaries of the same type of radical intervention (Maden modified radical mamectomy), the number of the patients in group I who received complex adjuvant treatment (radiotherapy, chemotherapy, hormone therapy) in group I was larger than in group II, the difference actually lying in the oncology services that took and treated the patients after the completion of the surgical stage
- for toilet mamectomy, the survival did not exceed two years, averaging one year in most cases.
- in the metastatic disease, the survival was 20 months on average, ranging between 18 and 31 months.

CONCLUSIONS

1. Breast cancer – a major public health problem (25% of all cancers in women), with very high incidence and an obvious tendency to increase, represented 53.9% of the total mammary gland diseases (the ratio cancer / malignant disease of 1.17 / 1).
2. The average age higher than that cited in the literature at the time of diagnosis (61.97 years old group A and 59.42 years old group B), with the patient distribution mainly in decades VI and VII, while the literature ranges the maximum incidence in decades IV VI.
3. The higher incidence in women from social classes with high economic and educational status, probably due to a combination of factors relating to diet, the age of the first menstruation, the use of estrogens, alcohol, coffee, tobacco, etc. (average urban / rural ratio = 2.21 / 1).
4. The constant involvement of endo- and exogenous endocrine factors: early menarche (60.21%), followed in order by late menopause, the first birth after 30 years old and the permanent contraceptive use over 10 years.
5. The existence of breast cancer in first degree relatives (5.89% group A and 16.99% group B) and also the presence of benign or malignant breast pathology in history (19.4% group A and 3.50% group B) - important risk factors.

6. The poor clinical expression (22% pain, nipple discharge below 5%) makes the chance discovery of the tumor the main way to detect breast cancer (73.68% in group A and 73.30% in group B).

7. Significant delays in diagnosis, although breast cancer is located in a region that is accessible to both anatomical self examination and clinical examination; the diagnosis was established during the first months under 25% of cases, between 4-6 months in 21.48% of cases, between 7-12 months in 25% of cases, and over 1 year in 15.69% of cases.

8. The semiological characters of the tumor are important parameters for staging and defining pretreatment malignancy:
   - Topography - approximately equal distribution between the two breasts, the most common location in the upper outer quadrant (43.9% group A and 41.7% group B).
   - Variable dimensions (0.2 to 20 cm) standardized in the TNM classification; the majority (52.65% group A and 59.40% group B) belonged to T2, with notable differences for the other stages: T3/T1 = 33/24 group A and 28/54 group B, with implications in treatment management.
   - Characters of malignancy: irregular shape, firm flesh (83% group A and 71% group B), adherence to skin (38% group A and 24% group B) and the infiltration of deep plans (25% group A and 8% group B).

9. The adenopathy evaluation highlights malignancy characters: > 1 cm in size, hard consistency, irregularity, multiple or grouped lymph nodes, fixed in the adjacent tissues.

10. Mammography and ultrasound (49% / 45%) - routine investigations in breast cancer, provide sufficient data to determine malignancy and stage classification. System lung X-ray and the CT with targeted indications complete image investigations, which are particularly useful for the detection of systemic secondary metastases.

11. The morphological diagnosis, an important sequence in the diagnostic and therapeutic algorithm of breast cancer, develops in stages:
   - Before the operation, performed cytology - the examination of a nipple discharge smear (4.09% group A and 4.81% group B) or fine needle aspiration puncture (76.02% group A and 62.62% group B), positive in more than 95% of cases in both groups - useful for determining the malignancy and appropriateness of neoadjuvant therapy.
   - Intraoperative - extemporaneous histopathology of the tumor and / or resection margins (31.57% group A and 80.52% group B) – confirms the diagnosis and represents a last milestone in the choice for conservative or radical surgery.
   - Postoperative – the histopathological examination of the resection piece, useful for the pTNM staging, the main guide in adjuvant therapy.

12. The invasive ductal carcinoma – the dominant histological form (80.15% group A and 80.88% group B), G3 predominant in group A (57.40%) and G2 in group B (51.45%).

13. TNM clinical staging - the maximum scope for stages II and III, with the predominance of stage IIA suitable for conservative surgery in group B, and of stage IIB, with eclectic indications in group A; the patients with stage IIIB breast cancer were far more numerous in group A (29.15% compared to 22.84%).

14. Surgery - the main treatment sequence in the complex treatment regimen of breast cancer (350 operated patients, operability index = 92.8%), with two basic treatment options: conservative surgery and radical surgery.

15. Conservative surgery, reserved for early stages in group A (5 stage I, 14 stage IIA, 4 stage IIB and 1 stage IIIA) was extended to more advanced stages (31 stage IIB, 8 stage IIIA and 2 cases in IIIB), as the therapeutic choice for group B (50.97% of cases).

16. Radical surgery, represented by the Maden operation in both groups, reserved for locally advanced stages, was the dominant therapeutic option for group A, particularly imposed by the group structure: the predominance of locally advanced stages IIB, IIIA and IIIB and of invasive histological forms objectified by the extemporaneous histopathological examination.
17. Neoadjuvant therapy, without leading to a true tumor regression has several advantages (it reduces the local recurrence rate, increases the disease-free interval and the percentage of conservative operations) that make it useful both in early stages and in locally advanced stages where it is possible to perform an intervention with curative visa.

18. Postoperative radiotherapy (100% group A and 97% group B) is mandatory after the conservative surgery, loco-regional recurrences (3 in group B) being attributable rather to failure or to the absence of adjuvant radiotherapy.

19. Adjuvant chemotheraphy, hormonal therapy and targeted molecular therapy have specific guidelines, based on the risk group, established by the histologic type and the grade of tumor differentiation, the number of invaded lymph nodes, and the hormonal and molecular profile indicated by the immunohistochemical examination.

20. Local relapse with close values after conservative surgery (2.83%) and radical surgery (2.29%), somewhat at odds with the literature data, which indicate significantly higher differences.

21. Adjuvant therapy significantly increases survival rates after radical surgery (group A).

SELECTIVE BIBLIOGRAPHY:

1. Albu I. - Anatomie topografică, Ed. All, Ediția II-a, București 1998;
2. Ranga V. & all - Anatomia omului, Ed. Cerna, 1993;
11. Centrul de Statistică al Ministerului Sănătății – București, România, 2008;
33. Lazăr L. - The role of lymph node dissection in cancer patients, Romanian Journal of Surgical Oncology, Vol.1, Nr. 4, 211-214, 2002;
34. Blidaru A.- Sentinel node in surgical oncology, Chir. (Bucur), 2006, Jul-Aug, 101 (4) 357-8;
35. Albertini JJ., Lyman GH, Cocs C. - Lymphatic mapping and sentinel node biopsy in the patients with breast cancer, JAMA, 1966, 276: 1818-1822;