CONSERVATIVE SURGERY - THE ALTERNATIVE WITH GOOD RESULTS IN MAMMARY CANCER

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ABSTRACT

THE MAMMARY NEOPLASM IS THE MOST FREQUENTLY MET ANOMALY FOR THE FEMININE GENDER CONSTANTLY BEING A TOPICAL ISSUE IN THE FIELDS OF ONCOLOGY AND SURGERY.

IN ROMANIA THE PROBLEM OF BREAST CANCER CAN BE CONSIDERED A REAL ALERT , DUE TO THE FACT THAT MORE THAN 50 % OF THE WOMEN ARE DIAGNOSED WHEN THE STAGE OF THE DISEASE IS ADVANCED.

THE MAIN THERAPEUTICAL PROCEDURES ARE SURGERY, RADIOTHERAPY, CHEMOTHERAPY, HORMONE THERAPY, IMMUNOTHERAPY OR MOLECULAR THERAPY AND GENE THERAPY.

THE CLINICAL STUDY WAS MADE BY MEANS OF A RETROSPECTIVE ANALYSIS OF MAMMARY NEOPLASM CASES USING THE INFORMATION FROM OBSERVATION AND ONCOLOGICAL SHEETS OF THE PATIENTS WHO UNDERWENT SURGERIES. THE DOUBLE PURPOSE OF CONSERVATIVE SURGERY IS TO GET A GOOD LOCAL CONTROL OVER THE DISEASE ON THE LONG TERM AND A MINIMUM LEVEL OF LOCAL MORBIDITY .

THE POST SURGERY RESULTS AND THE CONCLUSIONS WE HAVE REACHED WERE ENCOURAGING BEING IN ACCORDANCE WITH SPECIALISED LITERATURE.

KEY WORDS: CONSERVATIVE SURGERY, MAMMARY CANCER, CHEMO-RADIOTHERAPY.

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I. INTRODUCTION

Breast cancer is the most frequently met anomaly for the feminine gender [8], constantly being a topical issue in the fields of oncology and surgery. This fact is due to the frequency of this disease which continues to persist at high values, and its evolution is severe especially when it is diagnosed in a late stage of the disease[9]. Over time, however, new ways have emerged to reduce breast cancer mortality. Thus, breast screening that allows the discovery of the disease in less advanced stages or prior to clinical manifestations, where the number of healings increases considerably.[10]

In Romania the breast cancer issue can be considered a real alert when referring to the fact that more than 50% of the women with mamary cancer are diagnosed when the disease is in an advanced stage and that is why the therapy costs a lot more and the results are less satisfying.[11] This warning sign must lead to a prevention and early detection programme for the neoplasm of the mammary gland.[12]

THE MAMMARY CANCER TREATMENT

The surgical oncology treatment of the breast is complex and adjusted to each case according to: age, patient's characteristics, the clinical and histological stage of cancer , the evolution stage of the disease, [13]the hormone status and the evolution rhythm of the tumor.[14]

Before the treatment, a balance is established which can offer information about the real extension of the disease (the TNM stage), the agresivity of the tumor (how fast it evolved in the last 2-3 months)[15] and the condition of the vital organs.[16] The minimal investigations are compulsory to allow the observation of the vital organs are: CBC (Complete Blood Count), glycaemia, hepatitis tests, renal function tests, coagulation tests, tumoral markers like CA 15-

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[11]Peltecu G., Ionescu M., Lesaru M., Anghel R., Minea N., Laura O, Median D. – Cancerul de sân. În: *Irinel Popescu (sub red.)* Tratat de Chirurgie, vol. VIII. Editura Academiei Române, Bucureşti, 2008, 779-802.
[12]Bland K., Vezeridis M. – Sânul. În: *Schwartz S., Shires T., Spencer F. (sub red.)* „Principiile chirurgiei", vol. I. Editura Teora, Bucureşti, 2005, 544-610.
[13]Bălănescu I., Blidaru Al. – Cancerul sânului. În: *Angelescu N. (sub red)* „Tratat de patologie chirurgicală". Editura Medicală, Bucureşti, 2001, 1187-1206
[14]Angelescu N., Jitea N., Cristian D. – Actualităţi în diagnosticul şi tratamentul cancerului mamar. În: Dragomirescu C., Popescu I. (sub red.) „Actualităţi în Chirurgie", Ed. Celsius, Bucureşti, 1998, 48-586. Olsen O., Gotzsche PC. – Screening for breast cancer with mamography (Cochrane review), Cochrane Database Syst Rev 2001:4.
[15]Bland K., Vezeridis M. – Sânul. În: *Schwartz S., Shires T., Spencer F. (sub red.)* „Principiile chirurgiei", vol. I. Editura Teora, Bucureşti, 2005, 544-610.
[16]Greenal M.J. – Cancer of the breast. In „Oxford Textbook of Surgery on CD-ROM". Oxford University Press – AND Electronic Publishing B.V., 1995, 808-838.

3, EKG and imagistic studies: pulmonary Rx, liver ultrasonography, skeleton Rx, bone scintigraphy and CT-computed tomography (thorax, skull, abdomen) if needed.[17]

The main treatment ways are surgery and radiotherapy (which allow local control over the disease), chemotherapy, hormone therapy, immunotherapy or molecular therapy and genetic therapy (which allow sistemic control over the disease).

CONSERVATIVE SURGERY

After classical surgery, conservative treatment has become a remarkable way of progress [18] in the issue of mammary cancer of limited dimensions.[19] The greatest advantage of conservative techniques is that it modifies the breast the least[20] and thus it can be considered both an advantage for the patients mental state.[21]

The conservative therapy is recomended in certain selected cases: in malignant tumors stages I and II, with tumor dimensions smaller than 2 cm and in the case in which the patient wishes to keep her breast; relatively contraindicated in the case of : tumors with dimensions between 3-5 cm, multiple tumors in the same quadrant, deep tumor, enlarged axillary adenopathy , recurrences after conservative surgeries [22], Ductal carcinoma in Situ and Lobular Carcinoma in Situ, history of colagen diseases (LES or scleroderma); and totally conterindicated: tumors with bigger than 5 cm dimensions, 2 tumors in different quadrans, pregnacy (irradiation is counterindicated), diffuse microcalcifications difuze on the mammography.[23]

The conservative treatment reffers especially to the primary mammary tumor and axillary lymph nodes.

a. The surgery of the primary tumor is dictated by the tumor dimension compared to the size of the breast, a lot of *conserving techniques* have been described in this respect*:* wide local excision(sectorectomy, quadrantectomy).

Regardless the peritumoral excision, there is a high probability that neoplastic cells are still present. That is why, in order to diminish the recurrence risk, post surgery irradiation is absolutely necessary, which has the capacity to control the disease locally. Radiotherapy can start two weeks after the surgery or when the wound has healed. The results of conservative surgery post-irradiation indicate total survival and no recurrences for 90% of the cases. Lack of post-surgical irradiation increases the risk of loca recurrence 25-45%.[24]

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[17]Angelescu N., Popa E., Bordea A., Jitea N., Burcoş T., Florea I., Aldea C., Zodieru Ileana – Strategia terapeutică în cancerul mamar local avansat. Chirurgia, 2002, 97(4):357-363.

[18]Bland K., Vezeridis M. – Sânul. În: *Schwartz S., Shires T., Spencer F. (sub red.)* „Principiile chirurgiei”, vol. I. Editura Teora, Bucureşti, 2005, 544-610.

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[21]Mogoş D., Vîlcea D., Vasile Ionescu M., Păun I., Teodorescu M., Ţenovici Mihaela, Florescu M. – Chirurgia conservatoare a sânului – 7 ani de experienţă, Chirurgia, 2003, 98(3):225-236.

[22]Bălănescu I., Blidaru Al., Duţu Rodica – Criteriile şi locul chirurgiei limitate în tratamentul cancerului mamar, Revista de Chirurgie, 1991.

[23]Farrar W.B. LaValele G.J., Kim J.A. –Breast Cancer, Cancer Surgery, McKenna R.J., Murphy Lippincott Company Philadelphia, 1994.

[24]Bălănescu I., Blidaru Al. – Cancerul sânului. În: *Angelescu N. (sub red)* „Tratat de patologie chirurgicală”. Editura Medicală, Bucureşti, 2001, 1187-1206

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Moreover, it is also very important that, intraoperative, the histopatological extemporaneus test should be done from the removed pieces/margins, in order to determine the positivity or negativity of the piece and establish the surgical procedures. [25]

b. The surgery of axillary lymph nodes is part of the conservative surgical treatment as the mammary cancer metastases frequently in the axillary lymph nodes.

The surgery of the sentinel lymph node is a technique which revolutionizes the surgery of the axillary lymph nodes. The concept of the "sentinel lymph node" reffers to the first axillary lymph node, which can be invaded by neoplastic cells through lymphatic drainage. The state of the sentinel lymph node reflects the situation of the whole axilla/ armpit.[26] If the sentinel lymph node is located and it proves to be non-invaded histopathologically, then a useless axillary disection is avoided.[27]

RADIOTHERAPY

It is an essential component in the treatment of mammary cancer, especially for the local or regional control of the disease, being recomended in the incipient stages of the disease when the conservative surgery is advisable or in the case of postmamectomies taking into consideration the dimensions of the tumor (>5 cm); the invasion of the regional lymph nodes, of the tegument and muscles and also the positive resection margin.

CHEMOTHERAPY

According to the moment (before or after the surgery) when it is applied, there is:

a. Adjuvant chemotherapy: is applied post surgery .

b.Neo-adjuvant chemotherapy: is applied preoperative, in advanced tumors for conversion to surgery state or in the case of smaller but more agressive tumors;

It is advisable in IIA – IIIC stages.

c. Palliative Chemotherapy : is advisable especially in the case of patients with metastatic disease without hormone rceptors and with distant metastases or who have hormonoresistance.[28]

In the case of anthracycline resistance we can use Taxanes (paclitaxel, docetaxel), VinorelbinE, Gemcitabine.[29]

HORMONE THERAPY

It is the essential key in the treatment of mammary cancer for the patients with positive estrogen and progesterone receptors (HR+). Tamoxifen reduces the recurrence risk up to 10

[25]Tartter P.I., Kaplan J., Bleiweiss I. – Lumpectomy margins, reexcision and local recurrence of breast cancer, The Amercan Journal of Surgery, 179; 81-85, 2000.
[26]Bălănescu I., Blidaru Al. – Cancerul sânului. În: *Angelescu N. (sub red)* „Tratat de patologie chirurgicală". Editura Medicală, Bucureşti, 2001, 1187-1206
[27]Giuliano A.E., Guenther J.M., morton D.L. – Lyumphatie mapping and sentinel lymphadenectomy for breast cancer. Ann Surg. 1994, 220(3):391-398.
[28]Peltecu G., Ionescu M., Lesaru M., Anghel R., Minea N., Laura O, Median D. – Cancerul de sân. În: *Irinel Popescu (sub red.)* Tratat de Chirurgie, vol. VIII. Editura Academiei Române, Bucureşti, 2008, 779-802.
[29]Bălănescu I., Blidaru Al. – Cancerul sânului. În: *Angelescu N. (sub red)* „Tratat de patologie chirurgicală". Editura Medicală, Bucureşti, 2001, 1187-1206

years and aromatase inhibitors (Anastrozole, Letrozole, Exemestane) are better tolerated, without any adverse effects and without inducing any resistance. Alos, Gn-RH agonists (Zoladex) can be used - which attempts a medical castration, which has, however transitory effects. [30]

MOLECULAR TARGET THERAPY

The election indications of target therapy aims at metastatic mammary cancer types which are also resistent to chemo-hormone therapy. Recently, the Transtuzumab is advisable for HER2/neu positive patients whith the presence or absence of lymph nodes invasion, but with tumoral dimensions bigger than 1 cm. [31]

For HER2/neu negative patients Bevacizumab is advisable , which is an anti-angiogenic therapeutic agent, more precisely anti-VGEF.[32]

II. THE IMPORTANCE AND OBJECTIVES OF THE STUDY

About 25 years ago, the treatment of mammary cancer types, even of reduced dimensions, still stipulated radical techniques of approaching the breast, such as: radical Halsted mastectomy, radical or modified Patey mastectomy, which had a mutilating character and major aesthetic-cosmetic consequences, and most times young patients remained with a psichological trauma. Today, due to knowledge extinction in the domain of mammary cancer biology, asociation of radiotherapy, chemotherapy and molecular target therapy became possible that the surgical act to be limited, without affecting survival at 5 and 10 years.

Of the total 142 cases with breast cancer, operated in the clinic, only 53 cases benefited from conservative surgical treatment. From the 1st of January 2014 until the 31st of December 2017, depending on the distribution according to years there were:

- in 2014 – 9cases;
- in 2015 – 15cases;
- in 2016 – 12 cases;
- in 2017 – 17cases;

The major advantages of the surgical conservative treatment are:

- they offer acceptable cosmetic results;
- psichological morbidity is much lower ;
- major effects like (anxiety, depressive episoades) are reduced;
- they give trust to the patient;
- sexual life is less affected.

[30]Peltecu G., Ionescu M., Lesaru M., Anghel R., Minea N., Laura O, Median D. – Cancerul de sân. În: *Irinel Popescu (sub red.)* Tratat de Chirurgie, vol. VIII. Editura Academiei Române, Bucureşti, 2008, 779-802

[31]Peltecu G., Ionescu M., Lesaru M., Anghel R., Minea N., Laura O, Median D. – Cancerul de sân. În: *Irinel Popescu (sub red.)* Tratat de Chirurgie, vol. VIII. Editura Academiei Române, Bucureşti, 2008, 779-802

[32]National Comprehensive Cancer Network – Clinical Practice Guidelines in Oncology – v 2007 – Breast Cancer – http://www.nccn.org.

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III. MATERIAL AND METHOD

This clinical study was done using a retrospective analysis of the neoplasm mammary cases, using informations from patient's observation and oncological sheets who have underwent a conservative surgery on the breast. The patients were diagnosed and treated in The Surgery Clinic of the Railway Clinical Hospital of Craiova, over a period of 4 years (1st of January 2014 – 31st of December 2017).

The conservative surgery of the breast was made following the surgery protocol of Milan, which supposes practicing this type of surgery for the mammary tumors in stages I or II (T1N0-1M0 or T2(<3cm)N0M0 (sectorectomy + axillary lymph nodes removal + radiotherapy on the breast; if post surgery N is positive (N+), chemotherapy amd hormone therapy are applied, but if N is negative (N-) hospital care and periodical controle is necessary).

Over the last 4 years (2014-2017) thanks to the good results obtained through conservative surgery (absence of local recurrences) the field of conservative surgeries has been enlarged for the tumors of more than 3 cm up to 5 cm.

IV. RESULTS

As we have already mentioned , the number of mammary neoplasm diagnosed cases in stages I and II in The Surgery Clinic of the Railway Clinical Hospital of Craiova registered a sudden growth between 2014 and 2015, decreasing in 2016, slightly increasing again in 2017 *(Table 1).*

YEAR	NUMBER OF CASES
2014	*9*
2015	*15*
2016	*12*
2017	*17*
TOTAL	***53***

Table no. 1 – The distribution according to years of the mammary neoplasm cases which underwent conservative surgeries

From the **etiopathogenic** point of view it was difficult to establish which risk factors were involved and up to what proportion they dominated the pathology of breast, however, the genetic factor (the family genetic inheritance) was present in 15 of the 53 cases. In 6 of the 15 cases, the patients had first degree relatives diagnosed with mammary cancer (mother and one sister), and in the other 9 cases the patients had second and third degree relatives diagno with mammary neoplasm.

Sex	Men	Women
Number of cases	*1*	*52*
%	*1,88*	*98,11*
Residence area	**Urban**	**Rural**
Number of cases	*31*	*22*
%	*58,49*	*41,50*

Table no.2 – Patients distribution according to sex and origin

From Table no. 2 we can notice a prevalence of the patients in the urban areas (31cases) in contrast with the rural areas (22 cases). The larger number of patients from the urban area can be due to the addressability of a large number of patients in The Surgery Clinic of the Railway Clinical Hospital of Craiova or due to the age group (51-60 years old) with a higher frequency of cases in the urban area. *(Figure 1).*

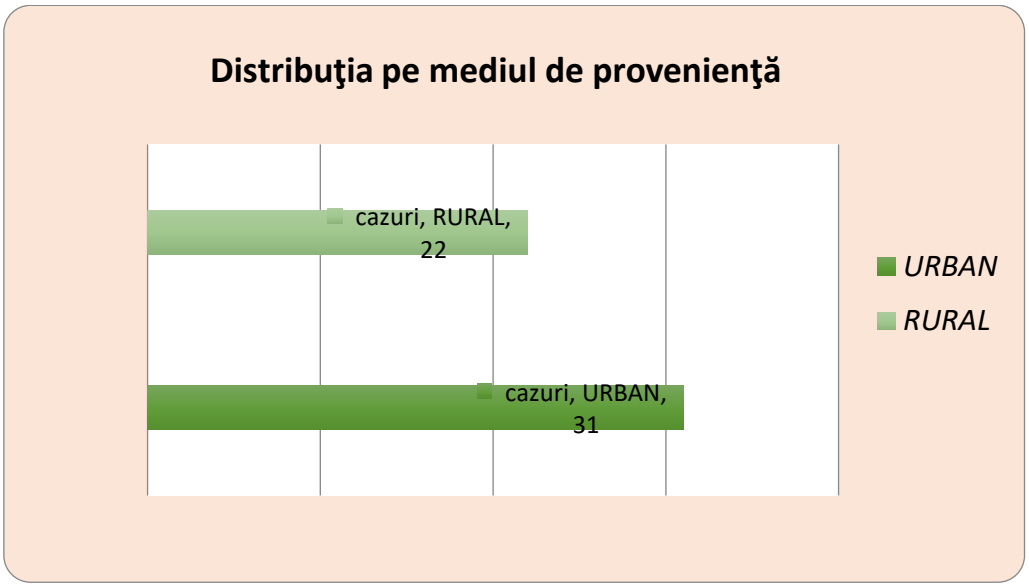

Figure 1. Patients distribution according to residence area

Among **the risk factors** encountered in the group of patients there can be mentioned:

- *obesity* – 13 cases (24,8%), but without making a distinction between the premenopausal or postmenopausal obesity;

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- *hormone imbalance;*
- *administration of oral hormone products* (estrogen or mixed) – met in 7 cases, used for the treatment of certain problems in the genital sphere and not as a contraception method;
- *small and repeated traumas* – were met in only one case, as an effect of long lasting professional activities (35 years of work at the sewing machine);
- *exposure to röntgen radiations* –3 persons had a history of more than 3 X-rays a year;
- *breast exxposure to UV radiations* – 2 cases;
- *endocrinological disorders;*
- *stress* – 11 cases, in which the following stress factors were present (deaths of family members, long-lasting conflicts) *(Figure 2)*

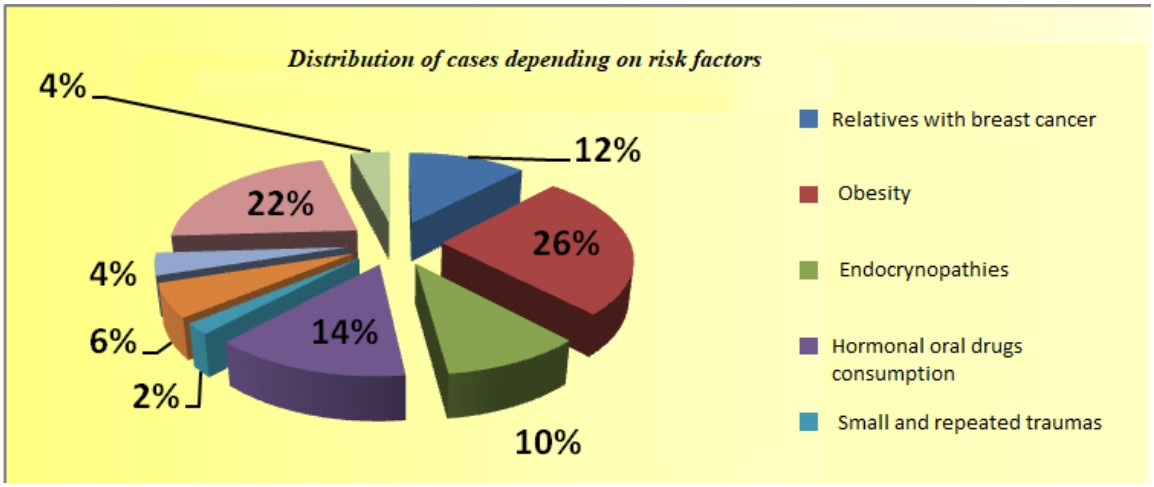

Figure 2 – Distribution of cases depending on risk factors

The average age of the patients with mammary neoplasm was 50 years old clasified on group ages between 25 to 89 years old. *(Figure 3)*

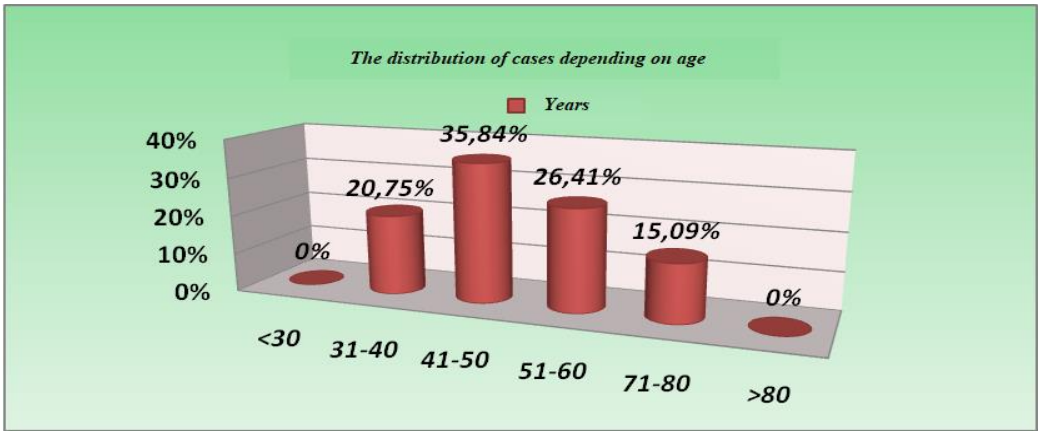

Figure 3 –The distribution of cases depending on age

According to personal medical history, we noticed that in 9 cases of the 53 studied cases there were presented significant personal medical history facts *(Figure 4)*:

- 3 cases with bilateral carcinoma;
- 1 cases with contralateral mammary neoplasm;
- 2 cases with ipsilateral neoplasm ;
- 2 cases of ipsilateral mastitis;
- 1 cases with fibrocystic ipsilateral mastose;

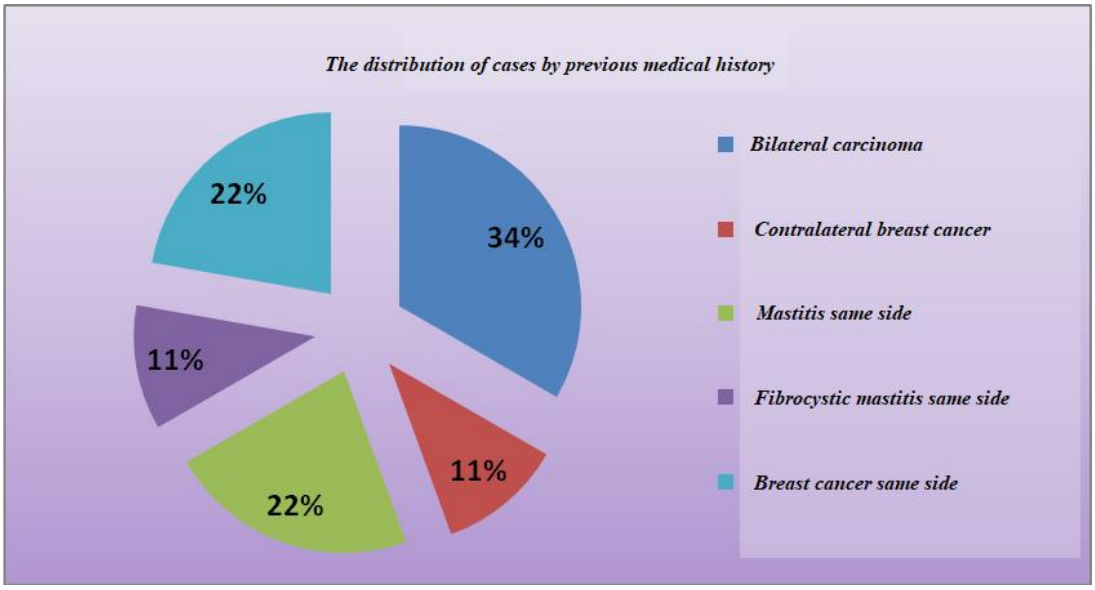

Figure 4 – The distribution pf cases by previous medical history

The macroscopic aspect of the tumor

From the macroscopic point of view all the tumors were solid, with an infiltrative aspect, of thick consistence, white- grey with yellowish zones, also, there were necrosis areas, bleeding, calcifications on a few pieces; most of the formations were unique.

The microscopical analysis of the tumor (the histologic types of tumors)

- *ductal carcinoma*:
  - ductal „in situ" (DCIS) – in 4 cases;
  - invasive ductal (DIC) – in 29 cazuri;
- *lobular carcinoma*:
  - lobular „in situ" (LCIS) – in 3 cases;
  - lobular invasive (LCI) – in 11cases;
- *mixed ducto-lobular carcinoma (MDL-C)*: 3 cases;
- *Paget Disease*: 1 case
- *Mucinous carcinoma:* 2 cases; *(Table no. 3)*

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HISTOPATHOLOGICAL TYPE	*NO. OF CASES (%)*
„in situ" tumors:	**7 (15,09)**
Intraductal solid carcinoma	2 (3,77)
Intraductal cribriform carcinoma	1 (1.88)
Intraductal comed type carcinoma	1 (1,88)
Intralobular carcinoma	3 (5,66)
Paget Disease	1 (1,88)
Invazive carcinoma:	**45 (84,90)**
Ductal invasive carcinoma	29 (54,71)
Lobular invasive carcinoma	11 (20,75)
Mixed Ducto-lobular carcinoma	3 (5,66)
Mucinous carcinoma	2 (3,77)

Table no. 3 – Histopatyological types

The analysis of cell differentiation / Nottingham grading (NG)

The BR degree is a useful and important parameter concerning the prognosis. In the study group we observed an important percentage of tumors with a high degree of differentiation, which is a bad prognosis. In the studied group we observed an important numbers of tumors with high differentiation degree, which is equivalent with a bad prognosis.

The mammary carcinomas which were analysed in system G through Nottingham grading *(Figure 5)*:

- First degree (well differentiated) score 3-5: 4 cases;
- Second degree (moderately differentiated) score 6-7: 9 cases;
- Third Degree(weakly-diferentiated) score 8-9: 40 cases.

According to the difference degree of mammary carcinomas we noticed that most of the cases were :

- weakly diferentiated carcinomas – third degree (75,47%),
- the fewest were the well-diferentiated – first degree (7,54%),
- the second were the moderately -diferentiated ones – second degree2 (16,98%).

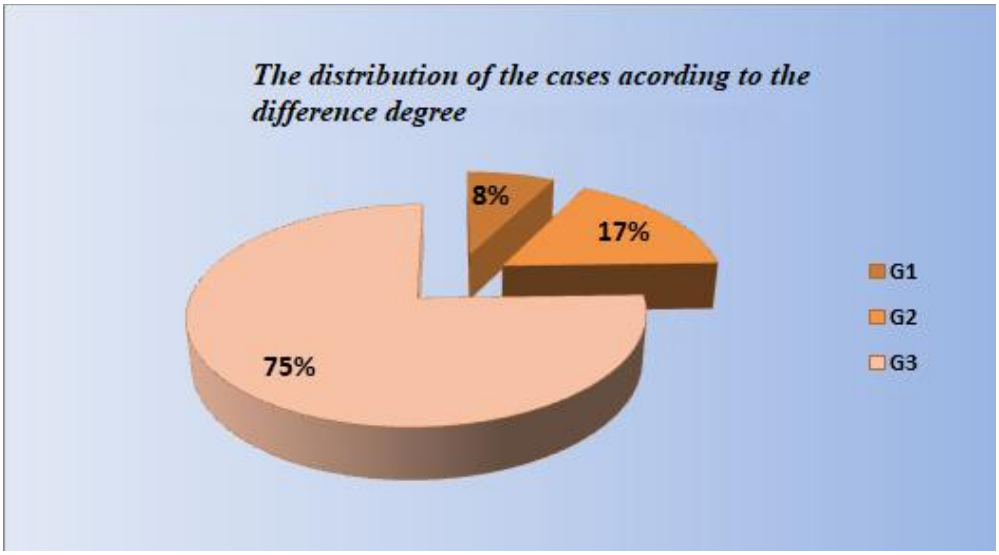

Figure 5 –The distribution of the cases acording to the differentiation degree (Nottingham grading)

Microscopic analysis of surgical edges of surgical parts

The microscopical study of the surgical edges revealed the fact that in 38 cases (72%) the remains were negative, in 8 cases (15%) the remains/margins were positive, and in 7 cases (13%) the status of the margins remained unknown.

After establishing the certain diagnosis and the TNM stage, it was possible to establish the treatment through reciprocal collaboration between the surgeon, the oncologist and the radiotherapist, thus the therapeutical protocole was adjusted to each case.

The purpose, the place and the techniques of the surgical conservative treatment

The double purpose of conservative surgery is to obtain a good local controle of the disease on long term and a minimum of local morbidity.

The selection of the patients for the use of conserving therapy was made following the indications and the contraindications of conserving surgery but also the particular cases taken separately. Some clinics have as a standard for the tumoral dimensions the limit of 3 centimetres of the tumor but in the Surgery Clinic of the Railway Clinical Hospital of Craiova, the conservative therapy is successfully made also for the tumors of 4 cm average, without any signs of local invasion.

The report between the tumoral dimension evaluated imagistically and the total volume of the breast is the one that dictates if the patient is suitable for conservative treatment. From this point of view it was noticed that if the patient has a bigger volume of mammary gland and the tumor is larger than 4 cm she is suitable for conservative surgery , while if the volume of the breast is small , even a small sectorectomy can have unacceptable cosmetic results.

The types of conservative surgical techniques which were used in the clinic:

- extended local excision (ELE) without axillary lymphadenectomy: in 8 cases;

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- extended local excision + ipsilateral axillary lymphadenectomy: in 41 cases;
- quadranectomy + ipsilateral axillary lymphadenectomy (LAI): in 3 cases.

Surgical treatment results:

The post-surgery evolution had the following results:

a) *deaths* intra or post-surgery : in 0 cases;

b)post-surgery *complications* (immediate and late) were represented by : hematoma, suppurating wounds, postoperative breast edema, arm lymphedema (swollen arm);

Immediate complications: *(Figure 6)*

1. After surgery bleeding –2 cases (3,77%):

- 2 cases of postoperative prepectoral hematoma, for which interventions were made with the aim of hemostasis completion , with positive results;

2. Wound suppurations – 1 case (1,88%);

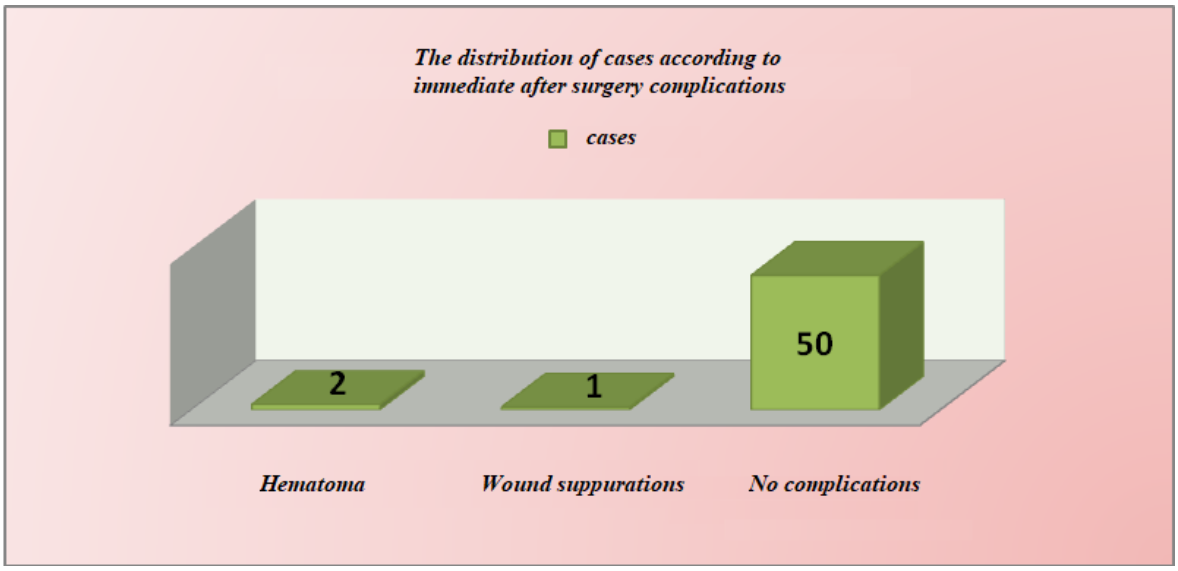

Figure 6: Case distribution according to immediate postoperative complications

Late complications: *(Figure 7)*

1. Swollen arm (after chronic edema) – appeared in 1 case (1,88%); the edema appeared gradually, becoming obvios 8 months after the surgery.

2. Fake recurrences – in 2 cases (3,77%):

- in one case an incomplely delimitated tumor was discovered;
- 1 case of post surgery sanguinolent nipple discharge .

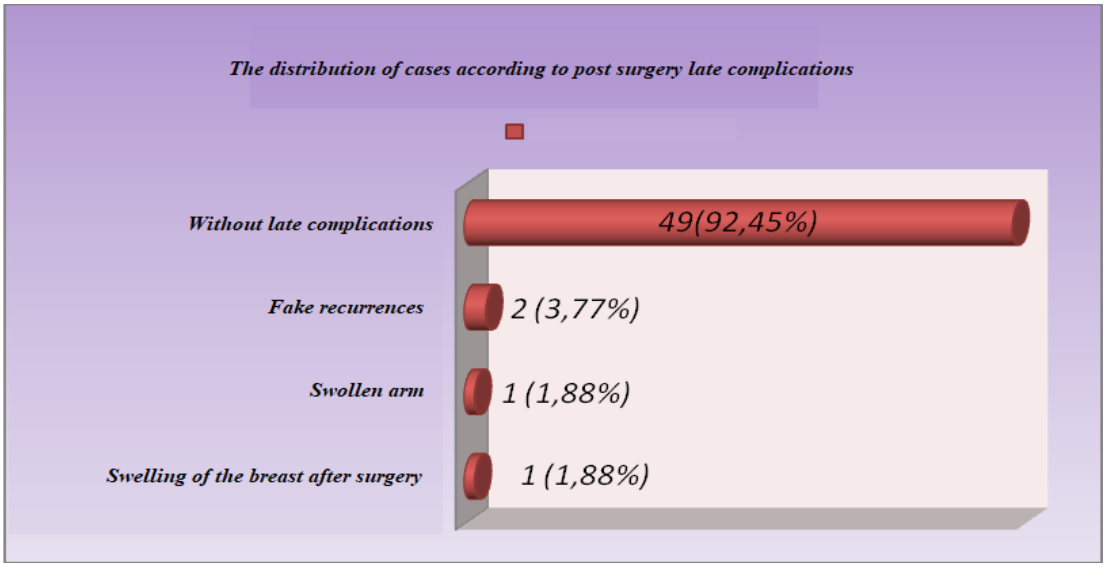

Figure 7 Cases distribution according to postoperative late complications

Reccurences

It is very well known that the number of recurrences is much higher in the case of conserving surgery in comparison with radical surgery, this fact being highlighted in the study group.

Real recurrences at the level of the operated breast were registered in 2 cases (3,77%). *(Figure 8)*

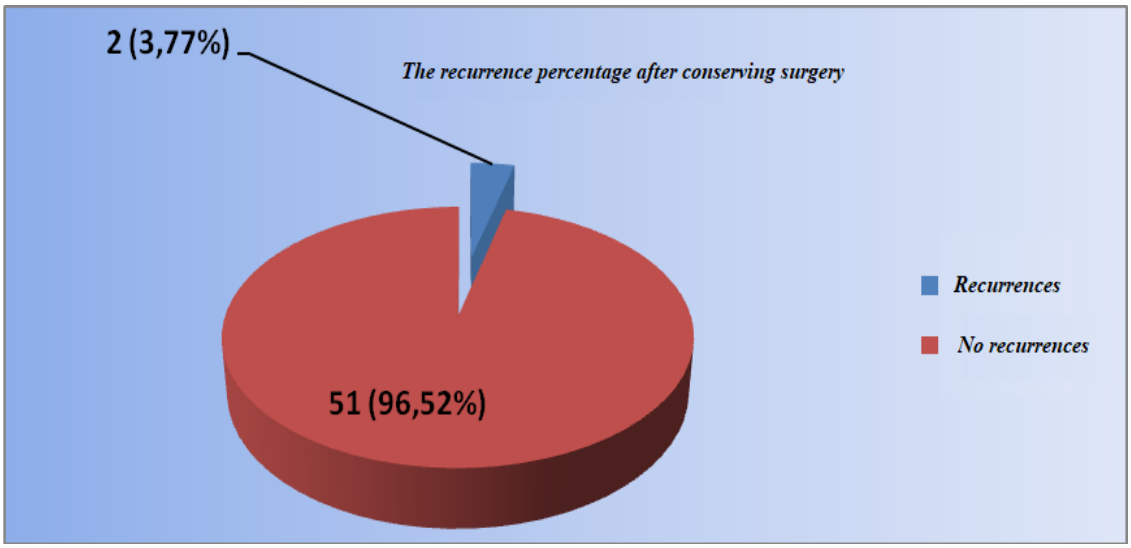

Figure 8 - The recurrence percentage after conserving surgery

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It is necessary to mention the fact that, in these 2 cases the patients did not respect the treatment according to the protocole the patients have to follow after they were diagnosed (they did not benefit from radiotherapy).

The way to solve the 2 recurrences which appeared post conservatory surgery were:

- in one case we used sectorectomy.
- in the other case radical the patient asked for total mamectomy .

V. CONCLUSIONS

1. The surgical conservatory treatment of mammary neoplasm in stages I and II represent a good option after which the survival chances post surgery are are the same as in mutilating surgery.
2. Apart from the patient's option, one of the most essential elements in applying conservative surgery is represented by the report between the volume of the tumor and the volume of the breast which has to be taken into consideration; such as the arbitrary decision of the maximum dimensions opted for in conserving surgery is excluded; what matters is obtaining an aesthetic result in maximum oncological safety regardless the dimension of the tumor, otherwise radical mastectomy is preferred followed by breast reconstruction.
3. Post surgery radiotherapy on the mammary gland is compulsory in order to get a satisfactory recurrence percent.
4. The complex oncological treatment applied post surgery can determine the conversion of some cases to the posibility of applying conservative surgery.
5. Conservative surgery in stages I and II must become *"the golden standard"* in the treatment of mammary cancer, because the results obtained over the years completely justifies this affirmation.
6. The age of the patients at the moment of the mammary tumor diagnosis is an important factor concerning ipsilateral recurrences which occured; from this point of view we observed that the occurence of ipsilateral recurrences is more frequently met at the patients under 40 years old in comparison with those who are over this age.
7. The improvement of the therapeutical results with the raise of life expectancy to 5 and 10 years and with the cost reduction of the treatment, can be obtained only by discovering the breast neoplasma at an early stage, which is possible through adopting and respecting screening programmes meant to discover the breast neoplasma as early as possible.

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