UNIVERSITY OF MEDICINE AND PHARMACY
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SURGERY OF BREAST CANCER AFTER NEOADJUVANT SYSTHEMIC TREATMENT

PHD THESIS SUMMARY

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SUMMARY

INTRODUCTION

Breast cancer represents an important health problem in the whole world with its increasing incidence and a mortality rate which is still high. Breast cancer screening allows early diagnosis and reduces mortality. In the United States of America breast cancer is diagnosed in early stages (stage I or II) in 63% of the cases [1]. In Western Europe while the incidence is still rising the mortality is decreasing. One cause for the downward trend of mortality rate is early diagnosis through screening. In Romania there is not a functional national screening program and this is why most of breast cancer patients are diagnosed in locally advanced breats cancer, over 50% in stage III or IV.

Besides early diagnosis the improvement of breast cancer treatment has determined the lengthening of the lifespan of patients as well as their quality of life.

The key to success is multidisciplinary management. This begins with an accurate, clinical, imagistic, histological, biochemical, immunohistochemical, genomic and genetical diagnosis followed by a personalized treatment.

The role of the “tumor board” in diagnosis and treatment is essential for success.

The association of different methods of treatment leads to the best results. Surgery, the oldest type of treatment for breast cancer, has evolved over the years due to: general anesthesia, the improved understanding of the biology of tumors, radiotherapy, systemic treatment, early diagnosis, individualized treatment, the identification of pathogenic mutations involved in the development of breast cancer, the involvement of patient in the therapeutic decision making as well as the association of the principles and techniques of oncological surgery with those of plastic surgery.

Surgery was forced to adapt to a new indication of systemic treatment, the preoperative one.

While at the beginning systemic preoperative treatment was indicated only to patients with a locally advanced breast cancer, more recently the idea of preoperative chemotherapy has been discussed. The principle is based on the reasoning of treating a systemic disease with a systemic treatment.

One of the advantages of systemic preoperative treatment, that impacts the breast cancer surgery, is that it increases the rate of the breast conservation [2].

The response to systemic neoadjuvant treatment is becoming better and better with the introduction of newer anti tumoral medication and the anti-Her2 therapy.

With the improvement of the response to treatment, surgery becomes a challenge. While neoadjuvant treatment is advantageous to improving the survival rate, it also makes surgery more difficult. In this situation, the paradigm of surgery needs to be adapted after neoadjuvant treatment from the surgery made as an initial treatment so the patient can benefit regarding the indication and surgical technique and the response to treatment.

The surgeon must anticipate and foresee the evolution of the disease under treatment and plan the time and technique of the surgery accordingly.

Modern oncological breast cancer surgery can no longer be based solely on the surgeon's senses because many times the lesion is microscopical and cannot be seen and palpated during the surgery, especially after neoadjuvant treatment. This is why the preoperative marking of the lesions and lymph nodes, the preoperative localisation, the preoperative ultrasound, the radiography of the excisional specimen, the identification of sentinel lymph nodes as well as the intraoperative histopatological exam are essential to the success of surgery.

In the Oncological Institute "Prof. Dr. Alexandru Trestioreanu" of Bucharest the diagnosis, research and treatment of breast cancer are prioritized domains.

The purpose of the thesis is the improvement of the surgical management for patients with breast cancer that are under systemic neoadjuvant treatment.

The study which included patients with unilateral breast cancer with indication for systemic preoperative treatment followed by surgical treatment has two phases.

In phase I we followed the evolution of patients under systemic preoperative treatment and analyzed the response to the treatment and its impact on surgical management.

Following the evolution of these cases, we noticed that in some of them, in a paradoxical way, the success of the oncologist, in terms of response to the treatment, becomes a challenge for the surgeon. The surgeon must be ready for the response to the systemic neoadjuvant treatment and this response can be complete in more than half of the cases [2].

If the response is not anticipated and monitored deciding on the best surgical approach is more difficult and the patient is at the risk of not benefiting from a surgical standpoint from the favorable evolution.

Starting from these ascertainments, the scientific objectives were the elaboration and implementation of a surgical protocol for a selected category of patients with a recommendation for neoadjuvant treatment and finding the best ways of validating the efficiency of this protocol.

The protocol is aimed at patients with breast cancer in advanced stages (II and IIIA) with a immunohistochemical aggressive type (triple negative and Her2 positive).

The implementation of this protocol in phase II of the study lead to an increase in the rate of breast conservation with the certitude of removing the tumor bed, the decrease of axillary surgery in cases with a clinical and imagistic complete response of the adenopathies following systemic preoperative treatment, the low rate of reintervention and better aesthetic results. In this way a selective, beautiful and safe surgery can be performed following neoadjuvant treatment.

These types of results can only be obtained in a multidisciplinary team which includes doctors from the following specialties: Radiology and imagistic, Anatomical Pathology, Oncology, Nuclear Medicine, Oncological Surgery and Plastic and Reconstructive Surgery.

In the future we intend to continue this research and include patients with an immunohistochemical luminal B type that may have a high rate of response to neoadjuvant treatment; evaluate the response to the treatment following the introduction of the dual Her2 blockade (Trastuzumab+Pertuzumab) in neoadjuvant therapy; decide on criteria for selection of cases in which the surgical intervention could be avoided with the documentation of the full histopathological response by vacuum aspiration and to analyze the extent of axillary lymphadenectomy in cases of residual disease following systemic preoperative treatment.

PERSONAL CONTRIBUTION

The purpose of the thesis

The purpose of the thesis is represented by the elaboration and implementation of a protocol of surgical management for patients with systemic neoadjuvant treated breast cancer.

This protocol consists in:

- selection of patients with breast cancer which have an indication for systemic neoadjuvant treatment, following the recommendation of “tumor board”
- pretherapeutic marking of the tumor and if it is the case of the positive lymph node
- clinical and imagistic follow-up (breast ultrasound, mammography and MRI) of the response to treatment
- establishing the indication and surgical technique after the end of the neoadjuvant treatment
- preoperative localization of the radio-opaque clip at the breast level and, if necessary, at the axillary level
- x-ray of the excised specimen to confirm the correct excision
- intraoperative evaluation of the resection margins and circumferential edges by intraoperative histopathological examination
- using the sentinel lymph node biopsy technique in case of patients with no clinical and imagistic signs of lymph nodes invasion before initiating neoadjuvant treatment
- extending the indication of this technique to patients with positive lymph nodes at diagnosis and clinical and imagistic complete response following neoadjuvant treatment
- targeted axillary dissection technique
- intraoperative exam of the sentinel lymph nodes and lymph nodes that have been marked before treatment
- intraoperative marking of the tumor bed to guide postoperative radiotherapy

The goals of this protocol are:

-safer surgery from an oncological standpoint

-a higher rate of conservative treatment

-elective surgery, avoiding mastectomy and the necessary axillar lymphadenectomy

-decreasing the rate of reintervention caused by the failure to identify the lesion, invasion of the resection edges or lymph node invasion

-lower death rate

-a better result from an esthetic point of view

Materials and methods

This prospective study included 523 consecutive patients with unilateral breast cancer, that needed systemic neoadjuvant treatment followed by surgery.

The study has two phases. The patients were divided in multiple groups depending on the stage of the disease and the immunohistochemical type.

Phase I

The main objectives of phase I were the evaluation of the pathological response to the systemic neoadjuvant treatment depending on the immunohistochemical type of breast cancer and the stage of the disease; the analyzes of the surgical intervention (mastectomy, conservative treatment, lymphadenectomy, sentinel lymph node biopsy) and the evaluation of the reintervention rate.

The secondary objective was appreciating the esthetic postoperative in case of patients with breast conservative treatment.

The criteria for inclusion were:

-unilateral breast cancer confirmed by “true-cut” biopsy

- IIA, IIB, IIIA, IIIB and IIIC stages

-immunohistochemical type: luminal A, luminal B, triple negative and HER 2 positive

The criteria for exclusion were:

- stage IV
- age (<18 or >70 years old)
- occult cancers
- bilateral breast cancers

Following these criteria 452 patients have been included between January 2016 and December 2018.

During the study several patients were excluded: 8 patients that have stopped coming to the surgical visits, 6 patients which stopped the neoadjuvant treatment, 3 patients that had comorbidities that were contraindications to the surgical intervention, 9 patients that had indications for preoperative radiotherapy after finishing neoadjuvant treatment, 4 patients that no

longer wanted the surgical intervention and 2 patients that died during the systemic neoadjuvant treatment.

Thereby, 420 patients were eligible for the first phase of the study.

The analysis of the results obtained in phase I have shown that the complete histopathological response after neoadjuvant systemic treatment is achieved in a higher rate in patients with less advanced stages and triple negative and Her2 positive types. The greatest difficulties in these categories of patients were deciding on the surgical indication as well as performing the surgical intervention.

Following the results obtained in phase I of the study a protocol of surgical management of patients with neoadjuvant treatment was elaborated.

Phase II

The main objectives of phase I were the evaluation of the pathological response to the systemic neoadjuvant treatment depending on the immunohistochemical type of breast cancer and the stage of the disease; the analyzes of the surgical intervention (mastectomy, conservative treatment, lymphadenectomy, sentinel lymph node biopsy) and the evaluation of the reintervention rate after the implementation of this protocol of surgical management in patients that have been treated with neoadjuvant treatment.

The secondary objective was appreciating the esthetic postoperative in case of patients with breast conservative treatment after the implementation of this protocol of surgical management in patients that have been treated with neoadjuvant treatment.

The results obtained have been compared to those obtained in the first phase in similar groups of patients.

The criteria for inclusion were:

-unilateral breast cancer confirmed by “true-cut” biopsy

- IIA, IIB, IIIA stages

-immunohistochemical type: triple negative and HER 2 positive

The criteria for exclusion were:

- IIIB, IIIC and IV stages

- age (<18 or >70 years old)

- occult cancers

- bilateral breast cancers

Following these criteria 119 patients have been included between January 2019 and July 2020.

Several patients have been excluded: 2 patients that no longer wanted to continue systemic neoadjuvant treatment, 4 patients that had comorbidities that were contraindications for the surgical intervention, 4 patients that had an indication for radiotherapy after finishing systemic preoperative treatment, 3 patients that no longer wanted to have the surgical intervention preformed and 3 patients that were infected with the SarsCov2 virus and needed a longer period for recovery.

Thereby 103 patients were eligible in the second phase of the study.

To appreciate the effectiveness of the implemented protocol we compared the results of patients in phase II from a surgical point of view with similar groups of patients (considering the stage and immunohistochemical type), selected from the phase I of the study. Only patients with the immunohistochemical triple negative and Her2 positive types and IIA, IIB, IIIA stages were selected from the phase I.

The group of patients with a triple negative molecular subtype from phase I contains 113 patients and the group of patients with the same molecular subtype in phase II contains 41 patients.

The group of patients with a molecular Her2 positive subtype in phase I contains 152 patients and the group of patients with the same molecular subtype in phase II contains 62 patients.

Patients under 40 years of age with family history of breast or ovarian cancer have been tested for a multigenic panel (used to establish the risk of contralateral breast cancer).

The therapeutic indication has been established in the “tumor board”, formed with doctors from different specialties (oncology, surgery, radiotherapy, imagistic, pathological anatomy).

The surgical interventions were performed by the same team of doctors of the Department II of Oncological Surgery of the Oncological Institute “Prof. Dr. Al. Trestioreanu, Bucharest.

The neoadjuvant treatment was decided considering the immunohistochemical type, the stage of the disease, and the characteristics of the patient.

We considered histopathological complete response at the level of the tumor to be the absence of invasive cells (ypT0) and at the level of the axilla the absence of lymph node invasion (ypN0). The presence of the “in situ” carcinoma only (ypTis) has considered to be a complete histopathological response as well.

Results

Phase II

Breast surgery

In the group with triple negative molecular subtype in phase I, among the 113 patients, only 53 patients (46.9%) underwent conservative treatment, and 60 patients (53.1%) underwent mastectomy. In the phase II group with the same molecular subtype, among the 41 patients, 26 patients (63.4%) underwent conservative treatment, and 15 (36.6%) underwent mastectomy.

In the group with positive Her2 molecular subtype from phase I, among the 152 patients, only 82 underwent conservative treatment, and 70 underwent mastectomy. In the phase II group with the same molecular subtype, among the 62 patients, 40 underwent conservative treatment, and 22 underwent mastectomy.

In the group with triple negative molecular subtype in phase I 27 patients (23.9%) performed conservative treatment by oncoplastic technique, while in the group in phase II 14 patients (34.1%) had carried out conservative treatment using the oncoplastic technique.

There are differences between the group with triple negative molecular subtype from phase I and that from phase II regarding the percentage of patients with conservative treatment by oncoplastic technique. In the phase II group, 54% of the patients with breast conservation underwent conservative treatment through the oncoplastic technique, while in the phase I group, the percentage is lower (50.9%). There are differences between the group with triple negative molecular subtype from phase I and that from phase II regarding the percentage of patients with conservative treatment by oncoplastic technique. In the phase II group, 54% of the patients with breast conservation underwent conservative treatment through the oncoplastic technique, while in the phase I group, the percentage is lower (50.9%).

From the point of view of conservative treatment, in the group with positive Her2 molecular subtype from phase I, 19 patients (12.5%) performed conservative treatment through the oncoplastic technique, while in the group from phase II 21 patients (33.9%) had performed conservative treatment by oncoplastic technique

There are differences between the group with positive Her2 molecular subtype from phase I and that from phase II regarding the percentage of patients with conservative treatment by oncoplastic technique. In the phase II group, 53% of the patients with breast conservation

performed conservative treatment through the oncoplastic technique, while in the phase I group, the percentage is lower (23%).

The Chi-square test was used to test whether there was an association between the type of intervention and the groups from which the patients came, or, in other words, whether the variables were correlated or independent.

TIP		Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)	Point Probability
HER 2+ și TNBC	*Pearson Chi-Square*	*12.407[a]*	*2*	*.002*	*.002*		
	Likelihood Ratio	11.790	2	.003	.003		
	Fisher's Exact Test	11.796			.003		
	Linear-by-Linear Association	10.576[b]	1	.001	.001	.001	.000
	N of Valid Cases	368					
a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 22.67.							
b. The standardized statistic is 3.252.							

Table 5.18. Chi-Square test for testing the association between intervention type and groups

The results of the Chi-square test support the hypothesis that there are significant differences between the two groups in terms of the type of intervention and more precisely the degree of breast conservation for both Her2 positive and triple negative patients (Pearson Chi-Square=12.407). Asymptotic Significance<0.05 demonstrates that we have sufficient evidence to reject the null hypothesis of independence of the variables and accept the existence of the link between them. This corelation, i.e. the greater degree of breast preservation in group 2 is statistically significant.

Moreover, when the patients were separated into two distinct groups (those who received conservative treatment and those who did not receive conservative treatment), group 2 patients were found to be 1.482 times more likely to receive conservative treatment compared to group 1 patients (Relative risk=1.482; Confidence level=95%; Confidence interval=1.048-2.095).

Breast conservative treatment	Value	95% Confidence Interval	
		Lower	Upper
Odds Ratio for Tratament conservator (Da/Nu)	.582	.364	.931
For cohort LOT = 1	.863	.761	.979
For cohort LOT = 2	*1.482*	*1.048*	*2.095*
N of Valid Cases	368		

Table 5.19. Estimating the odds of conservative treatment versus mastectomy

Axillary surgery

The percentage of patients with triple negative molecular subtype who also performed sentinel lymph node/s biopsy was approximately 34% in the phase I group and approximately 68% in the phase II group.

The percentage of patients with Her2 positive molecular subtype who underwent identification and sentinel lymph node biopsy was 29% in the phase I group and 71% in the phase II group.

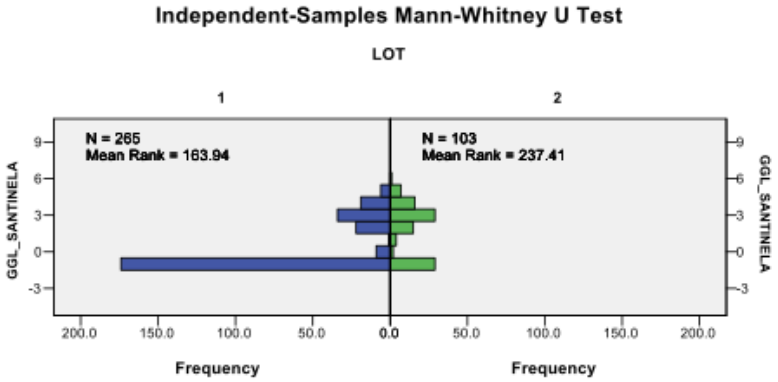
The Kolmogorov-Smirnov statistical test was applied to test the null hypothesis that the two lots (lot 1 and lot 2) come from a normal distribution. For the 'sentinel lymph node' variable the test value is 0.404 (with 265 degrees of freedom) for batch 1 and 0.213 (with 103 degrees of freedom) for batch 2. In the case of both batches Sig. Kolmogorov-Smirnov is 0.000 ($p<0.001$), which means that there is sufficient evidence to reject the null hypothesis that the variable follows a normal distribution. The same result is supported by the Shapiro-Wilk test.

Testing for normality							
Sentinel lymph node		Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	LOT	Statistic	df	Sig.	Statistic	df	Sig.
	1	.404	265	.000	.671	265	.000
	2	.213	103	.000	.862	103	.000
a. Lilliefors Significance Correction							

Table 5.30. Testing the normality of the distribution of the Sentinel Lymph node variable

Given that the data do not come from a normally distributed population, to test whether the distribution of the 'sentinel ganglion' variable is different in the two groups (group 1 and group 2) the non-parametric Mann Whitney U statistical test was applied.

The Mann Whitney U test quantifies whether there are significant differences between the average ranks calculated for each batch (163.94 for batch 1 and 237.41 for batch 2). How Asymptotic. Sig. (2-sided test), is 0.000 ($p<0.001$), it can be stated that there is sufficient evidence to reject the null hypothesis that the distribution of the variable 'sentinel ganglion' is the same in the two groups. Thus, batch 2 has a higher average rank than batch 1, which implies that in batch 2 the sentinel node technique was used more widely compared to batch 1, this difference being statistically significant.



Total N	368
Mann-Whitney U	19,097.000
Wilcoxon W	24,453.000
Test Statistic	19,097.000
Standard Error	832.220
Standardized Test Statistic	6.548
Asymptotic Sig. (2-sided test)	.000

Figure 5.42. Testing the independence of the distribution of the Sentinel Lymph node variable

For the variable 'excised lymph nodes' the value of the Kolmogorov-Smirnov statistical test is 0.142 (with 265 degrees of freedom) for group 1 and 0.290 (with 103 degrees of freedom) for

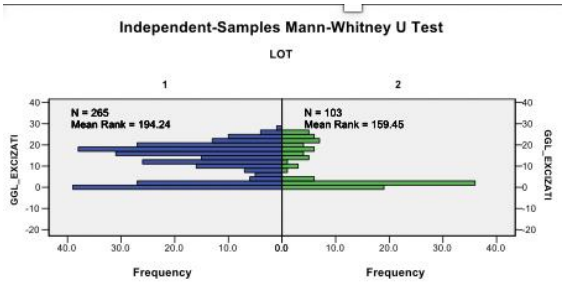
group 2. In the case of both groups the p-value is 0.000 (p<0.001), which implies rejecting the null hypothesis that the variable follows a normal distribution. The two tests, Kolmogorov-Smirnov and Shapiro-Wilk demonstrate that the variable is not normally distributed in any of the groups.

Testing for normality							
Excised lymph nodes	LOT	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
		Statistic	df	Sig.	Statistic	df	Sig.
	1	.142	265	.000	.911	265	.000
	2	.290	103	.000	.786	103	.000
a. Lilliefors Significance Correction							

Table 5.31. Testing the normality of the distribution of the variable excised lypmph nodes

Testing the normality of the distribution allowed the choice of the appropriate test to verify the hypothesis that the distribution of the variable 'excised ganglia' is different in the two groups (group 1 and group 2). Thus, the Mann Whitney U non-parametric statistical test was applied.

The mean ranks in the two batches were: 194.24 for batch 1 and 159.45 for batch 2. Asymptotic. Sig. (2-sided test) is 0.000 (p<0.001) and thus rejects the null hypothesis that the distribution of the variable 'excised ganglia' is the same in the two groups. Thus, group 1 has a higher mean rank than group 2, which implies that more nodes were excised in group 1 compared to group 2, this difference being statistically significant.



Total N	368
Mann-Whitney U	11,067.500
Wilcoxon W	16,423.500
Test Statistic	11,067.500
Standard Error	913.225
Standardized Test Statistic	-2.825
Asymptotic Sig. (2-sided test)	.005

Figure 5.43. Testing the independence of the distribution of the variable Excised Lymph Node

Rate of reinterventions for positive margins

The reintervention rate for positive margins in phase I in the triple negative and Her2 positive comparative groups was 6.03% (16 patients out of a total of 252) and 0.97% in the triple negative and Her2 positive comparative groups in phase II

Regarding the re-excision rate, the chi-square test results support the hypothesis that there are significant differences between the two groups for both HER 2 and TNBC patients (Pearson Chi-Square=4.322). Asymptotic Significance<0.05 demonstrates that we have sufficient evidence to reject the null hypothesis of independence of the variables and accept the existence of the link between them. This corelation, i.e. the lower degree of re-excision in group 2 is statistically significant.

HER 2 și TNBC	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	4.322[a]	1	.038		
Continuity Correction[b]	3.248	1	.072		
Likelihood Ratio	5.646	1	.017		
Fisher's Exact Test				.049	.026
Linear-by-Linear Association	4.310	1	.038		
N of Valid Cases	368				
a. 1 cells (25.0%) have expected count less than 5. The minimum expected count is 4.76.					
b. Computed only for a 2x2 table					

Table 5.39. Chi-Square test for testing association between re-excision rate and lots

The tests showed that group 2 patients were 4.940 times more likely not to undergo re-excision compared to group 1 patients (Relative Risk=4.940; Confidence Level=95%; Confidence Interval=0.733-33.310).

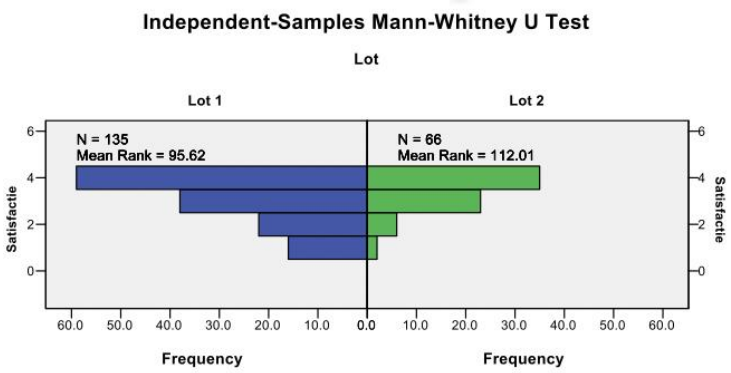
Re-excizie	Value	95% Confidence Interval	
		Lower	Upper
Odds Ratio for Re-excizie (Nu / Da)	.153	.020	1.166
For cohort Lot = 1	.754	.658	.864
For cohort Lot = 2	4.940	.733	33.310
N of Valid Cases	368		

Table 5.40. Estimation of the risk of re-excision

The aesthetic result after conservative treatment

The aesthetic result after conservative treatment was appreciated by the patients in phase II as being 53.03% very good result, 34.85% good result, 9.09% satisfactory result and 3.03% unsatisfactory result, unlike the patients in phase II and who appreciated the aesthetic result 43.7% very good result, 28.15% good result, 16.29% satisfactory result and 11.86% unsatisfactory result.

Regarding satisfaction with the aesthetic outcome, the Mann Whitney U Test demonstrates (Asymptotic. Sig.< 0.05) that there is sufficient evidence to reject the null hypothesis that the distribution of the variable is the same in the two groups. Thus, batch 2 has a higher average rank than batch 1, which implies that in batch 2 the degree of satisfaction with the aesthetic result was higher, this difference being statistically significant.



Total N	201
Mann-Whitney U	5,181.500
Wilcoxon W	7,392.500
Test Statistic	5,181.500
Standard Error	360.475
Standardized Test Statistic	2.015
Asymptotic Sig. (2-sided test)	.044

Figure 5.53. Testing the independence of the distribution of the variable Satisfaction with the aesthetic outcome

DISCUSSIONS

The results obtained in phase I of this study confirmed the beneficial effect from the oncological point of view of the neoadjuvant systemic treatment.

We followed the response to neoadjuvant systemic treatment, depending on the immunohistochemical type and the stage of the disease.

We observed that the response rate to systemic neoadjuvant treatment was the highest in case of breast cancer patients with less advanced stages, with a more aggressive immunohistochemical type (triple negative and Her2 positive).

The complete imagistic response rate, regardless of the immunohistochemical type, was higher than the histopathological complete response rate (37.61% vs. 33%). This means that, after neoadjuvant systemic treatment, there must not be a complete histopathological response, but it is sufficient that the response is complete imagistic to create difficulties regarding surgical management.

In the case of the complete imagistic response, difficulties arose regarding the indication and performance of the surgical intervention at the breast level. Complete imagistic response as well as complete histopathological response was more frequent in patients with less advanced stages and triple negative and Her2 positive immunohistochemical type.

In phase I of the study, 68% of the surgical interventions were mastectomies.

At the level of the axilla, sentinel lymph node biopsy was performed in the cases that were N0 before the neoadjuvant systemic treatment, but in the majority of N1, even if they had a complete clinical and imagistic response, axillary lymphadenectomy was performed.

The rate of re-interventions for positive margins in the histopathological paraffin examination was 7.3%.

We analysed the postoperative aesthetic result after conservative breast treatment or oncoplastic surgery. Appreciation of the aesthetic result can be from the point of view of the patient, from the point of view of the operating surgeon or from the point of view of a third person. We chose to evaluate the degree of appreciation of the aesthetic result from the patient's point of view, considering that her opinion is the most important.

The percentages were: 43.7% very good result, 26.67% good result, 15.55% satisfactory result and 14.08% unsatisfactory result.

These unsatisfactory results are probably due to the fact that wide mammary excisions were performed to make sure that the oncologically affected tissue was removed. Even so, reinterventions were necessary for additional excisions that damaged the aesthetic result. Even more, the deformation after axillary lymphadenectomy was detrimental to the aesthetic result.

In the literature, the assessment of the aesthetic result after conservative breast treatment after neoadjuvant systemic treatment is: 55% excellent, 25% good, 15% satisfactory and 10% unsatisfactory [3].

High rate of mastectomies (some performed even if the response to the treatment was complete), axillary lymphadenectomies (even in the situation where the axillary adenopathies have disappeared), high rate of re-excisions, a higher rate than we would have liked of unsatisfactory aesthetic result and the desire to improve these results are the reasons why we developed and implemented a surgical management protocol that is the subject of phase II research.

The protocol tried to address the problems that we observed in the analysis of phase I patients when we found that the beneficial effect of the neoadjuvant treatment, namely the response to the treatment with the reduction to the disappearance of the breast tumor and the axillary adenopathies, makes it more difficult to establish a surgical indication and technique. This response was not accompanied most of the time by the decrease in the extent of breast and axillary surgery, nor by the improvement of the aesthetic aspect.

The protocol that we developed and implemented aims to improve the surgical management of patients treated with neoadjuvant systemic therapy. We wanted to develop a protocol of proactive action, in which we are prepared so that the answer does not take us by surprise, by adapting the indication and the surgical technique to the local situation after the completion of the preoperative systemic treatment and thus the patient benefits from the point of view of surgical intervention by the response to neoadjuvant systemic treatment.

The most important elements of the protocol were: the pre-therapeutic marking with a radio-opaque markings of tumors and histopathologically confirmed axillary adenopathies, the pre-operative localization of the radio-opaque landmark and the implementation of the sentinel lymph

node identification and biopsy technique in patients with nodal invasion who responded to treatment.

All these measures were proposed for a safe and selective surgery. In addition, this type of surgery led to better aesthetic results.

From the results obtained in phase I, we considered that radio-opaque clips should be placed in patients in less advanced stages (stages II and IIIA) with aggressive immunohistochemical types (triple negative, Her2 positive) with an indication of neoadjuvant systemic treatment.

When a needle biopsy was also performed in the axilla, we tried to place a radio-opaque clip in the positive lymph node.

Radio-opaque clips were not placed in all patients because some refused axillary needle biopsy and in other cases the position of the adenopathy made such maneuvers risky.

The marking before neoadjuvant treatment of tumors with a radio-opaque clip allowed targeted breast resections, guided by the preoperative localization. The identification of the tumor remnants and the marked tumor bed was possible in all cases.

An important role in the correct performance of the conservative surgical treatment is played by the preoperative localization of the tumor relict and the radio-opaque clips. This marking is all the more important in oncoplastic surgery techniques in which the incisions are not necessarily at the level of the quadrant where the tumor is located. This is the case with the different oncoplastic techniques: "batwing", "round-block", "key-hole", "wise-pattern", "J-plasty", "L-plasty" that we have used and which must be adapted depending on the location of the breast tumor.

These techniques allow safe excision of the tumor, tumor remnants or tumor bed (depending on the response) as well as obtaining a good postoperative aesthetic result. In the case of macromastia and breast ptosis, the aesthetic appearance of the breasts can be more beautiful than the preoperative one.

Preoperative localization is very useful even in cases where mastectomy is performed, especially when a type of subcutaneous mastectomy with skin preservation is used, which aims at immediate breast reconstruction. In these situations, knowing exactly where the tumor bed is, we can excise circumferential resections to have an intraoperative histopathological examination. Of course, the intraoperative histopathological examination has limits, but through the intraoperative examination we have reduced the rate of re-interventions for positive margins.

The most used method of preoperative localization, when the clinical and even imagistic response is complete, is the placement of a wire.

There are several options for performing preoperative localization. These include the percutaneous placement within or adjacent to the lesion of magnetic seeds ("Magnetic Occult Lesion Localisation"), radioactive seeds ("Radioactive seed localisation"), radioactive tracer injection ("Radioguided Occult Lesion Localisation") or carbon marking (coal poweder) [4].

The excised specimen is sent during the surgical intervention to the radiology service to have its radiography performed so that there is confirmation of the correct resection. Afterwards, an intraoperative histopathological examination of the margins can be performed.

The intraoperative histopathological examination of the resection margins, which has limits because the accuracy of the histopathological examination with paraffin is superior, allows the number of re-interventions to be reduced.

In this way, breast surgery is safe and selective. Modern surgery exceeds the sensory dimension with the help of these techniques that represent a kind of augmented reality.

By using this protocol, we obtained a significant difference between the patients treated in phase I and the patients treated in phase II in terms of the breast conservation rate. In the case of the triple negative molecular subtype, the breast conservation rate was 63.4% in the phase II group vs. 46.9% in the phase I group, and in the case of the Her2 positive molecular subtype, the rate was 64.5% in the phase II group vs. 53.9% in the group from phase I.

In the case of oncoplastic surgery, the rearrangement of the breast tissue makes it difficult for the radiotherapist to locate the area on which the "boost" must be applied [5]. Marking the resection margins with clips before plastic reconstruction of the breast is essential for the correct delimitation of the field for postoperative radiotherapy [6].

The implementation of the protocol allowed the more frequent use of oncoplastic surgery techniques (triple negative: 34.1% in the phase II group vs. 23.9% in the phase I group; Her2 positive: 33.9% in the phase II group vs. 12.5% in the group from phase I).

Secondly, the strictness in all stages of the protocol had a beneficial impact on the re-excision rate for positive margins or recuperation. In the comparative batches from phase I and phase II, the difference is significant by 5 %.

Another component of breast cancer surgery is regional lymph node surgery. As the main lymphatic drainage of the breast is towards the axilla, axillary surgery is most often associated with breast surgery in oncological pathology.

Axillary surgery has a double purpose: curative, local control of the disease and obtaining prognostic and predictive information.

The extent and techniques of axillary surgery have constantly evolved. If initially axillary surgery was represented by a lymphadenectomy as complete and detailed as possible, it became more and more selective.

The landmarks of axillary surgery were: the introduction of the sentinel lymph node identification and biopsy technique, ACOSOG Z011, the introduction of the sentinel lymph node identification and biopsy technique after neoadjuvant treatment for patients who were cN0 too and then also in those who had positive lymph node at the time of diagnosis, but favourable response to treatment.

So axillary lymphadenectomy is currently indicated only in cases where there is significant lymph node invasion (>3 invaded nodes), in cases where surgery is the first intention or in cases of residual lymph node burden after neoadjuvant treatment.

Sentinel node identification and biopsy after neoadjuvant treatment is a valid alternative to axillary lymphadenectomy with an acceptable false-negative result rate [7-10].

The NCCN guideline recommends the use of the sentinel lymph node identification and biopsy technique in the case of patients with breast cancer and positive lymph node who, after neoadjuvant systemic treatment, have a complete clinical and imagistic response in the axilla to avoid axillary lymphadenectomy [11].

In phase II of the study, we extended the indication for the use of the sentinel lymph node/nodes identification and biopsy technique in the case of patients with pre-therapeutic positive lymph node, who had a complete clinical and imagistic response after neoadjuvant systemic treatment

Sentinel node identification and biopsy was performed in 68% of the cases with triple negative patients and 71% of the cases of Her2 positive patients, phase II.

In phase II of the study, the aesthetic result was assessed as being significantly better than before the implementation of the protocol. The percentages were: 87.88% good and very good result compared to 71.85%.

The implementation of this surgical management protocol led to a safer, from an oncological point of view, selective and beautiful surgery.

A safer surgery because of the certainty that the residual tumor or tumor bed have been excised, selective because there is no need for wide resections and beautiful because a result of this protocol is a more aesthetically pleasing result.

CONCLUSIONS

Breast cancer surgery after neoadjuvant treatment represents a challenge because the response to treatment often makes the indication and surgical technique more difficult. And as the complete answer is obtained more and more frequently, this subject is topical.

My personal contribution was to develop and implement a surgical management protocol for neoadjuvant systemically treated breast cancer patients with less advanced stages (stages II and IIIA) and more aggressive immunohistochemical type (triple negative and Her2 positive).

This protocol consisted of:

- pre-therapeutic marking of the tumor and if it is the case of positive lymph node
- clinical and imagistic follow-up (breast ultrasound, mammography and MRI) of the response to treatment
- establishing the indication and surgical technique after the end of the neoadjuvant treatment
- preoperative localization of the radio-opaque clip at the breast level and, if necessary, at the axillary level
- x-ray of the excised specimen to confirm the correct excision
- intraoperative evaluation of the resection margins and circumferential edges by intraoperative histopathological examination
- extending the indication of this technique to patients with positive lymph nodes at diagnosis and clinical and imagistic complete response following neoadjuvant treatment
- targeted axillary dissection technique
- intraoperative exam of the sentinel lymph nodes and lymph nodes that have been marked before treatment
- intraoperative marking of the tumor bed to guide postoperative radiotherapy

The use of this protocol allowed a significant increase in the breast conservation rate (63.4% vs. 46.9% in the case of the triple negative molecular subtype and 64.5% vs. 53.9% in the case of the Her2 positive molecular subtype), the extent of sentinel lymph node/node identification and biopsy technique (63% vs. 33.6% in the case of the triple negative molecular subtype and 71% vs.

39% in the case of the Her2 positive molecular subtype) thus avoiding unnecessary complete axillary lymphadenectomies.

Using this protocol we improved the identification of the residual tumor or the tumor bed, which allowed an oncologically safe surgical intervention, thus reducing the re-intervention rate from 7.3% to 1%.

The use of the protocol allowed at the same time a precise, selective surgery reducing the volume of the breast excision, which together with the use of oncoplastic surgery techniques determined the significant improvement of the postoperative aesthetic aspect. The good and very good results increased from 71.85% to 87.88%.

The disadvantages are represented by the cost of these medical devices and the imagistic examinations required for monitoring during the neoadjuvant treatment.

The directions in which the research must continue are the in time validation of the results obtained from an oncological and aesthetic point of view and the development of a guide for good surgical practices for patients with neoadjuvant treated breast cancer.

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