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Neoadjuvant Treatment in Young Women with Breast Cancer

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Abstract

Objective: *This study aims to analyze neoadjuvant therapy in the complexity of unique clinical and biological features of breast cancer at young ages.*

Methodology: *A retrospective evaluation of the personal oncology records of 108 patients diagnosed with breast cancer up to the age of 40 and treated with neoadjuvant therapy at the Oncology Service in Albania from 2010 to 2020 was performed.*

Results: *From 108 female patients up to the age of 40, from 25 cities of Albania treated with neoadjuvant therapy for breast cancer in our Service, most were with locally advanced breast cancer, multifocal and inflammatory breast cancer. Only 4.6% of patients were in the early clinical stage and underwent neoadjuvant therapy to perform conservative breast surgery. Statistical analysis with Kendall's correlation coefficient found some significant links. A significant correlation was found between neoadjuvant therapy and clinical response ($p = 0.008$); between clinical response and pathological stage ($r = 0.719$, $p < 0.001$); between pathological stage and relapse ($r = -0.370$, $p < 0.001$).*

***Conclusion**: Neoadjuvant regimens based on anthracyclines and taxanes remain the preferred regimens. Targeted therapy increases the possibility of PCR in Her 2 positive patients. The clinical response can be considered as a predictive factor of the pathological response. Advanced pathological stages are associated with more frequent locoregional and distance recurrences.*

***Keywords**: breast cancer, young ages, neoadjuvant treatment*

Background:

Breast cancer is the most common malignant pathology in women, is mostly diagnosed in the post-menopausal period. However, breast cancer can be diagnosed at a younger age. About 11% of breast cancer cases occur in women under the age of 45 **[**1**]** and 5% of them are under the age of 40 **[**2**]**. Every year over 1000 women under the age of 40 die from this disease **[**2**]**. Identifying breast cancer at a young age poses a challenge due to the lack of screening at these ages. Generally, at younger ages the course is more aggressive, the prognosis less favorable and the survival rate lower than in older patients **[**3**]**.

Despite attempts to define "young age", the definitions are often ambiguous and open to different interpretations. However, in the case of breast cancer, "young ages" are considered women under 40 years of age diagnosed with this malignant pathology **[**3**]**. Many epidemiological studies have shown that younger ages with breast cancer have a lower survival compared to older ages which could potentially be associated with greater biological aggressiveness of the tumor. At a young age, breast tumors are mostly estrogen receptor-negative, have a high degree of differentiation, have increased lymph-vascular invasion, increased Ki-67 and p53 **[**4**]**. Younger ages have a higher incidence of triple-negative, luminal B and HER2-positive breast cancer compared to older ages **[**5**]**. Analysis of differential gene expression has shown that overexpression of genes associated with a poor prognosis is more common at younger ages **[**6**]**.

Research on the treatment of breast cancer at a young age should focus on two questions still without clear answers: (1) when oncologists should treat breast cancer at a young age aggressively regarding the impact of this treatment on mortality and (2) when the choice of aggressive treatment is based on the subtype, grade and stage of the disease regardless of age. Resolving this debate gives more and more importance to targeted therapy in the treatment of breast cancer at a young age **[**7**]**. However, it is widely accepted that the value of neoadjuvant systemic therapy is the key to treating breast cancer at a young age. Data from the NSABP (National Surgical Adjuvant Breast and Bowel Project) have shown that

neoadjuvant chemotherapy treatment is more effective in achieving a complete pathological response at these ages compared to older ages **[**8**]**. The initial goal of neoadjuvant treatment was to convert a locally advanced and inoperable cancer into an operable. However, from this initial concept to the present day the importance and role of neoadjuvant treatment have changed immensely. Today, neoadjuvant treatment is used in locally advanced breast cancer, inflammatory breast cancer, to reduce large tumors for conservative surgery, and in breast cancer with clinically negative lymph nodes but with an unfavorable tumor profile where systemic adjuvant treatment is predicted **[**9**]**. It should not be overlooked that neoadjuvant treatment offers an opportunity for individualized therapy and allows tumor sampling before, during and after treatment enabling further scientific research to be performed **[**10**]**. A meta-analysis of nine studies did not show a significant difference in disease progression, distance recurrence time, and overall survival between neoadjuvant treatment and adjuvant treatment, but in the second phase, a trend in favor of neoadjuvant chemotherapy was found in young ages about the disease-free period and overall survival **[**11,12**]**.

Purpose of the study

The main purpose of this study is to analyze the neoadjuvant treatment of breast cancer at young ages, through:

- Evaluation of selection criteria for patients candidates for systemic neoadjuvant therapy.
- Effectiveness of neoadjuvant treatment at young ages based on histopathological diagnosis, disease stage, molecular subtype.
- Evaluation of the type of neoadjuvant therapy used.
- Evaluation of various therapeutic agents.
- Evaluation of targeted therapy.
- Assessment of disease prognosis after neoadjuvant therapy.
- Assessment of quality of life and survival.

Material and methodology

This is a retrospective study that utilizes existing data and allows the formation of hypotheses based on the database. The stages of realization of this study took place during 2020.

Methods and criteria

Data for this study were collected from personal medical records of patients in the Oncology Service at the University Hospital Center "Mother Teresa", Albania, from 2010 to 2020. The search of the medical records was done by years in the relevant cabinets in our Service. The selection of the subjects of this study was carried out based on three main criteria:

- Gender: All subjects included in the study are female.
- Age: All patients included in the study are up to 40 years of age.
- Diagnosis and treatment: All patients included in the study underwent systemic neoadjuvant therapy for breast cancer.

Data

Data for this retrospective study were collected from the personal oncology records of female patients up to 40 years of age, diagnosed with breast cancer and treated with neoadjuvant therapy at the Oncology Service at University Medical Center “Mother Teresa” from 2010 to 2020. Age limit of patients reduces the number of subjects included in the study, but being the only public multidisciplinary service and reference center for cancer treatment in Albania we were able to collect data on patients from different cities obtaining a clearer picture of the situation in our country.

Statistical analysis

The data collected from the oncology files were transferred to the Microsoft-Excel program from where they were then processed in the Statistical Package for Social Sciences, version 25.0. Statistical procedures and techniques applied in the analysis of this data are described in detail below:

- For all categorical variables (nominal including binary/dichotomous and ordinal scale), absolute numbers and corresponding percentages were calculated.
- Random relationships between variables were analyzed through Kendall’s tau correlation technique.
- The presentation of the data was done through simple and composite tables, as well as through graphs of the type bar-diagram, line diagram, etc.
- The values of $p \leq 0.05$ were considered significant

Results

The total number of patients in this study is 108. All patients are female and up to 40 years old. The youngest patient was 25 years old, while the largest number of breast cancer cases was 40 years old. The mean age is 36. The number of patients treated with neoadjuvant therapy by age is shown in figure 1.1.

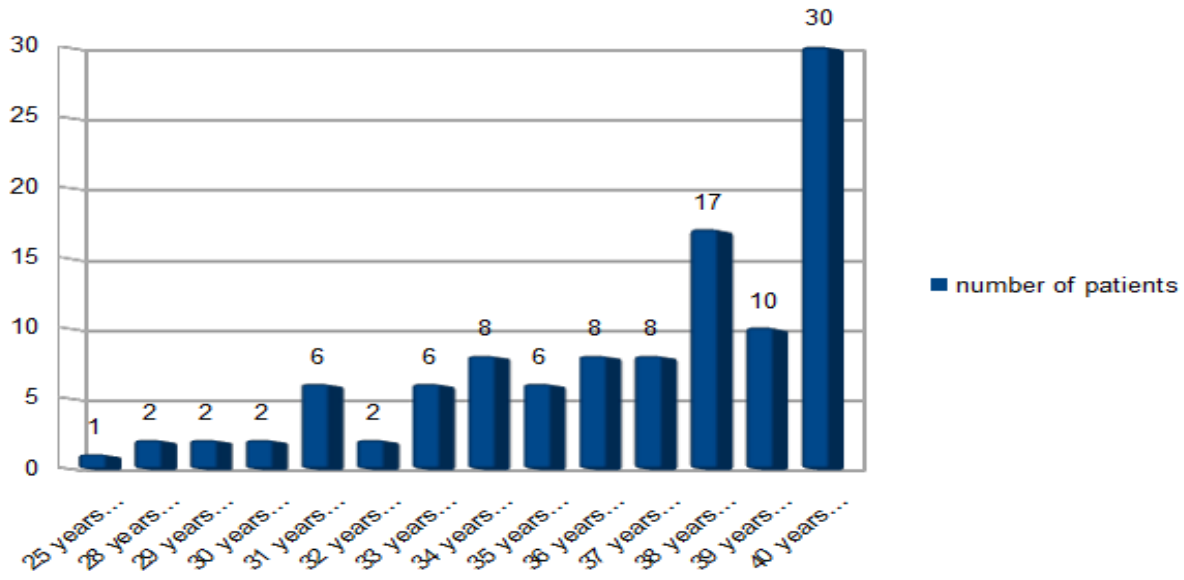

Fig. 1.1 *Number of patients treated with neoadjuvant therapy by age*

Also based on the data, the patients had a mean menarche age of 13.54 years and had performed an average of 2.0 births. Only 5% of patients had a family history of breast and gynecological cancer.

Data were collected from oncology medical records from 2010 to 2020 showing an increase in the number of patients treated with neoadjuvant therapy from year to year and especially the last 5 years. This is a result of improving the multidisciplinary approach to breast cancer treatment in our Service. The number of patients according to the years of study is reflected in the figure. 1.2.

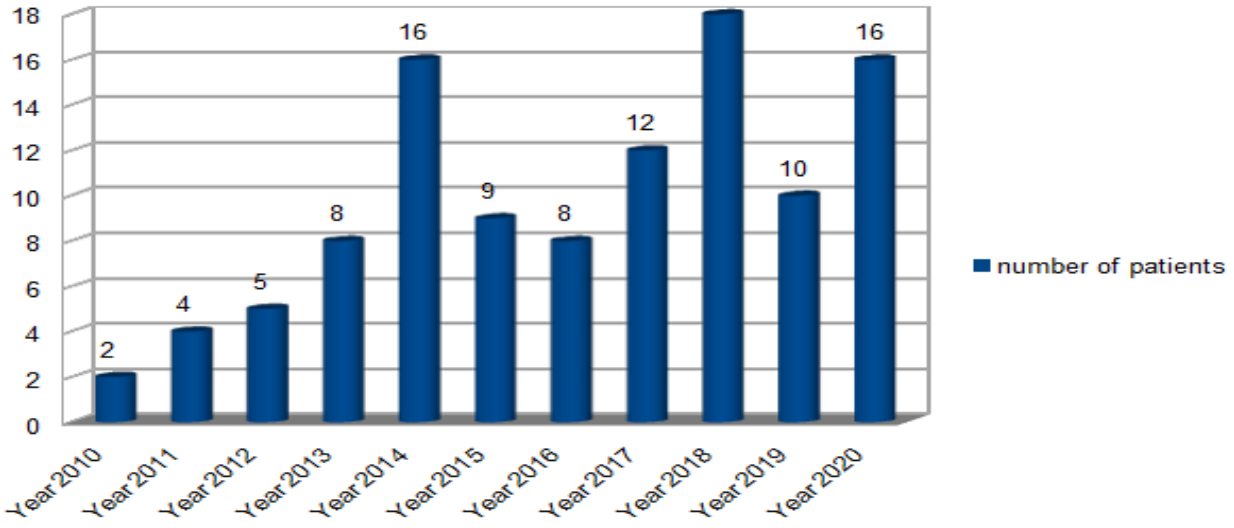

Fig. 1.2 *Number of patients by years of study*

TNM classification was done before the start of neoadjuvant therapy for each patient and comparison generally after the first 4 cycles and at the end of therapy to evaluate the clinical response. The presentation of the number of patients according to the classification of cT, cN and clinical stage at the time of diagnosis are presented in Figures 1.3, 1.4 and 1.5, respectively.

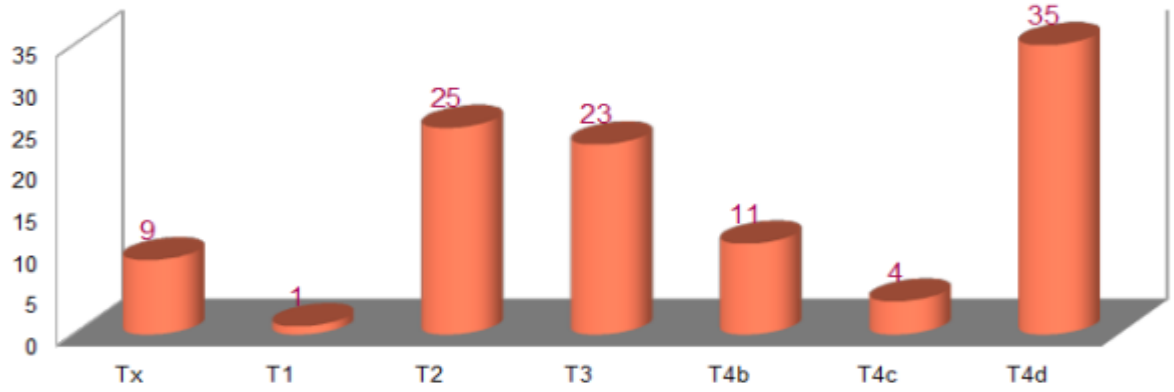

Fig. 1.3 *Number of patients according to clinical classification T*

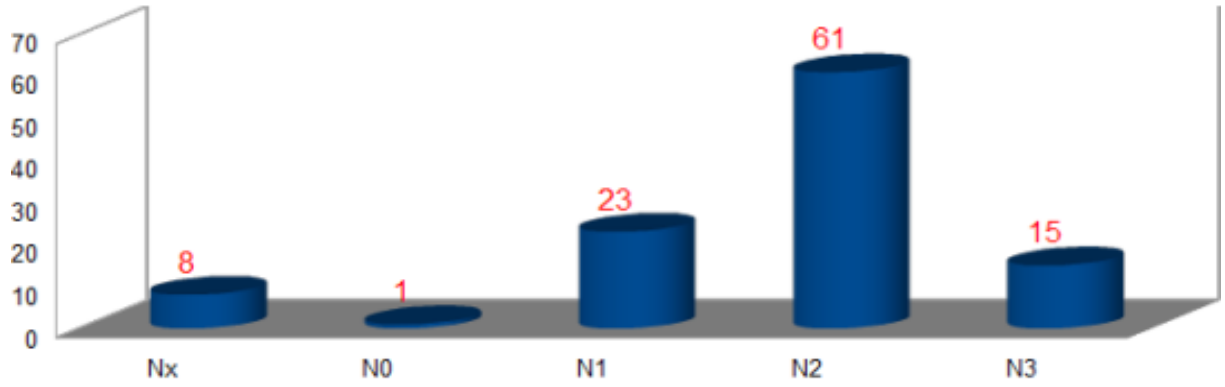

Fig. 1.4 *Number of patients according to clinical classification N*

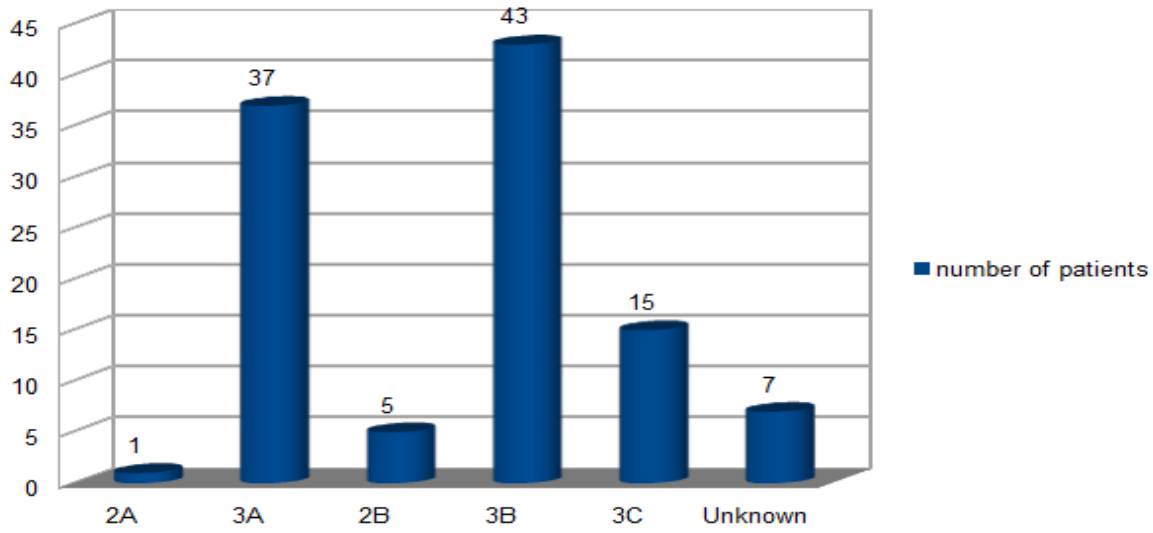

Fig. 1.5 *Number of patients according to the TNM classification*

To assess the presence or absence of distant metastases, pulmonary radiography and abdominal echography were used in some cases and other cases computed tomography (CT), when there was a suspicion of metastasis of the disease at a distance. The clinical classification was based on data from the 8th edition of the American Joint Committee on Cancer (AJCC). The largest number of patients were with breast cancer in stage 3B at the time of diagnosis, 43 patients from the total of the subjects in the study. Only for 7 patients, the clinical staging could not be done due to the lack of data in the respective medical records. Generally, the medical records documented the sampling method used for histopathological verification of the tumor. In our study, we found the use of three different methods: incisional biopsy, core biopsy and tumor resection. It should also be mentioned that in no case was performed the histopathological verification of the axillary lymph node. The most common histological

type was infiltrative ductal carcinoma, in 86 patients, followed by infiltrative lobular carcinoma, mixed carcinoma and some specific types of ductal carcinoma such as medullary, mucinous, papillary. Only in one case, the pathological report confirmed the infiltrative carcinoma of the non-specific type, while for three patients the pathological report could not be found on the medical records before the start of neoadjuvant therapy. Histopathological diagnosis according to the number of patients is illustrated in figure 1.6.

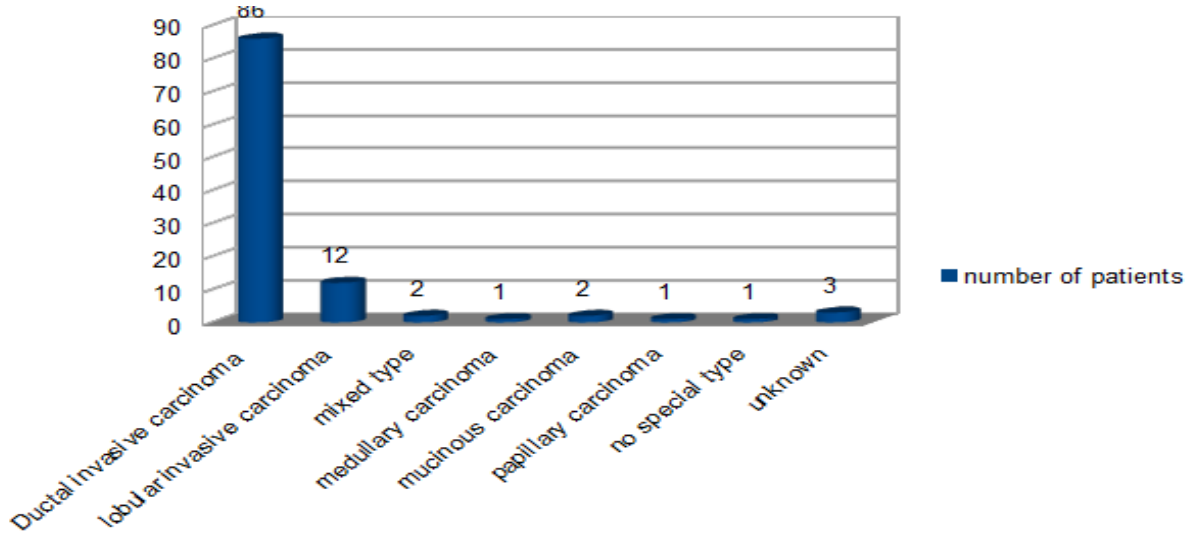

Fig. 1.6 *Histopathological diagnosis before NACT according to the number of patients*

In our study, the percentage was calculated for each molecular subtype based on only 58 subjects for whom immunohistochemistry was performed before NACT. This calculation showed that 57% of patients had Luminal B breast cancer. Patients with Luminal A and Her2 positive breast cancer were in almost the same percentage (17%), while TNBC was found in 9% of patients.

Neoadjuvant chemotherapy according to the 4 CAF or AC scheme (cyclophosphamide, doxorubicin, 5-fluorouracil / doxorubicin, cyclophosphamide) and 4T (taxane) was mostly used. Other schemes used were: CAF, FEC / EC + T (5-fluorouracil, epirubicin, cyclophosphamide + taxane). Only in three subjects the weekly taxol scheme AC / EC + 12T was used. In 19 patients due to HER2 positivity also targeted therapy with Trastuzumab was used during neoadjuvant therapy. In only two patients despite Her 2 positivity, Trastuzumab started as adjuvant treatment. Trastuzumab and Pertuzumab were combined in 5 patients. In those patients in whom the disease has progressed during a treatment regimen, other therapeutic regimens with preparations such as Gemcitabine, Carboplatin, Capecitabine, etc. have been tried. The number of cycles and neoadjuvant treatment schemes according to the number of patients are reflected respectively in fig. 1.7 and 1.8.

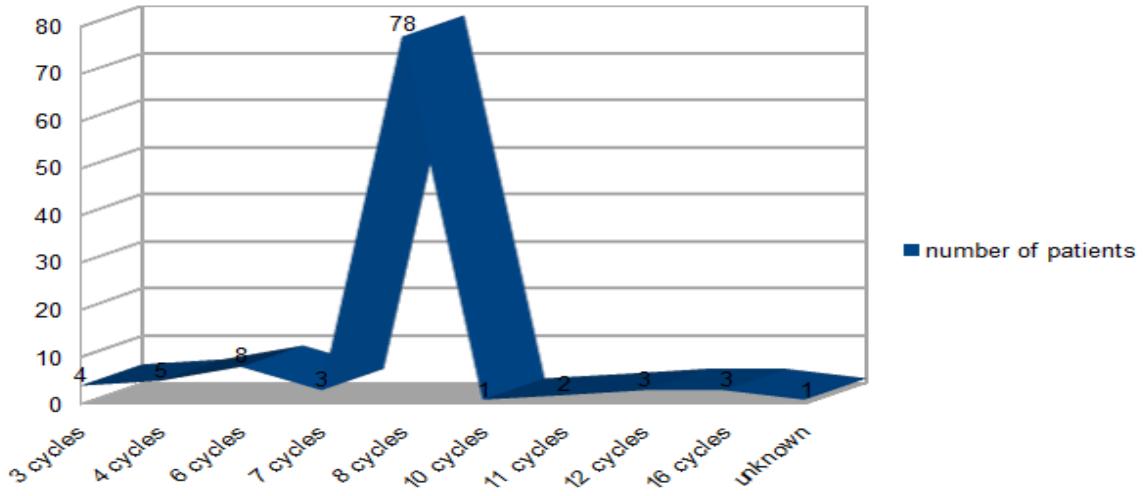

Fig. 1.7 *Number of cycles of neoadjuvant therapy according to the number of patients*

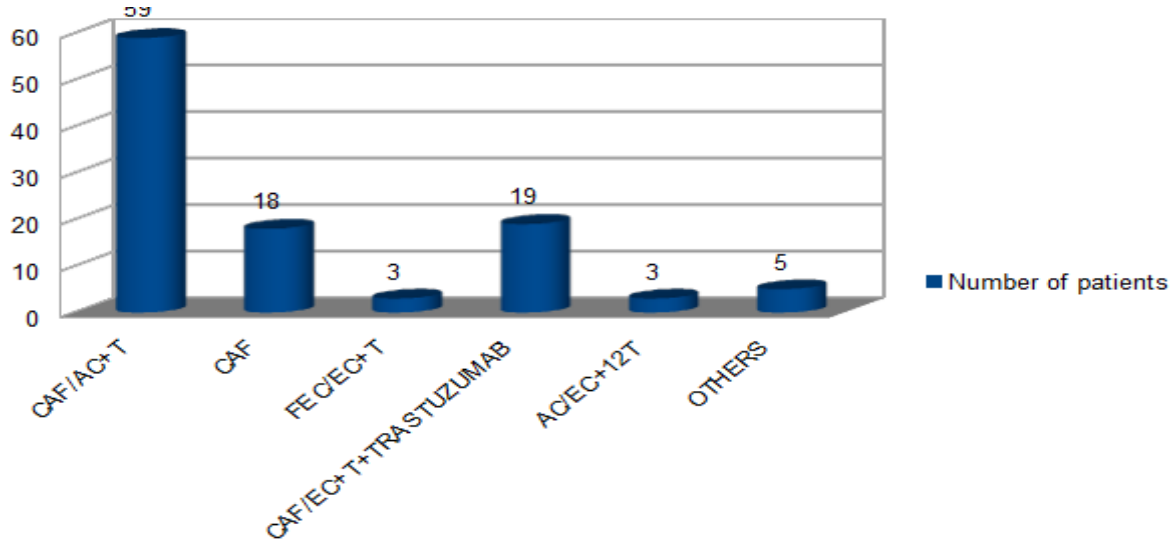

Fig. 1.8 *Neoadjuvant treatment schemes by the number of patients*

The evaluation of the clinical response to neoadjuvant therapy was performed by the oncologist, the objective examination by the oncologist surgeon and the imaging control through an ultrasound performed at least twice before the definitive surgery. The clinical response to neoadjuvant therapy is categorized according to RECIST (Response Evaluation Criteria In Solid Tumors) in complete response (CR), partial response (PR), stable disease (SD) and disease progression (PD), for patients in the study is shown in fig. 1.9 and 1.10, respectively according to the clinical response to breast mass and nodal status.

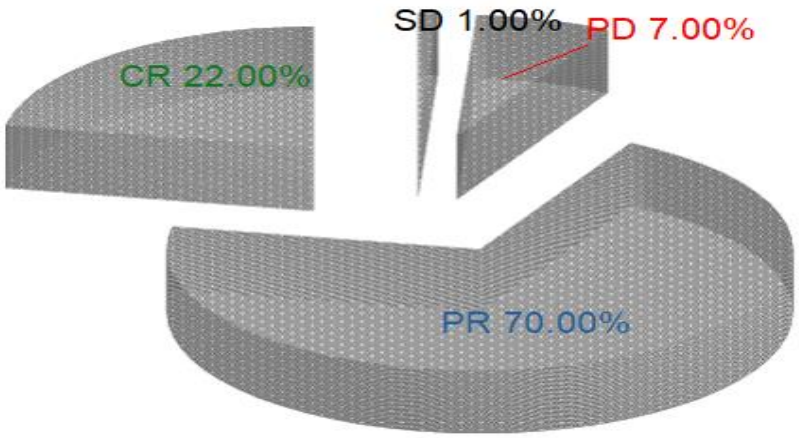

Fig. 1.9 *Clinical response to neoadjuvant therapy of breast mass (T)*

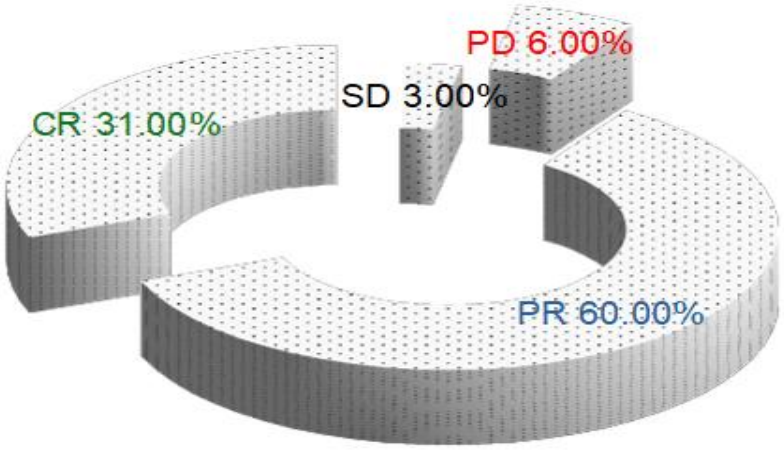

Fig. 1.10 *Clinical response to neoadjuvant therapy of nodal status (N)*

Distance disease progression at the end of neoadjuvant therapy was observed in 5 patients. One patient underwent pleural effusion, one patient underwent multiple cerebral metastases, one patient presented with supraclavicular adenopathy, and another with supraclavicular adenopathy and bone metastasis. Only one patient presents with contralateral breast cancer immediately after completion of systemic neoadjuvant therapy.

Statistical analysis showed a significant relationship between neoadjuvant therapy and clinical response (p= 0.008). This significance highlighted that neoadjuvant regimens with anthracyclines as well as the combination of anthracyclines and taxanes remain the preferred regimens giving a better clinical response. Also highlighted the role of targeted therapy in improving the clinical response to neoadjuvant breast cancer therapy Her 2 positive Luminal type and Her 2 positive non-Luminal.

While no statistically significant relationship was found between neoadjuvant therapy and pathological stage (p = 0.712), between neoadjuvant therapy and PCR (p = 0.124) as well as between neoadjuvant therapy and disease relapse (p = 0.078). However, the frequency of the variables showed a higher percentage of complete pathological response in anthracyclines and/or taxane regimens as well as in the use of targeted therapy.

Clinical response	**NACT**						
	CAF/ AC+T	CAF	FEC/ EC+T	CAF/EC+T+ TRASTUZUMAB	AC/EC+ 12T	others	Total
CR	5	3	0	6	0	0	14
	12.20%	25.00%	0.00%	66.70%	0.00%	0.00%	20.00%
PR	32	9	1	3	1	3	49
	78.00%	75.00%	50.00%	33.30%	100.00%	60.00%	70.00%
SD	2	0	0	0	0	0	2
	4.90%	0.00%	0.00%	0.00%	0.00%	0.00%	2.90%
PD	2	0	1	0	0	2	5
	4.90%	0.00%	50.00%	0.00%	0.00%	40.00%	7.10%
Total	41	12	2	9	1	5	70
	100.00%	100.00 %	100.00%	100.00%	100.00%	100.00%	100.00%

Pathological stage	NACT						Total
	CAF/AC + T	CAF	FEC/EC+ T	CAF/EC+T+ TRASTUZUMAB	AC/EC +12T	others	
No disease	6	3	1	7	0	0	17
	13.30%	20.00%	33.30%	53.80%	0.00%	0.00%	20.20%
Stage 1	18	1	0	4	1	3	27
	40.00%	6.70%	0.00%	30.80%	50.00%	50.00%	32.10%
stage 2	7	2	1	0	0	0	10
	15.60%	13.30%	33.30%	0.00%	0.00%	0.00%	11.90%
stage 3	11	8	0	1	1	2	23
	24.40%	53.30%	0.00%	7.70%	50.00%	33.30%	27.40%
stage 4	3	1	1	1	0	1	7
	6.70%	6.70%	33.30%	7.70%	0.00%	16.70%	8.30%
Total	45	15	3	13	2	6	84
	100.00%	100.00 %	100.00 %	100.00%	100.00 %	100.00%	100.00 %

PCR	NACT						Total
	CAF/AC+T	CAF	FEC/EC+ T	CAF/EC+T+ TRASTUZUMAB	AC/EC +12T	others	
There is no PCR	52	15	2	12	3	6	90
	89.70%	83.30%	66.70%	63.20%	100.00 %	100.00%	84.10%
PCR	6	3	1	7	0	0	17
	10.30%	16.70%	33.30%	36.80%	0.00%	0.00%	15.90%
Total	58	18	3	19	3	6	107
	100.00%	100.00 %	100.00%	100.00%	100.00 %	100.00%	100.00%

RELAPSE	NACT						Total
	CAF/EC +T	CAF	FEC/EC+T	CAF/EC+T+ TRASTUZUMAB	AC/EC+1 2T	others	
yes	10 17.20%	6 33.30%	2 66.70%	4 21.10%	0 0.00%	4 66.70%	26 24.30%
no	48 82.80%	12 66.70%	1 33.30%	15 78.90%	3 100.00%	2 33.30%	81 75.70%
Total	58 100.00%	18 100.00%	3 100.00%	19 100.00%	3 100.00%	6 100.00%	107 100.00%

No statistically significant relationship was found between the number of NACT cycles and variables (clinical response, pathological stage, PCR, relapse)

variable	Correlation coefficient	p	N
Clinical response	.165	.128	70
Pathological stage	-.101	.278	84
PCR	-.082	.372	107
RELAPSE	.034	.707	107

The final pathological report was obtained in full in 78 patients, while for one patient in the medical record it was possible to obtain information on the pathological stage but not the histological type of breast cancer. In most cases, the final histological diagnosis coincided with the preoperative histological diagnosis. Graphic presentation of the final histological diagnosis as well as ypT and ypN, according to the number of patients who were intervened, are presented respectively in fig. 1.11, 1.12 and 1.13.

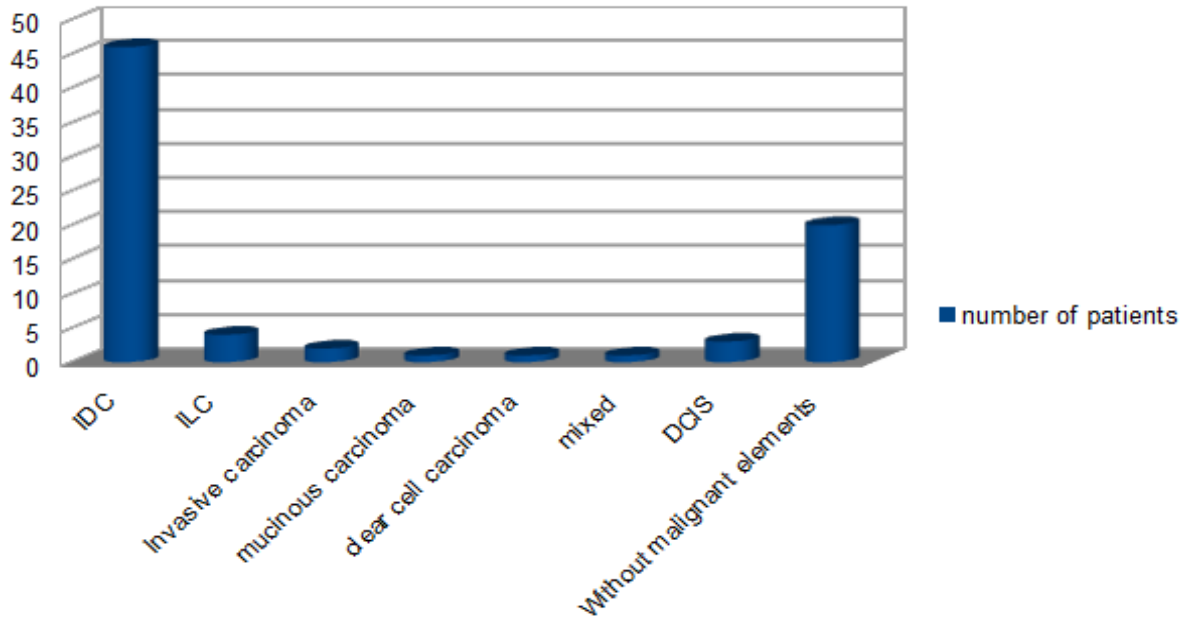

Fig. 1.11 *Final histological diagnosis*

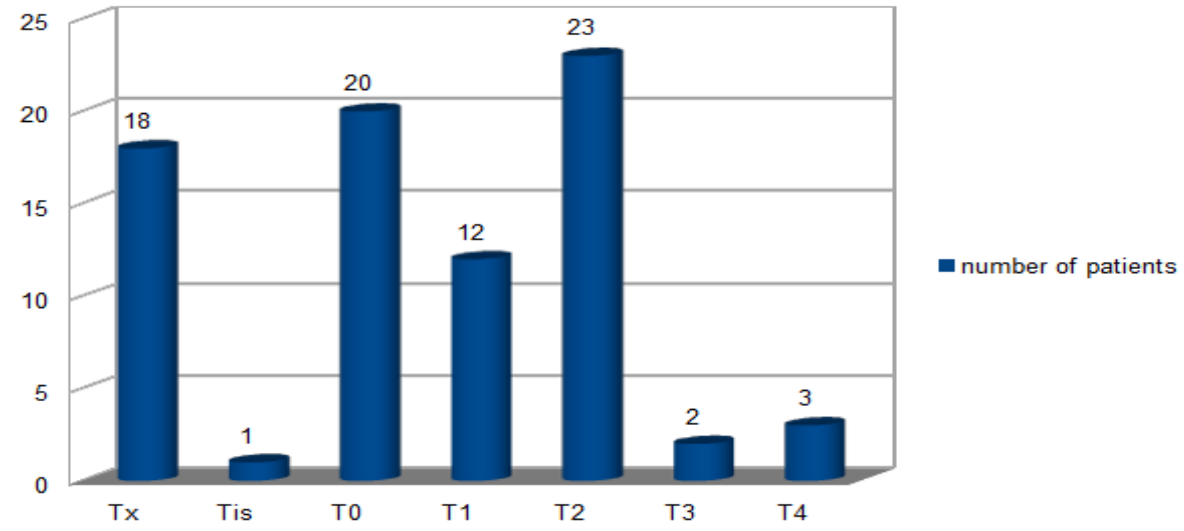

Fig. 1.12 *Graphic presentation of ypT according to the number of patients*

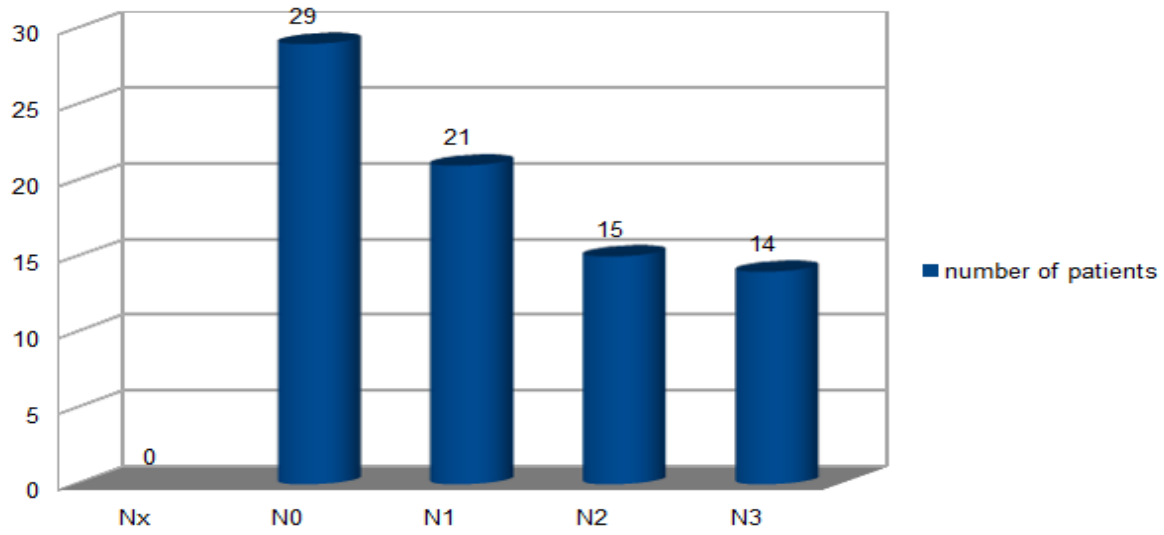

Fig. 1.13 *Graphic representation of ypN according to the number of patients*

Of 79 patients whose oncology records provided information on the pathological staging of ypTNM, 17 of them, 22%, resulted in complete pathological responses after neoadjuvant treatment.

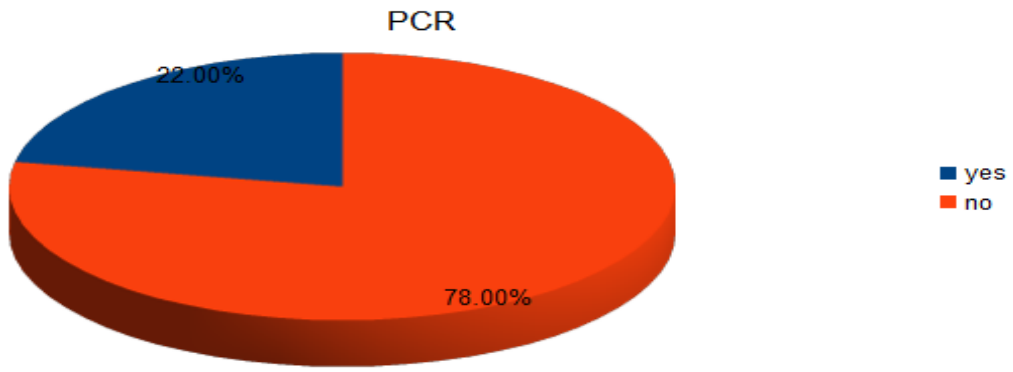

Fig. 1.14 *Percentage of patients undergoing PCR after neoadjuvant treatment*

From the statistical analysis, a significant correlation was found between the clinical response and the pathological stage ($r = 0.719$, $p < 0.001$). Therefore we can say that a good clinical response to neoadjuvant therapy can be considered as a predictive factor of pathological response.

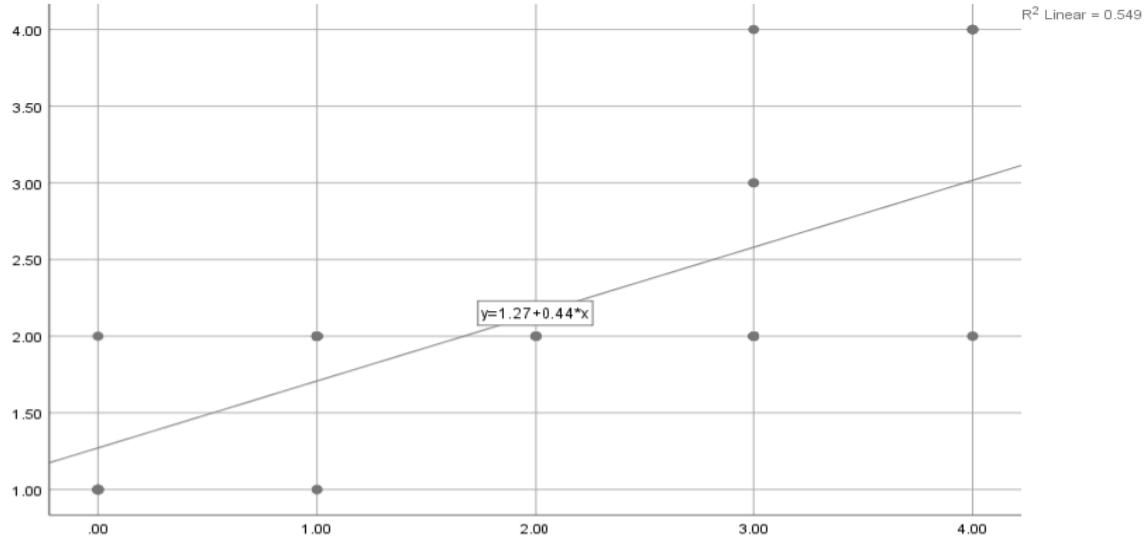

Fig. 1.15 *Relationship between clinical response and pathological stage*

The analysis also showed an inverse, statistically significant relationship between the pathological stage and relapse (r = -0.370, p <0.001). Advanced pathological stages are associated with a higher risk of local and distant recurrence of the disease.

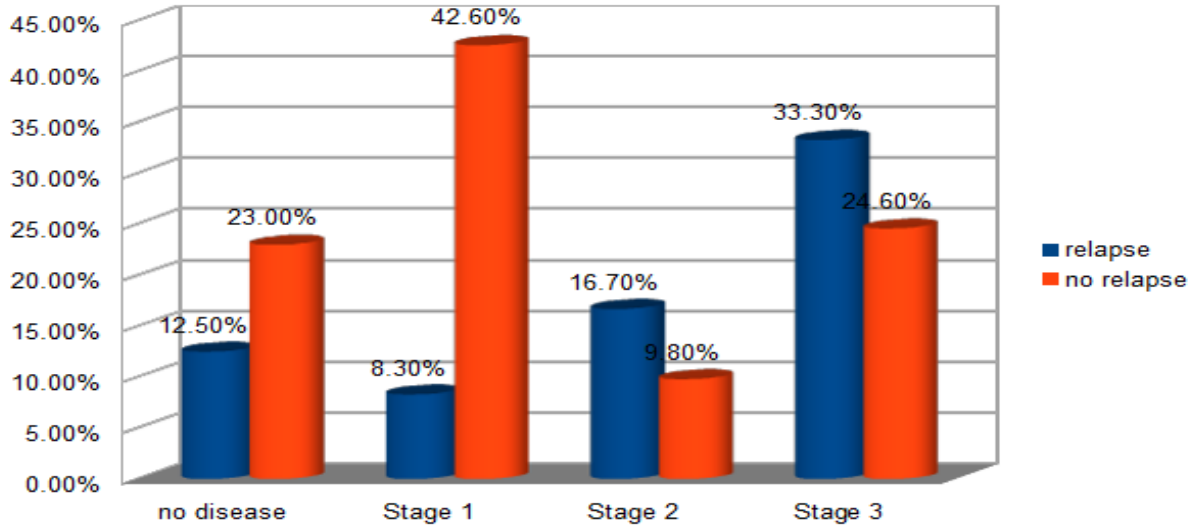

Fig. 1.16 *The relationship between the pathological stage and relapse*

Discussion

Breast cancer at a young age requires special attention not only because of the morphological and prognostic specifics but also of the age-specific aspects themselves. Any suspected case should be diagnosed by a multidisciplinary team of specialized physicians. Being a category that is not subject to screening often diagnosis occurs in advanced stages of the disease. Every decision-making must take into account the unique aspects that characterize this group of patients, such as preservation of fertility, pregnancy, preservation of sexuality, psycho-social aspects, economic aspects, etc.

The goals of neoadjuvant treatment of breast cancer have changed significantly and evolved significantly since the time this treatment was first applied to patients with locally advanced breast cancer and inflammatory breast cancer in the early years of 1970. Our study analyzed all breast cancer cases of patients up to the age of 40 from 2010 to 2020, generally showing an increase in the number of cases year after year and especially the last 5 years as a result of improving the multidisciplinary approach to breast cancer treatment in our Service. Today, the goal of systemic neoadjuvant therapy is not only the initial goal of converting a locally advanced and inoperable cancer into operability but also this treatment plays an important role in reducing large tumors to perform conservative breast surgery. An important role of systemic neoadjuvant therapy is the "in vivo" evaluation of the response to treatment, providing opportunities in the evaluation of new therapeutic agents and offering the possibility of individualized therapy. Today neoadjuvant treatment is as important as in locally advanced and inflammatory breast cancer, as well as in breast cancer with clinically negative lymph nodes but with an unfavorable tumor profile where the use of systemic therapy is envisaged.

In our Service in the neoadjuvant treatment of breast cancer during the years 2010-2020, the most used regimen was the one based on anthracyclines and taxanes: 4CAF + 4T. Her2-targeted therapy was used in 19 patients of our study of which 5 patients were treated with the combination of Trastuzumab with Pertuzumab. In no case was used neoadjuvant endocrine therapy. Other chemotherapeutic agents such as Gemcitabine, Carboplatin, Capecitabine were rarely used, in cases of lack of clinical response to standard treatments.

Evaluation of the clinical response to neoadjuvant therapy was performed by the oncologist, objective examination by the oncologist surgeon and imaging control through an ultrasound performed at least twice before performing definitive breast surgery.

Statistical analysis showed a significant relationship between neoadjuvant therapy and clinical response ($p= 0.008$). This significance highlighted that neoadjuvant regimens with anthracyclines as well as the combination of anthracyclines and taxanes remain the preferred regimens giving a better clinical response. Also highlighted the role of targeted therapy in improving the clinical response to neoadjuvant breast cancer therapy Her 2 positive Luminal type and Her 2 positive non-Luminal.

While no statistically significant relationship was found between neoadjuvant therapy and pathological stage (p = 0.712), between neoadjuvant therapy and PCR (p = 0.124) as well as between neoadjuvant therapy and disease relapse (p = 0.078). However, the frequency of the variables showed a higher percentage of complete pathological response in anthracycline and / or taxane regimens as well as in the use of targeted therapy.

A randomized TRAIN-2 study **[**13**]** involving patients with confirmed breast cancer in the second and third stages of the disease and the Her 2 positive molecular subtype from 37 Dutch hospitals aimed to evaluate the use of dual blockade anthracyclines to Her 2. Patients were categorized according to two treatment schemes. The first group treated with 5-fluorouracil (500mg / m2), epirubicin (90mg / m2), and cyclophosphamide (500mg / m2) every 3 weeks for 3 cycles, followed by paclitaxel (80mg / m2) on days 1 and 8 and carboplatin (6mg / mL per min on the first day or optionally according to hospital preference 3mg / mL per min on days 1 and 8), every 3 weeks for 6 cycles. The second group of patients as those who were treated with 9 cycles of paclitaxel and carboplatin, with the same doses as in the first group where anthracyclines were used. Patients in both groups received trastuzumab and pertuzumab. The first goal was to assess the proportion of subjects who achieved complete pathological responses to treatment. PCR was found in 67% in the group of anthracyclines and 68% in the group treated without anthracyclines. Despite the high proportion of complete pathological response in both groups, febrile neutropenia was more frequent in the first group ending the non-use of anthracyclines in patients with early breast cancer, her 2 positive, receiving dual blockade trastuzumab and pertuzumab may be recommended.

The NOAH study **[**14**]** also demonstrated the importance of using targeted therapy during neoadjuvant therapy in Her 2 positive breast cancer patients, comparing the disease-free period in patients treated with an anthracycline and taxane-based chemotherapy alone or CMF and patients which in addition to these same chemotherapeutic regimens was also treated with Trastuzumab. DFS was respectively 43% versus 58%, p = 0.016).

However, we can say that neoadjuvant therapy offers unique opportunities to directly observe the effect of treatment and therefore provides opportunities for the application of new strategies in patients who do not respond to therapy. Ongoing studies are needed to select the right patients for the right therapy to maximize the benefits with as little toxicity as possible.

The link between complete pathological response and disease prognosis has been extensively investigated in breast cancer patients treated with neoadjuvant therapy. The German Breast Group investigated the association of PCR and disease progression in 6,377 patients treated with neoadjuvant chemotherapy with the anthracycline-taxane-based regimen, in 7 randomized studies. In this study, patients without residual disease residues after neoadjuvation in both breast and nodal status (ypT0, ypN0) had a free period without disease and better overall survival, but the impact of complete

pathological response varied widely between different subtypes. . In patients with less aggressive tumors, PCR was much less predictive about DFS and OS. But its impact was much more significant for Her 2 positive, TNBC and Luminal B-Her2 negative tumors **[**15**]**.

Complete pathological response implies the absence of invasive carcinoma in the breast and axillary lymph nodes, while the presence of ductal carcinoma in situ is considered to be acceptable. So PCR is equivalent to ypT0 / is, ypN0. In our study PCR resulted in 22% of patients after neoadjuvant treatment. Although no statistically significant relationship was found between the clinical stage of the disease and the complete pathological response (p = 0.243), it was found that patients with clinical stages 2A and 2B had PCR at a higher rate. While the more advanced clinical stages 3A, 3B and 3C had lower PCR rates.

Statistical analysis with Kendall's tau coefficient found a significant correlation between clinical response to treatment and pathological stage (r = 0.719, p <0.001). Therefore we can say that a good clinical response to neoadjuvant therapy can serve as a predictive factor of pathological response.

The analysis also showed an inverse, statistically significant relationship between the pathological stage and relapse (r = -0.370, p <0.001). Advanced pathological stages are associated with a higher risk of local and distant recurrence of the disease.

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