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Impact of neoadjuvant chemotherapy in the surgical treatment of breast cancer

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ABSTRACT

Introduction: Neoadjuvant chemotherapy is an increasingly frequent option in the treatment of breast cancer. One of the goals of neoadjuvant chemotherapy is to change the indication for a mastectomy to a conservative surgery, and for axillary lymphadenectomy to sentinel lymph node assessment. **Methods:** This was an observational, cross-sectional, retrospective study that evaluated response to neoadjuvant chemotherapy in breast cancer patients undergoing surgical treatment. Patients were divided into three groups when the surgery indication was changed after neoadjuvant chemotherapy: downgrade, unchanged, upgrade. **Results:** During the study period, 355 patients were included with a mean age of 55 years. Neoadjuvant chemotherapy promoted a downgrade in 38.7% of patients with indication for mastectomy and an upgrade in 36.8% of patients with indication for conservative surgery; in the total group, the maintenance of indication for surgery was 62,2%. In the axillary approach, lymphadenectomy downgrade was 6.9% and sentinel lymph node biopsy upgrade was 34% with 27% being due to positivity and 7% due to disease progression. Multivariate analysis found a significant difference between clinical staging and change in surgical indication for both breast and axilla ($p<0.0001$). In the multivariate analysis of pathologic complete response and change of indication for breast and axilla surgery, triple negative and HER-2-positive tumors showed a significant difference ($p<0.0001$). **Conclusions:** Neoadjuvant chemotherapy was able to perform a downgrade of breast and axilla surgery in few patients and there was no relationship between the change of indication and pathologic complete response

KEYWORDS: breast cancer; neoadjuvant chemotherapy; prognosis; surgery; mastectomy, quadrantectomy.

INTRODUCTION

Breast cancer (BC) currently represents a public health problem due to its high incidence and high mortality among women in Brazil and around the world[1]. In Brazil, 66,280 new cases were estimated in 2022, with mortality of 17,500 women[2].

In the past, the diagnosis was made mainly through clinical examination, meaning that most cases were detected in late stages, requiring aggressive treatments, such as radical mastectomy, with removal of the pectoral muscles[3]. It is known that the breast plays an important role in a woman's life, and removing it is one of the main concerns of women diagnosed with BC[4].

Thanks to early detection programs (mammographic screening), BC cases have been diagnosed earlier. This early diagnosis associated with the screening of pre-neoplastic lesions allows the treatment to be increasingly conservative[5].

Neoadjuvant chemotherapy is a great and increasingly common option. Although in the past, it was used only in patients with locally advanced BC, it is currently used in patients with initial BC of the triple-negative subtype and positive human epidermal growth factor receptor 2 (HER-2) protein, not only with the aim of reducing the size of the tumor to provide less aggressive surgeries, but also to improve the prognosis of patients[6-8].

In patients with locally advanced disease, neoadjuvant chemotherapy presents a good objective and clinical and pathological response, besides increasing the chance of conservative surgery. For patients with inflammatory carcinoma, the increase in five-year survival increases from 2 to 5% to around 40%[9,10].

In patients with operable BC, neoadjuvant chemotherapy has the benefit of reducing tumor volume and axillary involvement (downstaging), increasing the possibility of conservative

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surgery and improving surgical outcomes, greater tendency to adequately complete the proposed treatment, allowing the assessment ***in vivo*** of the effectiveness of the treatment and making it possible to quickly test new theories[8,9].

Another advantage of neoadjuvant chemotherapy is that, in patients with aggressive tumors, such as triple-negative or HER-2 positive, a good response to neoadjuvant chemotherapy is strongly related to increased survival[11,12].

The most frequently recommended chemotherapy regimens are those that include anthracyclines, taxanes and, when indicated, biological therapy[13]. Others that are less used, but no less important, include alkylating agents and platinum compounds[14].

Anthracyclines, popularly known as "red chemotherapy", due to their reddish tones, inhibit the synthesis of DNA and RNA by intercalating DNA base pairs by inhibiting topoisomerase II. Among them, doxorubicin stands out, being the most used, in doses ranging from 60 to 550 mg/m^2, intravenously, every 21 days. The renal and cardiac functions of these patients must be monitored using a complete blood count, with differential count and platelets, because one of the major concerns regarding its use is cardiotoxicity[15].

Taxanes, popularly known as "white chemotherapy", promote the assembly of microtubules by increasing the action of tubulin dimers, stabilizing existing microtubules and inhibiting their disassembly, interfering in the late G2 mitotic phase and impairing cell replication. In Brazil, the taxanes paclitaxel and docetaxel stand out. Their doses are generally between 75 and 175 mg/m^2 IV for three hours, every three weeks. Monitoring of liver and kidney functions should be done using a complete blood count, with differential and platelet counts. Their main side effect is myelotoxicity[16].

Finally, in biological therapy, trastuzumab is notable; it is a recombinant humanized monoclonal antibody that selectively targets the extracellular domain of HER-2. Therefore, it is a specific antineoplastic agent for patients with cancer cells that overexpress HER-2. As it is specific for cells with HER-2 overexpression, it presents a lower rate of systemic complications, such as mucositis and myelotoxicity, compared to other chemotherapy drugs[17].

For triple-negative and HER-2-positive tumors, regimens containing anthracyclines and taxanes are proposed for neoadjuvant chemotherapy as they are associated with complete pathological response, as described in this work. More specifically, it is proposed that, in the case of triple-negative tumors from stage 2 onwards, treatment should be carried out with anthracyclines and taxanes. From there, alkylating agents, such as cyclophosphamide, or platinum compounds, such as cisplatin, are considered And for HER-2-positive patients in stage 2 or 3, treatment with taxanes and trastuzumab is acceptable[11].

As it is a condition with an important impact on the patient's quality of life, it is necessary to know the real impact of treatment with neoadjuvant chemotherapy in patients with BC.

METHODS

This was an observational, cross-sectional, retrospective study that evaluated the response to neoadjuvant chemotherapy in patients with breast cancer who underwent surgical treatment at the Hospital do Servidor Público Estadual (HSPE) de São Paulo, from March 2011 to December 2021.

The inclusion criteria were patients diagnosed with malignant breast neoplasia with anatomopathological examination confirming invasion on biopsy, who had undergone neoadjuvant chemotherapy and, subsequently, surgical treatment after neoadjuvant chemotherapy.

The exclusion criteria were male patients, patients undergoing previous radiotherapy and/or chemotherapy, patients diagnosed with metastasis during chemotherapy and patients with incomplete data in the medical records or lost to follow-up.

The information was collected from medical records and the hospital management system. The information collected was regarding age at diagnosis, menopausal status, tumor characteristics (expression of estrogen and progesterone receptors, HER-2 expression or amplification, proliferation index (Ki-67) and histological grade), clinical and pathological staging, submission to neoadjuvant chemotherapy and hormone therapy, adjuvant chemotherapy, radiotherapy and hormone therapy, type of surgery performed, diagnosis of metastatic disease, as well as its location and time of diagnosis of metastasis, and death and time since initial diagnosis.

Aiming to evaluate whether neoadjuvant chemotherapy was able to change the indication for surgical treatment of BC, the indication for breast and axillary surgery, pre and post-chemotherapy, was compared. When there was a change in indication, it was classified as upgrade (more aggressive surgery) and downgrade (more conservative approach) for both breast surgery and axillary surgery.

This can be seen in Supplementary Table 1 for breast surgery and Supplementary Table 2 for axillary surgery.

For breast surgery, conservative surgery was chosen when the tumor was <2 cm in size and the tumor/breast ratio was <20%. In cases where the tumor showed different characteristics, the option was radical surgery (Supplementary Table 1).

Regarding axillary evaluation, sentinel lymph node biopsy was recommended for patients who did not have a clinically positive lymph node and axillary dissection for those who already had one (Supplementary Table 2).

The work was submitted to Plataforma Brasil and approved under number C.A.A.E. 39097520.4.1001.5463. As this was a retrospective study, the informed consent form was waived.

RESULTS

The study included 375 patients who underwent neoadjuvant chemotherapy in the period from 2011 to 2020, of which twenty

Table 1. Epidemiological characteristics of patients who underwent neoadjuvant chemotherapy for the treatment of breast cancer at Hospital do Servidor Público Estadual, from 2011 to 2020.

Characteristics	All patients (n=355; %)	
Age, mean±standard deviation (range), years	55±9.7 (30–77)	
Menopause status		
Pre-menopause	108	(30.4)
Post-menopause	247	(69.6)
BMI, mean±standard deviation (range)	26.9±6.1 (15–54)	
Low weight	5	(1.4)
Normal weight	2	(0.6)
Overweight	120	(33.8)
Obesity grade 1	120	(33.8)
Obesity grade 2	74	(20.8)
Obesity grade 3	20	(5.6)
Family history		
Yes	192	(54.1)
No	163	(45.9)

were excluded for the following reasons: incomplete data in the medical record (ten), lost to follow-up (five) and already having a diagnosis of metastasis during chemotherapy (five) (Supplementary Figure 1).

All 355 patients who remained in the study had their medical records analyzed. The average age of these women was 55 years, the majority of them were postmenopausal (69.6%) and were obese (60.2%), while 54% had a family history of BC. Characteristics regarding body mass index (BMI), menopausal status and family history can be seen in Table 1.

Regarding data about BC, the most common histological type was invasive breast carcinoma (IBC) (98.6%), and nuclear grade 2 was the most prevalent (45.1%). The majority of tumors studied were HER-2-positive (28.4%) and had Ki-67≥14% (76.3%). Finally, regarding the classification of the disease, the most common was T2 (46.8%), N1 (34.1%) and clinical stage IIIA (34.1%). These findings were made considering that T2 represents the tumor between 2 and 5 cm in its largest dimension, N1 refers to the involvement of the ipsilateral axillary lymph node and stage IIIA is the one with a tumor smaller than 5 cm and an affected lymph node. These data can be seen in Table 2.

Regarding the type of surgery, 46.5% were indicated for mastectomy and 53.5% for conservative surgery before undergoing neoadjuvant chemotherapy. Regarding axillary treatment, axillary dissection was indicated for 69.3%, while sentinel lymph node biopsy (SLNB) for 30.7%. The pre-chemotherapy surgical indications and complete pathological response of these patients can be seen in Table 3.

Table 2. Tumor characteristics of patients who underwent neoadjuvant chemotherapy for the treatment of breast cancer at Hospital do Servidor Público Estadual, from 2011 to 2020.

Characteristics	All patients (n=355; %)	
Histological type		
IBC	350	(98.6)
ILC	1	(0.3)
Others	4	(1.1)
Histological characteristics		
Nuclear grade 1	62	(17.5)
Nuclear grade 2	160	(45.1)
Nuclear grade 3	133	(37.5)
Angiolymphatic Invasion present	38	(10.7)
Perineural invasion present	30	(8.5)
Immuno-histochemical characteristics		
Luminal A	57	(16.1)
Luminal B	58	(16.3)
Luminal B HER-2	56	(15.8)
HER-2	101	(28.4)
TNBC	84	(23.4)
Ki67 (%)		
<14	84	(23.7)
≥14	271	(76.3)
Tumor size		
T1c	16	(4.5)
T2	166	(46.8)
T3	113	(31.8)
T4	60	(16.9)
Axilla		
N0	109	(30.7)
N1	121	(34.1)
N2	116	(32.7)
N3	9	(2.5)
Clinical staging		
IA	2	(0.6)
IB	5	(1.4)
IIA	70	(19.7)
IIB	90	(25.4)
IIIA	121	(34.1)
IIIB	48	(13.5)
IIIB inflammatory	10	(2.8)
IIIC	9	(2.5)

IBC: invasive breast carcinoma; ILC: invasive lobular cancer; TNBC: triple negative breast cancer.

After neoadjuvant chemotherapy, the surgical indication was reevaluated and it was observed that the use of chemotherapy promoted a downgrade in 18.0% of patients with an indication for mastectomy and an upgrade in 19.2% in those with an indication for conservative surgery. Of the total group, the indication for surgery was maintained in 62.2%, while in the axillary approach, axillary surgery downgrade was 4.5% and SLNB upgrade was 12.3, 9.8% due to positive SLNB and 2.3% due to disease progression. These data are shown in Supplementary Table 3.

The correlation of pathologic complete response (pCR) with the change in surgical indication was also studied, as can be seen in Table 4. Of the patients with pCR, a downgrade of breast surgery was observed in 33.4% and an upgrade in 24.3%, and there was no significant difference between pCR and change in indication for breast surgery (p>0.05). For axillary surgery, the correlation of patients with PCR and downgrade was 41.1% and that of upgrade was 13.5%. There was also no significant difference between pCR and change in indication for axillary surgery (p<0.05).

Finally, in multivariate analysis, factors that could influence the change in the indication for surgical treatment were investigated. Among the variables studied, there was a significant difference between the clinical staging and the change in surgical indication for both the breast and the axilla (p<0.0001), as observed in Supplementary Tables 4 and 5.

When analyzing the association of pCR with change in indication for breast and axillary surgery and other qualitative variables, triple-negative and HER-2-positive tumors showed a significant difference (p<0.0001), as seen in Table 5.

Table 3. Pre-chemotherapy surgical indications and complete pathological response.

Pre-CT surgical indication	All patients (n=355; %)	
Breast surgery		
Mastectomy	165	(46.5)
Conservative surgery	190	(53.5)
Axillary surgery		
Axillary emptying	226	(63.9)
Sentinel lymph node biopsy	129	(30.7)
Complete pathological response		
Yes	76	(21.4)
No	279	(78.6)

DISCUSSION

The two main known risk factors for breast cancer are female sex and a positive family history of breast cancer[18,19]. Such

Table 4. Change in surgical indication post-neoadjuvant chemotherapy and pCR ratio.

Change in surgical indication post-neoadjuvant chemotherapy X pCR	Complete pathological response	
Breast surgery	Yes	No
Downgrade (to conservative)	21	43
Upgrade (to mastectomy)	17	53
Maintenance of indication	38	183
	p>0.05	
Downgrade X pCR correlation (%)	41.1	p<0.05
Upgrade X pCR correlation (%)	13.5	p<0.05

Table 5. Comparing the class of breast surgery/pCR for distribution of qualitative factors.

	Upgrade		Downgrade		Total		p-value
	n	%	n	%	n	%	
Luminal A							
No	266	82.6	32	97.0	298	83.9	0.032
Yes	56	17.4	1	3.0	57	16.1	
Luminal B							
No	145	45.0	24	72.7	169	47.6	0.002
Yes	177	55.0	9	27.3	186	52.4	
Triple-negative							
No	251	78.0	20	60.6	271	76.3	0.026
Yes	71	22.0	13	39.4	84	23.7	
HER-2							
No	99	30.7	4	12.1	103	29.0	0.005
Not done	205	63.7	23	69.7	228	64.2	
Yes	18	5.6	6	18.2	24	6.8	

findings justify the higher prevalence of patients with a positive family history in this study. Obese and postmenopausal women have a higher risk of hormone-associated neoplasms, such as breast cancer and endometrial cancer, because of the greater peripheral conversion of fat into estrogens[20]. Thes data explain the higher percentage of obese and postmenopausal patients in this study.

Although the most common breast tumors are luminal, due to the relationship with hormones, in this study, the most frequent were those of the HER-2-positive type, followed by triple-negative ones. This can be explained because neoadjuvant chemotherapy indications are more prevalent in triple-negative and HER-2-positive tumors, and this study only selected patients who underwent neoadjuvant chemotherapy[21].

Other important criteria for evaluating neoadjuvant chemotherapy are elevated Ki67, histological grade 3, lymphovascular invasion, age and lymph node involvement[11]. These aspects explain why this study showed a high prevalence of tumors with Ki67≥14%, N1 and clinical stage IIIA, since stage III is the one in which the patient has lymph node involvement[22]. Currently, it is known that lymph node involvement is one of the main prognostic factors in BC. It is also known that chemotherapy is the best systemic treatment compared to radiotherapy and surgery, which are local treatments[21].

The complete pathological response with neoadjuvant chemotherapy described in this study of 21.4% is compatible with that proposed in the literature, which varies from 4 to 31%, depending on the therapeutic regimen[21].

Although this study's rate of downstaging for breast surgery (18.0%) is higher than that proposed by another Brazilian study (10%), published by Costa & Chagas in 2013[23], it is still lower than that report in the international literature, which ranges from 48 to 58%[24,25]. This finding may be secondary to a higher rate of diagnoses in early stages or even to chemotherapy readily prescribed post-staging.

Patients treated at the Hospital do Servidor Público Estadual are encouraged to undergo a biopsy with the results being presented as quickly as possible, to allow treatment to begin within 30 days. Another factor is that most of the patients had histological grade 2 or 3, with high mitotic activity (Ki67>13%), which speaks volumes in favor of the breast tumor responding well to chemotherapy.

In this study, it was observed that the tumors of patients who changed from radical surgery to breast-conserving surgery had the most frequent characteristics of being triple-negative or HER-2-positive and clinical stage "IIIa". Such findings are compatible with those of the study published in 2021 by Petruolo et al.[24], which show that the main factors predicting successful downstaging are hormone receptor status and HER-2 positivity.

In the axillary approach, downstaging was 4.5%, lower than that reported in the Brazilian literature (20%). One explanation for these data may be the fact that the patients' BRCA status was not investigated. Platinum compounds, such as cisplatin, have gained increasing attention, especially in patients with BRCA1 mutation, in whom they have a complete pathological response of up to 72%[14].

The percentage of downstaging found in this study was lower than what the international literature considers, this can be explained by the fact that in the present study, patients with positive hormone receptors (luminal) were included, which are naturally more resistant to chemotherapy compared to triple-negative and HER-2-positive tumors. Furthermore, the study included the majority of patients starting the study with an already affected axilla, given that group N1 and clinical stage IIIA were the most prevalent. As proposed by Petruolo et al.[24] in 2021, lymph node involvement is an unfavorable predictive factor for downstaging.

The change from conservative surgery to mastectomy was necessary in few patients. Regarding upstaging of the axillary approach, disease progression was seen in only 2.3% of cases, a rate lower than that seen in the literature (10%)[23]. This finding can be explained by the association of a delay in surgery of more than four weeks after diagnosis with axillary upstaging, which generally does not occur in our service. Furthermore, in the other cases of axillary upgrade, the fact was repeated due to positive SLNB, not due to disease progression.

pCR alone was not able to predict the change in indication for breast and axillary surgery. In the group of patients who had pCR and changed the surgical proposal, a significant association was observed with clinical staging and triple-negative and HER-2-positive tumors, which was expected as they are tumors with high mitotic activity, exhibiting elevated Ki67 and responding well to chemotherapy[21].

Finally, the main limitations of the study to be mentioned are the failure to evaluate the presence of genetic mutations in BRCA, which are known to interfere with chemotherapy response, and the failure to divide downgrade and upgrade according to each type of chemotherapy regimen used and each tumor studied, which may have caused a bias in our results.

CONCLUSIONS

Neoadjuvant chemotherapy was able to downgrade breast and axillary surgery in a few patients and there was no relationship between the change in indication and complete pathological response. We found a relationship between clinical staging and changes in surgical indication, as well as triple-negative and HER-2 positive patients with complete pathological response showing greater changes in indication for surgery. Regarding the upgrade, it was necessary in a few patients and had no relation to the complete pathological response.

AUTHORS' CONTRIBUTION

MA: Conceptualization, Formal analysis, Investigation, Writing – original draft. AM: Formal analysis, Investigation, Writing – original draft. GDP: Formal analysis, Investigation, Writing – review & editing. OF: Resources, Validation, Visualization. RCGL: Supervision, Validation. LHG: Supervision, Visualization. JMR: Supervision. MACS: Writing – original draft.

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