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Evaluation of clinical and pathological response factors to neoadjuvant chemotherapy in breast cancer patients

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ABSTRACT

Objectives: To evaluate breast cancer (BC) patients treated with neoadjuvant chemotherapy (NACT) and to analyze clinicopathological features correlating with pathological complete response (PCR) and survival outcomes. **Methods:** Observational, descriptive, and retrospective study. The medical records of BC patients who underwent NACT were reviewed and analyzed using the Statistical Package for the Social Sciences (SPSS), version 20.0. **Results:** Of the 176 BC patints who underwent NACT, 62 patients (35.2%) achieved PCR. The PCR rate was 22% (n = 2) for luminal A, 15% (n = 9) for luminal B/HER2-negative, 45.5% (n = 15) for luminal B/HER2-positive, 50% (n = 14) for non-luminal/HER2-positive, and 47.8% (n = 22) for triple-negative (p = 0.01). Histological grade, estrogen receptor (ER) expression, progesterone receptor (PR) expression, and HER2 status were significantly associated with PCR (p = 0.022, p = 0.01, p = 0.01, and p = 0.02, respectively). The median follow-up was 35.9 months, the estimated 5-year disease-free survival (DFS) was 96.7% in the PCR group and 83.2% in the non-PCR group (p = 0.05). The estimated 5-year overall survival (OS) was 95.5% in the PCR group and 69.1% in the non-PCR group (p = 0.017). Overall, 11 patients (6.25%) presented with locoregional recurrence (LRR), one (1.6%) in the PCR group and 10 (8.8%) in the non-PCR group (p = 0.10). **Conclusion:** We observed higher PCR rates in triple-negative and HER2-positive molecular subtypes. DFS and OS were significantly better in patients who achieved PCR, regardless of clinicopathological features. We also observed lower rates of LRR in the population that reached PCR.

KEYWORDS: breast neoplasms; neoadjuvant therapy; molecular biology; residual volume.

INTRODUCTION

Breast cancer (BC) is a heterogeneous and complex disease[1]. During the last decade, genomic analyzes using microarrays have revolutionized the field of BC research[2]. Molecular subtypes were identified, outlining different risk factors[3,4], different prognoses[5], as well as different natural histories, different survival rates and sensitivity to local and systemic treatments[6-9].

Neoadjuvant chemotherapy (NACT) is equivalent in overall survival (OS) compared to adjuvant chemotherapy in the treatment of BC. Unlike adjuvant treatment, NACT has traditionally been relegated to patients with locally advanced, initially inoperable BC. However, NACT has played an increasingly important role in the treatment of early-stage disease[10]. NACT has benefits in several clinical strategies, including tumor size reduction and remission of the involvement of the axillary lymph nodes by metastases (downstaging), aiming at a less mutilating surgery, with breast preservation and with resection only of the sentinel lymph nodes in case of negative axillary lymph nodes.

One of the main benefits of NACT is the prognostic information obtained by the pathological evaluation of the tumor bed and axillary lymph nodes after surgery. The complete pathological response is strongly associated with a better prognosis of patients undergoing NACT, as observed in clinical trials NSABP B-18 and B-27[11,12].

Given the arguments presented, we believe that it is extremely important to analyze our population of patients with BC who underwent NACT and understand the subpopulation of responders and non-responders to conventional treatments, as well as to assess survival outcomes.

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METHODS

All the medical records of patients who underwent NACT with a diagnosis of breast malignancy, between March 2012 and June 2020, in the oncology service (UNACON) of the General Hospital (HG) in Caxias do Sul and in the clinic practice were reviewed. The study included all patients who received NACT diagnosis through anatomopathological examination of invasive carcinoma, selecting cases of both non-special invasive breast carcinomas and special breast carcinomas, with histological grades from I to III and with stages from I to IIIC. Data were recorded on forms, as shown in Appendix 1.

The status of estrogen receptor (ER)/progesterone receptor (RP), epidermal growth factor receptor 2 (HER2) protein, and Ki-67 antigen with the following primary antibodies were assessed: monoclonal antibody (MAb) to ER (Dako , clone EP1, prediluted), MAb to RP (Dako, clone PgR, prediluted), MIB-1 MAb to Ki-67 antigen (Dako, clone MIB-1, prediluted) and polyclonal antiserum (Biogen, clone SP3, 1/1,100 dilution) in HER2 protein. Intense and complete membrane staining in at least 10% of tumor cells was qualified for immunohistochemical expression (IHC) of HER2 3+ and considered to be HER2 positive. For this analysis, HER2 scores of 0 and 1+ were considered negative. All HER 2+ tumors were tested for gene amplification by fluorescence in situ hybridization (FISH). The Ki-67 labeling index value was divided into low (< 14%) and high (≥ 14%). Tumors were stratified into subtypes[13]:

- luminal A: ER positive and/or PR positive, HER2 negative, and low Ki-67 (< 14%);
- luminal B/HER2 negative: ER positive, PR positive, HER2-negative, and Ki-67 high (≥ 14%);
- luminal B/HER2 positive: ER positive, PR positive, HER2 positive, and any Ki-67;
- non-luminal/HER2 positive: ER negative, PR negative, and HER2 positive;
- triple negative: ER negative, PR negative, and HER2 negative.
- Pathologic complete response (PCR) was defined as the absence of invasive carcinoma in the breast and ipsilateral axilla after NACT[14].

Regarding the post-NACT pathological evaluation, the pieces were duly evaluated according to well-established international recommendations[15]. The piece was weighed and measured and the surgical margins were painted with India ink; subsequently, 0.5 cm slices were cut from anterosuperior to posterior inferior and each slice was labeled as 1, 2, 3, etc. and subdivided into letters A, B, C, etc. (from the upper to the lower axis), setting up a coordinate chart for the assessment of the tumor bed.

Data were entered into Excel and later exported to the Statistical Package for Social Sciences (SPSS), version 20.0, for statistical analysis. Categorical variables were described by frequencies and percentages. Symmetry of quantitative variables was verified using the Kolmogorov-Smirnov test. Quantitative variables were described by mean and standard deviation. Categorical variables were associated using the chi-square test. Quantitative variables were compared between the group with and without PCR using the Student's *t* test for independent samples. OS and disease-free survival (DFS) were assessed using the Kaplan-Meier curve and compared between groups using the log rank test. Factors associated with PCR with a p-value of less than 0.05 in the bivariate analysis or those considered to be potential confounders were included in a multivariate Cox regression analysis. A significance level of 5% was considered for the established comparisons.

The OS was analyzed from the date of diagnosis to the date of death or last follow-up (patients who lost follow-up), and the DFS was analyzed from the date of diagnosis to the date of disease progression (locoregional recurrence and/or distant recurrence), date of death (patients who did not show disease progression and evolved to death) or date of last follow-up (patients who lost follow-up).

RESULTS

One hundred and seventy-six patients with BC were submitted to NACT at the UNACON of the GH and in the private practice from March 2012 to June 2020. All were included in this analysis. Table 1 shows the clinical characteristics of the population.

The patient population in this sample had a median age of 47.3 years (ranging 24 – 77). It was observed that approximately half of the patients (n = 94; 53.5%) were aged between 35 and 49 years. Regarding the body mass index (BMI), it was noticed that the majority (n = 116; 65.9%) had a BMI ≥ 25. Furthermore, 86.4% (n = 152) had non-special invasive ductal carcinoma as histological subtype and 40.3% (n = 71) of the patients presented histological grade 3. The most frequent molecular subtypes were luminal B/HER2 negative (n = 60; 34.1%) and triple negative (n = 46; 26, 1%), and most patients were in clinical stage (CS) IIB (n = 56; 31.8%) and IIIA (n = 52; 29.5%). Of these patients, 145 (82.4%) received regimens based on anthracyclines and taxanes in NACT, 13 (7.38%) received anthracyclines, taxanes, and carboplatin in NACT, and 18 (10.22%) received other regimens. Fifty-eight (32.9%) patients received trastuzumab concomitantly with taxane in neoadjuvant therapy and only nine (5.11%) received pertuzumab concomitantly with taxane and trastuzumab. Only four HER2 positive patients did not receive trastuzumab in neoadjuvant therapy due to delayed delivery of the medication by the Unified Health System (*Sistema Único de Saúde* – SUS), but received it during adjuvant treatment.

Regarding the surgical modality, we observed that 84 patients underwent quadrantectomy, 36 adenomastectomy, 10 skin-sparing mastectomy, 39 modified radical mastectomy, and seven did not undergo surgery due to disease progression. According to

international recommendations, 162 (92%) patients underwent adjuvant radiotherapy after surgery.

After evaluating the surgical specimen, we observed that 62 patients (35.2%) had PCR and 114 (64.8%) did not have PCR.

Analyzing all clinical characteristics of patients who entered *versus* those who did not enter PCR, it was possible to observe a significant association between the molecular subtype and the presence of PCR (P = 0.001). By the adjusted analysis of previously standardized subcategories, it is possible to detect that patients with the triple negative and HER2 positive subtype had a statistically significant higher frequency of PCR, and that the luminal B/HER2 negative subtype had a significantly lower percentage of PCR (p = 0.01) (Table 2).

Table 1. Characteristics of the population.

Clinical characteristics	Categories	Number of patients	%
Total		176	100
Age (years)	< 35	15	8.5
	35–49	94	53.5
	50–64	59	33.5
	≥ 65	8	4.5
BMI	< 18.5	3	1.7
	18.5–24.9	57	32.4
	≥ 25	116	65.9
Histological Subtype	Lobular	3	1.7
	Ductal	152	86.4
	Medullary	14	8
Histological Grade	Others	7	3.9
	I	12	6.8
	II	57	32.4
	III	71	40.3
	Not rated	36	20.4
Molecular Subtype	Luminal A	9	5.1
	Luminal B/HER2 negative	60	34.1
	Luminal B/HER2 positive	33	18.8
	HER2 positive/ non luminal	28	15.9
	Triple negative	46	26.1
Clinical Stage	I IIA	4 34	2.3 19.3
	IIB	56	31.8
	IIIA	52	29.5
	IIIB	24	13.6
	IIIC	6	3.4

BMI: body mass index.

Pathological characteristics such as histological grade, ER expression, RP expression, and HER2 status are associated with PCR with statistical significance, with p = 0.022, p = 0.01, p = 0.01, and p = 0.02, respectively. The other clinicopathological characteristics analyzed, such as age, clinical stage, and Ki-67, did not show a significant correlation with PCR, with p = 0.92, p = 0.248, and p = 0.749, respectively, which demonstrates that they did not influence the outcome of PCR of this sample (Table 3).

Multivariate analysis by Cox regression showed that patients who presented PCR had better OS regardless of clinical characteristics related to the molecular subtype, ER, PR, and Ki67 (hazard ratio — HR = 0.15; 95%CI 0.04 – 0.54) (Appendix 2).

The median follow-up was 35.9 months. The five-year DFS for the total sample was 88.8%, for the group with PCR it was 96.7% and, for the group without PCR, it was 83.2%, with a difference in the limit of statistical significance between groups (p = 0.05) (Figure 1).

The estimated five-year overall survival was 77.8%. When patients were categorized into two groups, with and without CPR, it was possible to observe a significant difference in the estimate of overall survival at five years, with 95.5% in the group with PCR and 69.1% in that without PCR (p = 0.017) (Figure 2).

Among the 176 patients in the total sample, 11 evolved with locoregional recurrence (LRR) (6.25%); one LRR in the group with PCR (1.6%) and 10 LRR were in the group without PCR (8.8%) (p = 0.10).

DISCUSSION

Among the 176 patients with BC who underwent NACT in our study, the PCR rate was 35.2%. Currently, one of the main benefits of NACT is the prognostic information obtained by the pathological evaluation of the tumor bed and axillary lymph nodes after surgery. The PCR is strongly associated with a better prognosis of patients undergoing NACT, as observed in the NSABP B-18 and B-27 clinical trials[11,16].

In our study, we observed a significant association between the molecular subtype and the presence of PCR (p = 0.001), with

Table 2. Association between molecular subtype and PCR.

Molecular Subtype	No. of patients	No. of patients who reached PCR (%)	p-value
Luminal A			p=wss
Luminal B/HER2 negative			p=0.01
Luminal B/HER2 positive			p=0.01
HER2 positive non luminal			p=0.01
Triple negative			p=0.01

wss: without statistical significance.

PCR rates ranging from 22 to 50% according to the molecular subtype. This finding is consistent with the literature, in which PCR rates are higher in patients with HER2 positive BC and triple negative BC (TN) when compared to patients with HER2 negative/hormone receptor positive BC[14,17].

In line with data from the world literature, we demonstrated that patients who achieved PCR had significantly higher survival rates compared to those with residual disease. In our study, the five-year DFS for the group with PCR was 96.7% *versus* 83.2% for the group without PCR (p = 0.05). The estimated five-year OS for the group with PCR was 95.5% *versus* 69.1% for the group without PCR (p = 0.017). Furthermore, among the patients in our total sample, 11 evolved with LRR (6.25%); one LRR in the group with PCR (1.6%) and 10 LRR were in the group without PCR (8.8%). In the NSABP B-18 study, patients who had post-NACT PCR had longer DFS and greater OS (HR = 0.47, p = 0.0001 and HR = 0.32, p = 0.0001, respectively)[18].

A therapy based on the assessment of prognostic and predictive factors enables the application of different therapeutic modalities used in cancer treatment with the intensity and effectiveness that are adequate and individualized for each specific patient[19]. In our study, pathological characteristics such as histological grade, ER expression, PR expression, and HER2 status are associated with PCR with statistical significance, with p = 0.022, p = 0.01, p = 0.01, and p = 0.02, respectively. The other clinicopathological characteristics analyzed, such as age, clinical stage, and Ki-67, did not show a significant correlation with PCR, with p = 0.92, p = 0.248, and p = 0.749, respectively, demonstrating that they did not influence the outcome of PCR in this sample.

The population in our study consisted mostly of young patients; 53.5% of them were aged between 35 and 49 years and had tumors in more advanced stages, and 61.3% had clinical stage

Table 3. Clinicopathological characteristics according to complete pathological responde (PCR).

Characteristics		All	PCR	Without PCR	P
			N (%)	N (%)	
Total		176	62	114	
Age (years), mean ± SD		176	46.0 ± 11.7	48.0 ± 10.1	p = 0.25
Age (years)	< 35	15	9 (14.5)	6 (5.3)	p = 0.92
	35–49	94	32 (51.6)	62 (54.4)	
	50–64	59	18 (29.0)	41 (36.0)	
	≥ 65	8	3 (4.9)	5 (4.3)	
Histological grade	I	12	2 (3.2)	10 (8.7)	p = 0.022
	II	57	16 (25.8)	41 (36.0)	
	III	71	31 (50.0)	40 (35.1)	
	not available	36	13 (21.0)	23 (20.2)	
Clinical Stage	I	4	1 (1.6)	3 (2.6)	p = 0.249
	IIA	34	12 (19.4)	22 (19.3)	
	IIB	56	19 (30.6)	37 (32.5)	
	IIIA	52	17 (27.4)	35 (30.7)	
	IIIB	24	10 (16.1)	14 (12.3)	
	IIIC	6	3 (4.9)	3 (2.6)	
ER	0–9	73	36 (58.1)	41 (36.0)	p = 0.01
	10–49	15	6 (9.7)	9 (7.9)	
	≥ 50	84	20 (32.2)	64 (56.1)	
PR	0–9	89	43 (69.4)	51 (44.7)	p = 0.01
	10–49	30	8 (12.9)	22 (19.3)	
	≥ 50	52	11 (17.7)	41 (36.0)	
Ki-67	< 14	11	3 (4.8)	8 (7.0)	p = 0.749
	≥ 14	165	59 (95.2)	106 (93.0)	
HER2	Positivo Negativo	62 114	29 (46.8) 33 (53.2)	33 (28.9) 81 (71.1)	p = 0.02

ER: estrogen receptor; PR: progesterone receptor.

IIB (31.8%) and IIIA (29.5%). However, clinical stage and age did not have a significant correlation with PCR, which shows that age and tumor size at diagnosis probably do not influence PCR rates in the neoadjuvant setting.

NACT is equivalent in OS compared to adjuvant chemotherapy in the treatment of BC. In contrast to adjuvant treatment, NACT has traditionally been relegated to patients with locally advanced, initially inoperable BC. However, NACT has played an increasingly important role in the treatment of early-stage disease[10], especially in patients with triple negative BC and HER2 positive, regardless of patient age, with benefits even in elderly patients in good clinical condition.

Another key point in the neoadjuvant scenario is the proper interaction between the pathologist and the surgeon, as the former needs adequate clinical and imaging information, such as tumor size and location, in addition to the presence or absence of a clip in the tumor bed for a careful evaluation of the residual tumor. This was a positive point of our work: the pathologist

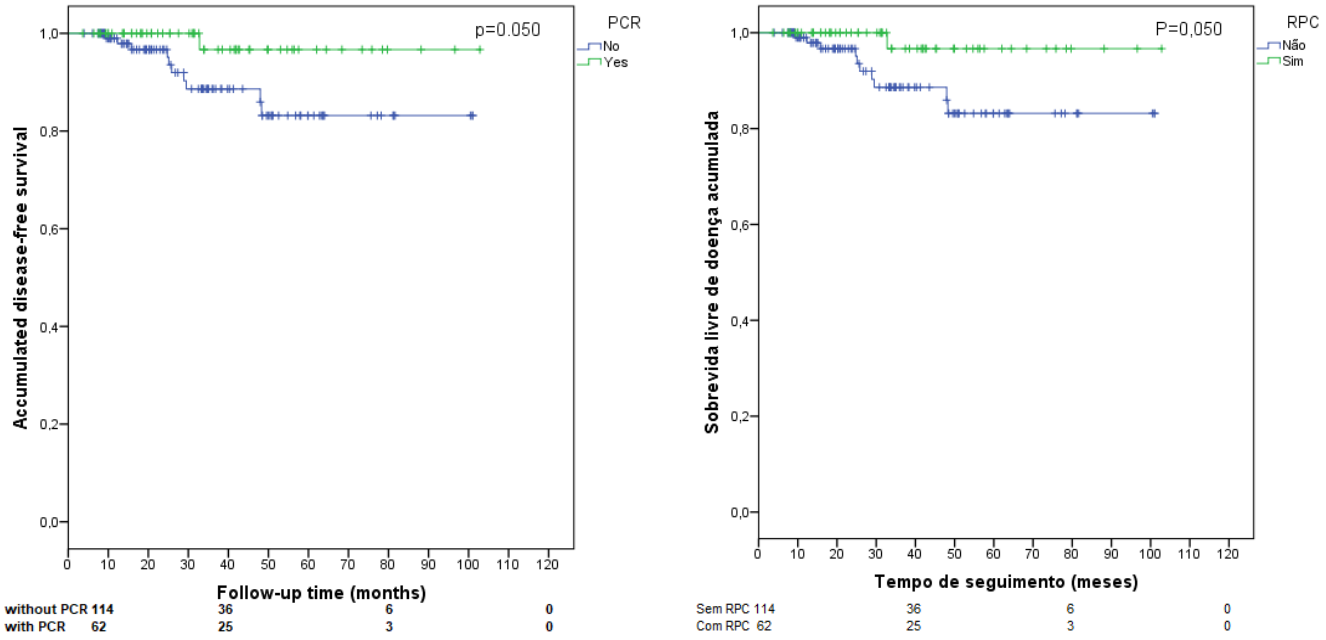

Figure 1. Disease-free survival estimate of patients according to the PCR.

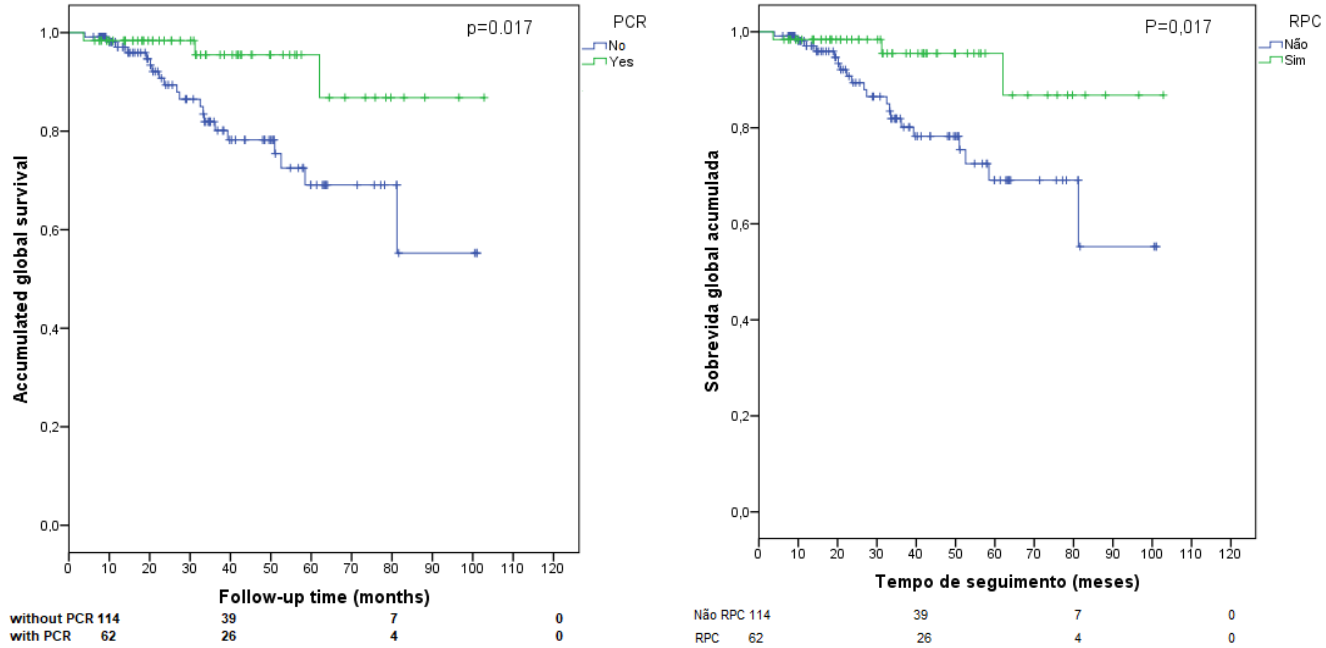

Figure 2. Estimate of overall survival in patients according to PCR.

presented this necessary and important information before the macroscopic examination of the surgical specimen, directing it to specific serial sections post-NACT according to well-established international recommendations and allowing the anatomopathological result to mirror the extension of post-NACT residual tumor with high accuracy[15].

Although our study has shown relevant and expected data according to the world literature, we understand that the limitations of this work are related to the small sample, the retrospective nature, and the short follow-up time. In addition, we also observed that a small sample of patients (5.11%) underwent double HER2 blockade in neoadjuvant therapy.

CONCLUSION

In our sample of patients with BC undergoing NACT, we observed higher rates of PCR in the triple negative and HER2 positive molecular subtypes. PFS and OS rates were significantly better in patients who achieved PCR, regardless of clinicopathological factors. We also observed lower LRR rates in the population that reached PCR. Thus, we increasingly emphasize the importance of NACT in the approach of the initial BC.

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AUTHORS' CONTRIBUTIONS

R.F.: Conceptualization, Data curation, Formal analysis, Writing — original draft.
Maximiliano Cassilha Kneubil: Conceptualization, Data curation, Formal analysis, Writing — original draft.
J.B.: Project administration, Methodology, Writing — review & editing.
L.H.B.L.T.: Investigation, Writing — review & editing.
K.B.G.: Methodology, Data curation, Formal analysis.
I.E.L.: Methodology, Project administration, Validation.
M.R.E.: Project administration, Writing — review & editing.
J.A.P.H.: Project administration, Writing — review & editing.

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Apêndice 1. Ficha de avaliação.

Nome: _____ Prontuário:_____

Data de nascimento: ___/___/___ Idade ao diagnóstico: _____

Sexo: ☐ 1. Feminino; 2. Masculino

Etnia: ☐ 1. Branca; 2. Negra; 3. Asiática 4. Parda; 5. Outra.

IMC: _____ Peso: ____ kg Estatura: ____ cm

Performance status: ☐ 0. 0; 1. 1; 2. 2; 3. 3; 4. 4

História prévia de tabagismo: ☐ 0. Não 1. < 20 maços/ano 2. > 20maços/ano

Status menopausal: ☐ 0. Pré-menopausa; 1. Pós-menopausa

Data do diagnóstico: ___/___/___ Laboratório:_____

Tipo histológico: ☐ 1. Lobular invasor; 2. Ductal invasor; 3. Outros _____

Grau histológico (Nottingham): ☐ 1. G1; 2. G2; 3. G3 99. Não disponível

Expressão ER: ☐ valor:_____ 0. Ausente (0%); 1. Baixa (≥ 1% e < 10%); 2. Positiva (≥ 10% e < 50%); 3. Fortemente positiva (≥ 50%)

Expressão PgR: ☐ valor:_____ 0. Ausente (0%); 1. Baixa (≥ 1% e < 10%); 2. Positiva (≥ 10% e < 50%); 3. Fortemente positiva (≥ 50%)

HER2: ☐ 0. 0+; 1. 1+; 2. 2+; 3. 3+; 99. Não disponível

Se 2+: ☐ 0. FISH não amplificado; 1. FISH amplificado; 88. Não se aplica 99. Não disponível

Ki67: ☐ valor:_____ 1. Baixo (< 14%); 2. Alto; 3. Não disponível

Subtipo Molecular: 1.Luminal A 2.Luminal B 3.Luminal-HER2 Positivo

4. HER2 Puro 5. Triplo Negativo

TNM inicial

T: ☐ valor:_____(cm) 0. T1mi; 1. T1a; 2. T1b; 3. T1c 4. T2; 5. T3; 6. T4a; 7. T4b; 8. T4c; 9. T4d

T: ☐ Avaliado por: 0. Exame Físico; 1. Ecografia mamária bilateral; 2 Ambos

N: ☐ 0. N0; 1. N1; 2. N2a; 3. N2b; 4. N3a; 5. N3b; 6. N3c

M: ☐ 0. M0; 1. M1

Estádio clínico: ☐ 1. IA; 2. IB; 3. IIA; 4. IIB; 5. IIIA; 6. IIIB; 7. IIIC; 8. IV

Se 8 (EC IV), sítio metastático: ☐ 8a. Fígado; 8b. Pulmão, pleura ou derrame pleural; 8c. Osso; 8d. SNC ;

8e. Outros _____

TRATAMENTO SISTÊMICO NEOADJUVANTE

Quimioterapia neoadjuvante: ☐ 0. Não realizou; 1. Realizou

Se 1, protocolo ☐ (ver Anexo 1)

Data início:___/___/___ Data término:___/___/___ Nº ciclos:_____

Progressão em vigência de quimioterapia neoadjunte: 0. Não 1. Sim

Terapia de alvo molecular ☐ 0. Não realizou; 1. Trastuzumab; 2. Lapatinib; 3. Pertuzumab 4. Trastuzumab+Pertuzumab 5. Trastuzumab+Lapatinib 6. Outra

Data início:___/___/___ Data término:___/___/___ Nº ciclos:_____

Resposta patológica completa: ☐ 0. Não 1. Sim 88. Não se aplica

Tumor residual ypT___ valor:____(cm) ypN____(___/___)

TNM Patológico pós-quimioterapia neoadjuvante

yT: valor:_____(cm) 0. T1mi; 1. T1a; 2. T1b; 3. T1c; 4. T2; 5. T3; 6. T4a; 7. T4b; 8. T4c; 9. T4d; 10. Carcinoma ductal ***in situ*** 88. Não se aplica

yN: ☐ 0.N0; 1.N1; 2.N2; 3.N3 88. Não se aplica

Laboratório AP Cirurgia:_____ ICR:_____

Se não houve resposta patológica completa, Tumor residual: ☐ 0. CDIS; 1. Carcinoma Invasor; 2. CDIS+Carcinoma invasor

Tipo histológico: ☐ 1. Lobular invasor; 2. Ductal invasor; 3. Outros _____88. Não se aplica 99. Não disponível

Grau histológico (Nottingham): ☐ 1. G1; 2. G2; 3. G3 88. Não se aplica 99. Não disponível

Se não houve resposta patológica completa. ☐ 1. Doença estável; 2. Resposta parcial; 3. Progressão da doença

Em caso de progressão de doença. ☐ 0. Local; 1. Regional; 2. Locorregional

IMH do tumor residual 0. Não realizada; 1. Realizada

Se realizada:

Expressão ER: ☐ valor:_____ 0. Ausente (0%); 1. Baixa (≥ 1% e < 10%); 2. Positiva (≥ 10% e < 50%); 3. Fortemente positiva (≥ 50%)

Expressão PgR: ☐ valor:_____0. Ausente (0%); 1. Baixa (≥ 1% e < 10%); 2. Positiva (≥ 10% e < 50%);3. Fortemente positiva (≥5 0%)

HER2: ☐ 0. 0+; 1. 1+; 2. 2+; 3. 3+; 4. Não disponível

Se 2+: ☐ 0. FISH não amplificado; 1. FISH amplificado; 2. Não disponível

Ki67: ☐ valor:_____1. Baixo (<14%); 2. Alto; 3. Não disponível

CIRURGIA
Cirurgia: ☐ 0. Não; 1. Sim Data: ___/___/___ 88. Não se aplica 99. Não disponível
Se sim: ☐ 1a. Setorectomia/Quadrantectomia; 1b. Adenomastectomia (*nipple sparring*); 1c. Mastectomia (*skin sparring*); 1d. Mastectomia radical modificada
Linfonodo sentinela: ☐ 0. Não realizado; 1. Realizado
Se 1: ☐ 1a. Negativo; 1b. Positivo (___/___)
Se 1b: ☐ 1ba. Micrometástase (<2mm); 1bb. Macrometástase
Esvaziamento linfonodal: ☐ 0. Não; 1. Sim (___/___) Se 1, presença de extravasamento extracapsular: ☐ 1a. Não; 1b. Sim

RADIOTERAPIA ADJUVANTE
Radioterapia adjuvante: ☐ 0. Não; 1. Sim _____Gy _____sessões
Se sim: ☐ 1a. ELIOT; 1b. Mama; 1c. Mama + *boost* leito tumoral; 1d. Mama + áreas de drenagem; 1e. Plastrão 1f. Plastrão+áreas de drenagem
1g. outro _____

TRATAMENTO SISTÊMICO ADJUVANTE
Quimioterapia adjuvante: ☐ 0. Não realizou; 1. Realizou
Se 1, protocolo ☐ (ver Anexo 1)
Data início:___/___/___ Data término:___/___/___ Nº ciclos:_____
Terapia de alvo molecular adjuvante ☐ 0. Não realizou; 1. Trastuzumab; 2. Lapatinib; 3. Trastuzumab+Lapatinib 4. Outra
Data início:___/___/___ Data término:___/___/___ Nº ciclos:_____
Hormonioterapia adjuvante ☐ 0. Não realizou; 1.Tamoxifeno; 2. Anastrozol; 3. Letrozol 4. Tamoxifeno+IA 5. IA+Tamoxifeno 6. Exemestane
7. Outro
Data início:___/___/___ Data término:___/___/___ Nº meses:_____
Supressão ovariana: ☐ 0. Não; 1. Sim Nº meses:_____

Progressão de doença: ☐ 0. Não; 1. Sim Data da progressão: ___/___/___
Sítio de progressão: _____
Recidiva locorregional: ☐ 0. Não; 1. Plastrão; 2. Mama ipsilateral; 3. Axila ipsilateral; 4.Fossa supraclavicular; 5. Mama+axila ipsilateral 6. Outro
Data da recidiva: ___/___/___
Carcinoma mama contralateral: ☐ 0. Não; 1. Sim Data: ___/___/__
Paciente vivo: ☐ 0. Não; 1. Sim Se não, data do óbito: ___/___/__
Data do último *follow-up*: ___/___/___
Pesquisador responsável: _____
Data: ___/___/___

ANEXO 1
1. AC (Doxorrubicina+Ciclofosfamida);
2. DC (Docetaxel+Ciclofosfamida);
3. AT (Doxorrubicina+Docetaxel);
4. TAC (Docetaxel+Doxorrubicina+Ciclofosfamida);
5. AC-D* (Doxorrubicina+Ciclofosfamida+Docetaxel)
6. AC-T** (Doxorrubicina+Ciclofosfamida+Paclitaxel);
7. AC-T*** (Doxorrubicina+Ciclofosfamida+Paclitaxel dose densa);
8. T-AC (Paclitaxel+Doxorrubicina+Ciclofosfamida);
9. CMF (Ciclofosfamida+Metotrexato+5-FU);
10. FAC (Ciclofosfamida+Doxorrubicina+5-FU);
11. FAC-D(Ciclofosfamida+Doxorrubicina+5-FU+Docetaxel);
12. FEC100-T (Epirrubicina+5-FU+Ciclofosfamida+Docetaxel);
13. FEC90-T (Epirrubicina+5-FU+Ciclofosfamida+Paclitaxel)
14. Outro _____

Appendix 2. Cox regression tables of factors associated with overall survival.

Model 1

	P	HR	95.0%CI	
			Lower	Upper
PCR	0.003	0.153	0.045	0.524
Age at diagnosis	0.448	0.982	0.938	1.029
PRvalue	0.119	0.982	0.960	1.005
ERvalue	0.678	1.004	0.986	1.022
Ki67value	0.019	1.028	1.005	1.052

HR: *hazard ratio*; CI: confidence interval; PCR: pathologic complete response; PR: progesterone receptor; ER: estrogen receptor.

Model 2

	P	HR	95.0%CI	
			Lower	Upper
RPC	0.003	0.151	0.043	0.528
Molecular subtype	0.044			
Molecular subtype (1)	0.796	0.755	0.090	6.363
Molecular subtype (2)	0.693	1.583	0.162	15.496
Molecular subtype (3)	0.652	1.687	0.174	16.334
Molecular subtype (4)	0.196	3.913	0.494	30.989
Age at diagnosis	0.230	0.973	0.932	1.017

HR: *hazard ratio*; CI: confidence interval; PCR: pathologic complete response.