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Predictive factors of pathological Complete Response (pCR) in locally advanced breast cancer

Facteurs prédictifs de Réponse Complète Histologique (pCR) dans les cancers du sein localement avancés

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ABSTRACT

Introduction : Breast cancer is the 1st cancer and the 1st cause of cancer death in women. The proportion of locally advanced breast cancer (LABC) is highly variable across the world and its prognosis is reserved. In addition to operability, the goal of Neoadjuvant chemotherapy (NACT) is pathological response, in particular complete (pCR) considered a good prognostic factor. The heterogeneity of the histological response points to the study of predictive factors to adapt treatments. This study aims to determine the predictive factors of pCR after NACT for LABC.
Patients and methods : A prospective, multicenter study focused on LABC (stage III), treated by 8 cycles of NACT. After surgery, the histological response is evaluated and cases of pCR noted. Data analysis is first descriptive: admission data, treatment, clinical, radiological, and histological response. Then analytic study is to determine the factors statistically associated with pCR.
Results : 86 patients, median age 47.8 (29-65 years). More than 55% are T4 and 10% are T4d. More than 20% N2. Stage IIIB represents 55.4%. The Her2-positive group is the most frequent (53%), the luminal group 30%, and Triple-negative 17%. The rate of pCR is 35.6%, in addition to 18.4% of npCR. This rate is different depending on the molecular group. The main predictors of pCR are: radiological size of T, RE, histology, and final radiologic response.
Conclusion : Our study has shown that certain factors are associated with pCR. Their integration into a predictive score and its prospective validation would make it possible to orient the personalization and intensification to improve the pCR rates, since it is directly linked to the prognosis.

KEYWORDS: Breast cancer 1, pathological complete response (pCR) 2, neoadjuvant chemotherapy 3, predictive factors 4,

RESUME

Introduction : Le cancer du sein est le 1er cancer et la 1ère cause de mortalité par cancer chez la femme. La proportion de Cancer du sein localement avancé (CSLA) est très variable dans le monde et son pronostic est réservé. En plus de l'opérabilité, le but de la Chimiothérapie néoadjuvante (CTNA) est la réponse histologique, en particulier complète (pCR) considérée comme facteur pronostique. L'hétérogénéité de réponse demande l'étude des facteurs prédictifs afin d'adapter les traitements. Le but de cette étude est de déterminer les facteurs prédictifs de pCR après CTNA pour un CSLA.
Patients et méthodes : Etude prospective, multicentrique portant sur les CSLA (stade III) ayant reçu 8 cures de CTNA. Après chirurgie la réponse histologique est évaluée y compris la pCR. Une analyse descriptive : données

d'admission, thérapeutique, de réponse clinique, radiologique et histologique. Suivie d'une étude analytique pour déterminer les facteurs statistiquement associés à une pCR.
Résultats : 86 patientes, l'âge médian 47.8 (29-65 ans). Plus de 55 % de T4 et 10 % T4d. Plus de 20 % N2. Le stade IIIB représente 55.4 %. Le groupe HER-2 positif le plus fréquent (53 %), le groupe luminal 30 % et Triple-négatif 17 %. Le taux de pCR 35,6 %, en plus de 18.4 % de npCR. Ce taux diffère selon le groupe moléculaire. Les principaux facteurs prédictifs de pCR sont : la taille radiologique de T, le statut RE, l'histologie, et la réponse radiologique finale.
Conclusion : Certains facteurs sont associés à la pCR. Leur intégration à un score prédictif et sa validation prospective permettrait d'orienter la personnalisation et l'intensification de la CTNA pour améliorer la pCR, directement liée au pronostic.

MOTS CLES : Cancer du sein 1, Réponse complète histologique (pCR) 2, Chimiothérapie néoadjuvante 3, Facteurs prédictifs 4

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Introduction

Breast cancer is the 1st cancer (24.5% of all cancer cases) and 1st cause of cancer death (15.5% of all cancer-related deaths) in women worldwide **[1]**. In Algeria, during the year 2019, the incidence was 77.9 for 10^5 women according to data from the Cancer Registry of Algiers, representing 37.8% of all female cancers **[2]**. The proportion of locally advanced breast cancer (LABC) is highly variable throughout the world, representing 11.2% of invasive cancers in the USA, and ranging from 20 to more than 50% in developing countries **[3]**. A national study (BreCaReAl) published in 2020 reported a 28.8% rate **[4]**. This type of cancer has a rather poor prognosis, mainly due to the risk of locoregional recurrence and the development of distant metastases **[5]**.

LABC is usually defined by stage III tumors according to the classification of the American Joint Committee on Cancer (AJCC) **[6]**, comprising a heterogeneous group from large operable tumors to inflammatory tumors. Thus, the management of LABC is complex, always multimodal, combining systemic treatments as 1st modality in order to reduce tumor burden and allow surgery with negative margins. In some cases, a major response can allow breast conserving surgery, and recently the possibility of minimal intervention on the axilla in selected cases. Some tumors are particularly resistant to systemic treatment and may need néoadjuvant or definitive radiotherapy. Where, palliative surgery must be avoided unless justified by an alteration of quality of life due to bleeding or infection.

Neoadjuvant chemotherapy (NACT), also called induction chemotherapy, or first, was introduced in the 1980s, first in the treatment of LABC and inflammatory diseases **[7-8]**. The main goal was to obtain an objective response compatible with secondary surgery, which was initially impossible or incomplete. It is recommended to continue all planned neoadjuvant chemotherapy even if there is a good clinical response **[9]** to increase the rate of pathological complete response (pCR) considered as an intermediate prognostic factor, which can predict the disease-free survival (DFS) and overall survival (OS) **[10-11]**. The NACT has become an interesting framework for evaluating the efficacy of new drugs in-vivo, and the Food and Drug Agency (FDA) has retained the neoadjuvant context for accelerated registration of new molecules based on the pCR rate **[12-13]**, which becomes the primary objective for clinical trials **[14-17].**

The differences noted in terms of quality and time to clinical response were at the origin of the concept of predictive factors of response or resistance, which remains an important line of research and is currently the subject of numerous publications. The main parameter remains the molecular group, whose simplified classification is based on immunohistochemistry, comprising: luminal-A and B, triple negative and HER2-positive **[18-19]**.

This paper aims to determine the predictive factors of pCR after NACT for LABC.

Material and Methods

We conducted a prospective, multicenter study in the medical oncology departments of 3 centers: Annaba, Constantine, and Setif. From October 1st, 2015 to October 31st, 2018. Study design represented in Figure 1.

Patients eligible for inclusion are females aged between 18 and 65 years old, with breast carcinoma histologically confirmed, stage III according to the

AJCC 2009, agreeing to participate in the study by informed consent.

The main objective of our study, presented in another paper, is improving pCR by a personalized chemotherapy schedule. This paper reports the analysis of the secondary endpoint.

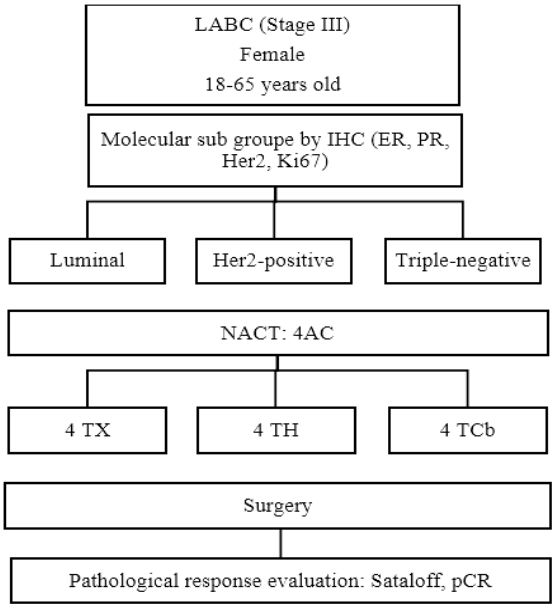

Figure 1. Study design

Sample calculation: In the case of our studies with a single sample, for:

- A pCR rate to be tested equal to around 25% according to the literature,
- An expected pCR rate of 40% through the personalized care offered,
- A level of significance of 5%, test power of 90%.

The minimum sample required is calculated at 80 patients.

The molecular sub-groupe was defind according to the immunohistochemisty as: luminal if estrogen receptor (ER) positive divided into luminal-A or B according to progesterone receptor level (A if >30%) and Ki67 (A if <20%) **[9].**

The neoadjuvant treatment consisted of eight cycles: four AC cycles (doxorubicin-cyclophosphamide), followed by four docetaxel associated with trastuzumab, carboplatin, or capecitabine depending on whether it was a Her2-positive, triple-negative or luminal tumor, respectively. In case of progression, patients received second-line chemotherapy, according to the choice of the investigator.

The evaluation of the response was clinico-radiological, every 2 cycles by clinical examination and echo-mammography, according to the RECIST 1.1 criteria, defined according to the initial sum of the major axes for the primary tumor and the short axes for the nodes, as: Progressive Disease (PD) if increase >20%, Partial Response (PR) if decrease >30%, Stable Disease (SD) between the two, and Complete Response (CR) if no proof of tumor and no node with short axes >10mm **[20].**

Mastectomy is scheduled beyond 2 weeks of the last cycle of chemotherapy. Radiotherapy is scheduled beyond 3 weeks after surgery after wound healing. Adjuvant treatment combined: trastuzumab in case of HER2-positive tumors to complete one year of treatment, and hormone therapy according to genital activity in case of HR-positive.

The assessment of the histological response is made according to the Sataloff system, specifying whether it is a pCR defined by the absence of infiltrating carcinoma in the breast and lymph nodes.

The follow-up is done simultaneously, as well as the collection of data until the anatomopathological results, for this study. Data is collected on individual CRFs (Case-Report-Forms) and then injected by manual entry into a database in Microsoft Office Excel. Once the recruitment is complete, the database is codif, frozen,zen and analyzed using the XLStat software, integrated into Excel.

A descriptive study covers all the data identified: demographic, clinical, radiological, histological, immunohistochemical, clinical and radiological response, histological response, and follow-up data.

An analytical study focuses on the analysis of the predictive factors of pathological complete response (pCR) among all the factors mentioned above. Initially, every factor is analyzed separately, then a multivariate analysis by logistic regression was performed. A $p<0.05$ is considered significant.

Results

1. General characteristics of the population

The study included 86 patients (one bilateral) between 2015 and 2018. The main characteristics of the patients at admission are summarized in Table 1.

The median age is 47.8 years (29-65 years). Maximum age was initially designated for inclusion in the study. Half of women are postmenopausal.

The main symptom leading to diagnosis is the breast nodule (84.3%). The average waiting time to the first investigation is 6.18 months (1-24). The majority of tumors are rapidly evolving: 43% PEV1 (*Poussée EVolutive*) and 41% show inflammatory signs.

The average body mass index BMI is 28.5 (15.79-42.97), and 38.2% are obese. On clinical examination: the average size of the evaluable primary tumor is 74.5 mm (30 – 160 mm). The most frequent site of the tumor is the upper outer quadrant (39.3%) and retro-nipple (38.2%). More than 55% of tumors are T4 with 10% carcinomatous mastitis. More than 20% present fixed nodes classified as N2. Stage IIIB represents 55.4% and no tumor is classified as stage IIIC.

Table 1. General characteristics:

		%
Age (y)	**Median 47.8 (29-65)**	
BMI	**Median 28,5 (15,8 – 42,9)**	
T clinical size (mm)	**Median 74,5 (30 – 160)**	
Nodes	**N1**	**66.6**
	N2	**21.1**
N clinical size (mm)	**Median 16 (10 – 40)**	
T radio. size (mm)	**Median 36 (7 – 115)**	
N radio. size (mm)	**Median 15.4 (6 – 30)**	
Histology	NSIC	**74.5**
	ILC	17.8
Grade	1	5,6
	2	**77,7**
	3	16,7
ER	**Positive**	**71,1**
PR	**Positive**	**65,5**
Ki-67	≤14	30,0
	15-20	24,4
	>20	**36,6**
Her-2	**Positive**	**53,0**
Molecular Group	Luminal	**30**
	Triple-negative	**17**
	Her2-positive	**53**

BMI, body mass index; T, tumor; N, node; NSIC, nonspecific invasive carcinoma; ILC, invasive lobular carcinoma; ER, estrogen receptor; PR, progesterone receptor; Her-2, human epidermal growth factor-2.

2. Preoperative response data

A difference is noted in terms of clinical and radiological response depending on the molecular group (Figure 1).

The average clinical response is 87%: 81.2% for the Luminal A group, 82.7% for Luminal B, 89.1% for Her2-positive, and 90.5% for triple-negative. The average radiological response is 80.4%: 68.1% for the luminal A group, 73.6% for Luminal B, 82.8% for Her2-positive, and for the tritriple-negatihe highest rate of complete clinical response is noted in the Triple-Negative group (66.6%) against 54.3% for the HER-2 group and 40.8% for the Luminal group.

The radiological complete response varies between 18.5% for luminal tumors and 33.3% for triple-negative tumors. The partial response is most often major (>50%): 71.8% for HER-2 positive tumors and 66.7% for luminal and triple-negative tumors.

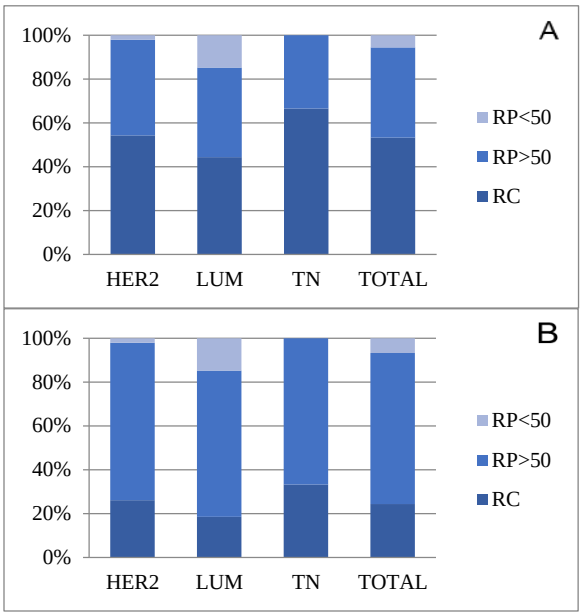

Figure 2: Preoperative response according to molecular group

(A) Clinical response. (B) Radiological response

3. Histological response data

The average time between the end of chemotherapy and surgery is 33.2 days (10 – 72 days). All patients underwent mastectomy with lymph node dissection according to Patey. Pathological response data are summarized in Table 2.

Table 2 : Pathological response data

		%
pT	**0**	**40.2**
	1a	12.6
	1b	9.2
	1c	18.4
	2	13.8
	3	4.6
	4	1.1
RESIDU SIZE (MM)		19 (0.1-60)
pN	**0**	75.9
	1	17.2
	2	6.9
pCR		**35.6**
npCR		18.4

No macroscopic residue was found on the primary tumor (ypT0) in 40%. About 30% of the residues are ypT1. It is most often a single site (88.4%). The tumor residue is fragmented in 48%. The average size of the largest residue is 19 mm. It is a non-specific invasive carcinoma in 86% of cases. A carcinoma in situ is found in 16 cases (18.4%).

The average number of lymph nodes removed during surgery is 11.3 (2 – 21). Thus in 32.2% of cases, the dissection is insufficient (<10 lymph nodes). The average number of N invaded is 0.8 (0 – 11). Four cases of capsule rupture are recorded (4.5%).

In 8% of cases, there is residual lymph node involvement despite a complete or almost complete response on the breast. Similarly, a complete response on the lymph nodes (NA) is noted despite the persistence of a residue in the breast in 8% of cases as well.

The pCR rate is 35.6%, in addition to 18.4% npCR.

Differences are noted in terms of histological response depending on the molecular sub-group (Figure 2). The average size of the residue is larger in the luminal tumor group (21.1mm) compared to Her2-positive (15.9mm) and Triple-negative (16.3mm) tumors.

The pCR rates for the HER-positive and Luminal groups are relatively comparable to the average (32.6 and 30.7% respectively), and higher for the Triple-negative group (53.3%).

Of 57 patients with residual tumors, only 8 (14%) IHC results are available. Three (37.5%) changes in hormone receptor status are noted. All concerns initially triple-negative tumors.

4. Predictors of pCR: The analysis of predictors of pCR is summarized in Table 3.

Clinical data: None of the clinical parameters (BMI, Size T, Presence of N, Size N, T of TNM, N of TNM, TNM stage) is a predictive factor of pCR+/-npCR in our study. Clinical tumor size and TNM T classification did not influence the rate of complete response on the primary tumor (TA) in our study. The clinical size of N influences the rate of complete response on the nodes.

Radiological data: The radiological size of T and N is significantly related to the pCR rate in our study. The radiological tumor size influences the complete response rate on the primary tumor (TA). Similarly, the radiological size N influences the complete response rate on N.

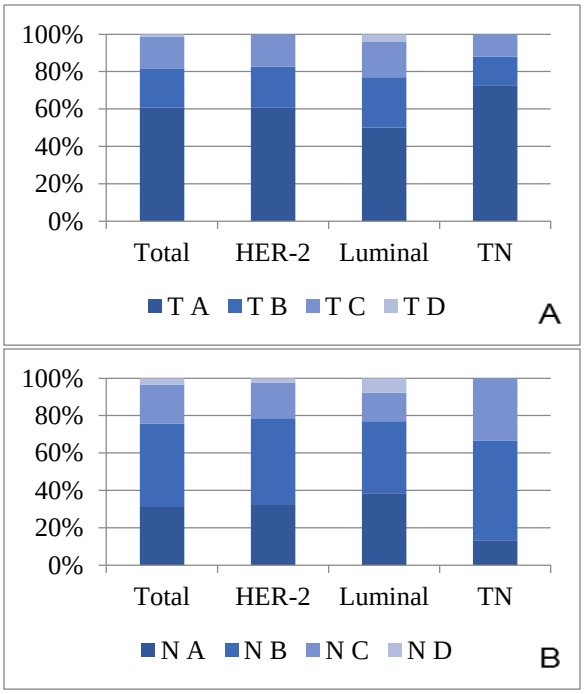

Figure 3: Pathological response according to molecular group
(A) SATALOFF T. (B) SATALOFF N

Histological data: Histology, SBR grade, mitotic index, vascular emboli, and the nature of the stroma do not influence the pCR rate.

Immunohistochemical data: Positive ER is a predictive factor for pCR, unlike the PRs. The percentage of HER-2 positivity does not influence the pCR rate in HER-2 positive tumors under trastuzumab, but the difference is significant (p 0.004) if we add the

pCR and npCR. A low Ki-67 is associated with a low pCR rate.

Molecular group: The difference between the sub-groups is not significant in multivariate analysis in terms of pCR. Distinguishing luminal tumors A and B the pCR rate is 25% and 31.5%, respectively. For HER-2 tumors, the pCR rate is 28.2% in ER-positive cases vs. 57.1% in ER-negative cases.

Preoperative response data: Early responders (after CT2) have a higher rate of pCR. The final clinical and radiological response is significantly associated with the pCR rate. This difference was significant in multivariate analysis.

In a multivariate analysis as shown in table 3, only tumor radiologic size, histology, ER level, and early radiologic response, were associated to pCR.

Table 3. Predictive factors of pCR by multivariate analysis:

	Sig.	Exp (B)	CI 95% EXP(B)	
			Inf.	Sup.
Initial Radiologic size	.013	.935	.887	.986
KI67_1	.748	1.011	.944	1.083
HER2(1)	.990	.987	.130	7.492
SBR	.949			
SBR(1)	.999	.000	.000	.
SBR(2)	.746	1.389	.190	10.160
ER	.038	1.047	1.003	1.094
PR	.051	.946	.896	1.000
1st Radiologic evaluation	.287	.959	.888	1.036
Last Radiologic evaluation	.000	1.166	1.072	1.268
Molecular groupe	.806			
Molecular groupe(2)	.806	1.372	.110	17.132
Histology	.059			
Histology(1)	.0230	22.567	1.541	330.455
Histology(2)	.303	3.539	.319	39.247
T of TNM(1)	.141	.260	.043	1.566
N of TNM	.441			
N of TNM(1)	.518	2.222	.198	24.946
N of TNM(2)	.210	6.470	.348	120.242
Constante	.002	.000		

Discussion

To discuss the anamnestic and clinical data of our series, we selected three main studies on locally advanced breast cancer, one Algerian [21] for local epidemiology, the other Moroccan [23] for regional Maghrebian epidemiology, and finally a French [23] study for global epidemiology:

Anamnestic data: Age and menopause were not predictive of good histological response (pCR+npCR) in the 3 studies.

Clinical data: None of the clinical parameters (BMI, T-size, Presence of N, TNM) is proven as a predictor of pCR+/-npCR in our study.

Regarding BMI, a meta-analysis of 8 studies including 8872 patients treated with NACT. The pCR rate was significantly higher (p 0.003) for patients with a normal BMI (<25). With significant impact on DFS and OS. [10]

For initial clinical tumor size, a study of 608 patients demonstrated that the probability of pCR decreases if the tumor size exceeds 5cm (p 0.022). This decrease concerns TN and HER-2 tumors. But with multivariate analysis, tumor size was not significant in any of the groups. [11]

In our study, the clinical tumor size and the T classification of TNM do not influence the rate of complete response on the primary tumor (TA). The clinical size of N influences the rate of complete response on the nodes (p 0.027)

Radiological data: The T size is not significant in the Quentin study [23] and not studied in the Sakhri study [21].

The radiological tumor size influences the pCR rate in our study (p 0.013).

The radiological size N influences the response rate only on N (p 0.023).

Histological data: Regarding the histological type, a large study of 860 patients, including 14% ILC, treated with NACT demonstrated that the pCR rate was significantly higher on the IDC (p 0.002) [24] as in our study.

Immunohistochemical data: It is established that in case of negative ERs, the pCR rate is significantly higher, based on several studies with different protocols [25-26, 18]. In our study 57.1% in case of RH (-) versus 28.2% in case of RH (+), statistically significant.

The percentage of HER-2 positivity significantly influences the pCR rate in HER-2 positive tumors under trastuzumab.

A low Ki-67 is associated with a low level of pCR in the literature [19] where high Ki-67 is considered predictive of pCR, a value > 25% can be considered as a threshold.

Molecular group: In the literature, the highest response rate is recorded with the HER-2 group when trastuzumab is associated with neoadjuvant treatment (55%), followed by the triple-negative group (37.1%), and finally luminal B and A, 8.7% and 6.1% respectively. [8] In our study, the pCR rates achieved in these last 2 groups can be explained by personalized dual therapy in the 2nd sequence.

The pCR rates for the HER-positive and Luminal groups are relatively comparable to the average (36.6%). This rate is higher for the Triple-negative group (46.7%).

In the meta-analysis by Von Minckwitz et al. [27], the lowest pCR rate was found in the luminal A group (6.4%), followed by the luminal B group (11%-22%), with maximum rates for HER2+ and TN tumors (27%-32%).

Concerning the HER-2 group: the pCR rate reported by the literature after addition of trastuzumab is 66.7% [28] when trastuzumab is associated with all treatments including anthracyclines, and 31.7% [29] when it is associated only with docetaxel, which is close to our series.

In all studies, for HER2-positive tumotumorse pCR rate was higher in the case of HR (-) [30]. Fact confirmed in our series, where a pCR is noted in 57.1% in case of HR (-) versus 28.2% in case of HR (+).

Preoperative response data: Early responders have a higher rate of pCR. The final clinical and radiological response is significantly associated with the pCR rate.

The intermediate radiological response is not predictive of pCR in our study. In the literature, a study of 159 patients with a mean initial size of 34 mm (36 for our series) demonstrated that intermediate ultrasound response is associated with a better pCR rate for the triple-negative and luminal-HER2 (-) group ($p< 0.05$) but not for HER-2 (+) tumors ($p > 0.05$). On the other hand, the evaluation of lymph node status was predictive for all groups ($p<0.05$). [30]

In a study that included 150 patients treated with NACT, with evaluation of the response by three methods (MRI, mammography and ultrasound). The negative predictive value of the three methods in terms of complete response was comparable. The false positive rate with ultrasound reached 44%. [31]

Some observations concerning the management of LABC identified in this study deserve to be mentioned in order to improve the subsequent care of our patients:

- The waiting time accumulated by the patients before the care testifies to a lack of information and support.
- The advanced state of our patients at the time of diagnosis testifies (as proven during their interrogation) to the absence of participation in a screening program.
- At the time of treatment, the results of immunohistochemistry are very often missing, and the average time to their acquisition remains very long.
- MRI was not available for the assessment of the response, although it is becoming the reference technique.
- All the patients undergo a mastectomy with axilla clearance despite the good response in some cases.
- We noted a frequent lack of information on the final histology reports, in the absence of a standardized report, but also the absence of continuous transmission of clinical information (neoadjuvant chemotherapy) between the various stakeholders (oncologist-surgeon-pathologist).

Conclusion

Our study of 87 cases of locally advanced breast cancer has demonstrated that certain anamnestic, clinical, radiological, histological, and immuno-histochemical factors are associated with higher rates of mainly pCR: initial small radiologic size, ER level, Histology, and final radiologic response. Which could be used for the proposal of a predictive score of histological response, which can be tested prospectively in the context of a larger-scale validation study.

There is an association between the clinico-radiological response and the histological response, but it is not absolute. The use of other imaging methods, in particular MRI currently seems more appropriate, remains the problem of accessibility and cost.

Conflicts of interest

Authors do not declare any conflict of interest.

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