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RESEARCH ARTICLE

TRIPLE NEGATIVE BREAST CANCER, EXPERIENCE OF MILITARY HOSPITAL RABAT: ABOUT 52 CASES

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Abstract

Objective: to review the epidemiological, clinical, anatomopathological, biological, therapeutic and prognostic characteristics of this histo-prognostic subgroup, namely triple-negative breast cancer

Material and Method: Our work consists of a retrospective study carried out at the military hospital of instruction Med v rabat between January 2010 and December 2017 on 52 cases of invasive breast carcinoma with a triple negative phenotype.

Result:

From an epidemiological point of view: a peak in frequency was noted between 45 and 50 years old, and 48.1% of patients still in genital activity.

On the anatomo-pathological level: invasive ductal carcinoma is the most predominant type representing 68.3% of cases with an average tumor size of 30mm. Histopronostic grades II and III each represent 43.2% and 56.8% of cases.

Therapeutically: more than 42.3% received conservative treatment and 57.7% underwent radical surgery of the Patey type. Adjuvant systemic chemotherapy was given in 86.5% of cases and 5.8% received neoadjuvant chemotherapy

On the evolutionary level, 17.3% or 9 cases developed systemic metastases with predilection for the lungs.

Conclusion: Despite advances in treatments and the emergence of targeted therapies, breast cancer remains the leading cause of death in women. Current clinical and histological classifications do not fully establish the prognostic and predictive parameters of response to treatment.

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Introduction:-

Breast cancer is the most common cancer in women in the world and the leading cause of female cancer death. In Morocco, it has the particularity of affecting young women and, through its progressively increasing incidence, represents a real public health problem [1, 2] It is characterized by heterogeneity on all levels: clinical, histological and molecular explaining the diversity of presentations, responses to treatment and prognosis [2].

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However, immunohistochemistry techniques have enabled the clinician to distinguish three main types of breast cancer: (1) those which express estrogen receptors (70% of cases); (2) those which express the growth factor HER-2 (20% of cases); and (3) "triple negative" breast cancers (12–17% of cases) because they do not express estrogen receptors (RO), progesterone receptors (RP) and absence of overexpression and amplification of HER2. "Triple negative" breast cancer currently does not benefit from any targeted treatment and the only validated systemic therapy is chemotherapy as well as surgery and standard radiotherapy techniques.

Despite the use of recent treatment regimens, the prognosis remains poor. It is associated with a higher risk of early recurrence, metastasis and death, especially in the first 5 years of follow-up [3].

Through the analysis of a series of 52 cases of TNBC collected in the obstetric gynecology department of the MHIMV over a period of 6 years, ranging from January 2010 to December 2015 with a follow-up of at least 2 years and a review of the literature we will focus on the epidemiological, clinical, anatomopathological, biological, therapeutic and prognostic characteristics of this histo-prognostic subgroup.

Method:-

Study design and Setting: this is a retrospective study directed at the obstetric gynecology department of the MED V military hospital and involving 323 patients, admitted for the treatment of breast cancer during a period of 6 years from January 2010 to December 2015 inclusive.

The aim of our study is to analyze the various epidemiological, clinical, paraclinical, anatomo-pathological, therapeutic and prognostic data to draw conclusions in relation to triple negative breast cancer.

After consulting all the files of patients hospitalized for mammary pathologies within the department:

Inclusion criteria:

- Patients with histologically confirmed breast cancer during the study period.
- Negative hormone receptor: RE -; RP -
- No HER2 expression or amplification

Exclusion criteria:

- Patients who have not done a complete histological analysis,
- Those which were not cases of cancer.
- The male sex.
- Clinical files that cannot be used.
- Patients lost to follow-up
- Patients treated outside of HMIMV

Data were collected on detailed operating sheets for each patient.

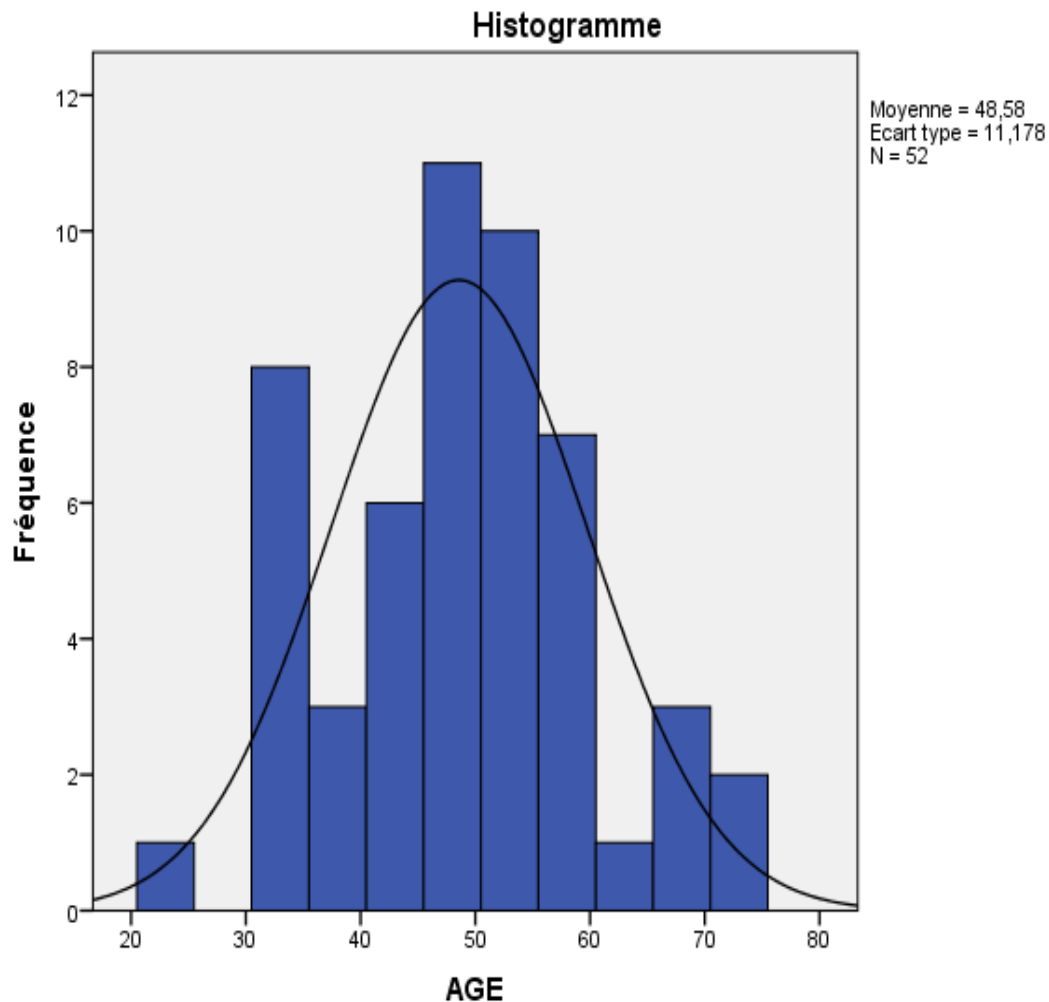
Text and tables were entered using Word XP software and graphics were entered using Excel XP software.

Statistical analysis of data was done using SPSS version 24 software.

Results:-

During a 6-year period from 2010 to 2015 inclusive, the records of 323 women with breast cancer were usable.

Among the patients, 52 women had TNBC with frequency of 16.09% of the total number of breast cancer. The average age of our patients was 48.58 years with extreme ages of 23 to 74 years. The 45 to 50 age group was the most affected.

Figure N ° 1:- Distribution curve of the population as a function of age.

A family history of breast cancer has been reported in 7 cases, or 13.5% of our patients. Knowing that we cannot say that these were the familial forms of breast cancer because no research has been done in our region regarding the mutation of the BRCA1 and BRCA2 genes.

The age of the first menstruation in our patients varied from 10 to 16 years with an average of 12.9 +/- 1.59 years. And the average age of the 1st pregnancy was specified in only 12 women, it was 22. years with extremes of 16 and 34 years.

The parity of our patients varied between 0 to 6 children and the majority are multiparous: 89.6% of cases. The use of oral contraception was noted in 22 patients. Among the 52 patients, 51.9% were postmenopausal

NB: The parameters: History of mastopathy, Body mass index (BMI), Breastfeeding concept, Mediastinal irradiation and toxic habits have not been studied.

Clinically, the median time to diagnosis was 3 [1.3] months, while the majority was diagnosed within one month, i.e. 26.2%

The discovery of a breast nodule was the most frequent reason for consultation in this series with 43 cases, i.e. 82.7%, The right breast was the most affected with a frequency of 52%, and there is a clear predominance of breast nodules. upper-outer quadrant with a percentage of 51.9%

The lymph node clinical study demonstrated the absence of lymph node involvement in 80.8% of patients. One case of supraclavicular lymphadenopathy was associated with axillary lymphadenopathy.

Paraclinically, Mammography was performed in all patients with a median size of 28 [15.28] mm. Mammographic abnormalities were classified according to the ACR (American college of radiology) classification. These anomalies were classified ACR4 in 75% of cases.

Histological confirmation prior to surgery was performed by microbiopsy: in 51.9% of cases and by extemporaneous examination for the rest. The CA15-3 assay was performed in all patients, it was elevated in one patient.

For the extension workup Chest x-ray was performed in 49 cases, or 94.2%, and did not show any abnormalities. Also, abdominal ultrasound was performed in 49 cases or 94.2%, and it did not show liver metastases.

Thoraco-abdominal CT was performed in 5 patients, ie 9.6%. She showed 2 liver and lung metastases. For bone scintigraphy was performed in all patients, it showed bone metastasis.

At the end of this assessment, two metastatic locations of breast cancer were detected, one case with pulmonary and bone metastases and another case with hepatic metastases.

TNM Classification:

At the end of this clinical and paraclinical assessment, all the patients were classified according to the 2010 AJCC TNM classification.

Table N ° 1:- Distribution according to the TNM classification.

Stage	number	Percentage
I	12	23,1
IIA	28	53,8
IIB	6	11 ,5
IIIA	1	1,9
IIIB	1	1,9
IIIC	1	1,9
IV	2	3,8

In our series, all the patients underwent surgery on the breast and axillary ADP: Modified radical surgery of the PATEY type was the most frequently used operation, it was performed in 57.7% of cases, so that conservative surgery such as lumpectomy with axillary lymph node dissection was performed in 42.3% of cases

In our study, the most frequent histological type is CCI in 68.3% cases, i.e. followed by metaplastic carcinoma in 11.5% cases then Infiltrating Medullary Carcinoma in 5.8%, CLI cases in 1 case, squamous cell carcinoma in 1 case , et al in 5 cases. With a median tumor size of 30mm with extremes of 6 and 210mm. 57% of patients had a tumor size between 2 and 5 cm.

The breast cancers detected in our series were graded according to the histopronostic grading of Scarff-Bloom-Richardson (SBR). The SBR III grade was the most predominant in our study (56.8%). Vascular emboli were positive in 40.4% of cases. Lymph node involvement was found in 28 patients, or 54%. This invasion affected 4 or more lymph nodes in 11 patients, while in 17 cases it was less than 4 lymph nodes All the excisional boundaries were healthy The intracanal component associated with the invasive carcinoma was noted in 9 patients. Proliferation index Ki 67 was sought by immunohistochemical technique in 4 patients.

At the end of the pathological study, the pTNM classification could be established. Thus, 50 patients had tumors classified M0 and 2 patients M2 (one case of lung and bone metastases and one case of hepatic metastasis)

Table N ° 2:- Distribution according to the pTNM classification.

Stage	Frequency	Percent
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1	4	7,7
2A	19	36,5
2B	10	19,2
3A	11	21,2
3B	2	3,8
3C	2	3,8
4	2	3,8

In our series, among the 52 patients who underwent oncological surgery, 52 received external radiotherapy by linear accelerator for curative purposes. The times between surgery and radiotherapy varied between 1 month and 12 months with an average of 5.3 ± 1.9 months. The target volumes differed from one case to another and were represented by tumor bed (breast or chest wall) 44.2% associated or not with one or more lymph node areas: the axillary area, the supraclavicular fossa and the internal mammary chain 55.8%. A boost on the tumor bed was administered to 18 patients with a dose of 16 Gy. A base dose of 50 Grays was delivered over 35 days ± 2 , 31. Radiotherapy complications was noted in 17 patients, ie 28.8% of cases: grade 1 radiodermatitis in 9 patients, grade 2 radiodermatitis in 5 patients, grade 3 radiodermatitis in 2 patients and one case of dysphagia.

Of all the patients, 48 received chemotherapy. Thus, this chemotherapy was indicated as an adjuvant in 45 patients, or 86.5% of cases, while 5.8% received it as a neoadjuvant. The time between surgery and adjuvant chemotherapy varied between 1 month and 6 months with an average of 2.3 months. Patients received different chemotherapy regimens using Anthracyclines, Taxanes, or both. The number of cures varied between 6 and 8 in the case of adjuvant or neoadjuvant chemotherapy. (FEC + TXT in 77.1%)

In our series, the patients were followed up until January 2018. The average follow-up was 36.49 ± 20.7 months. Monitoring was provided every 3 to 6 months during the first 3 years which followed at the end of treatment, then every 6 months for the next 2 years and once / year throughout the patient's life.

In our series, 2 cases of locoregional relapse in all patients and 9 cases of metastatic relapse in 17.3% of cases.

Table 3:- Distribution of patients by type of relapse.

Site of metastasis	Number	Percent (%)
Lung	3	5,7
Liver	1	1,9
Bone	2	3,8
Brain	1	1,9
Lung + bone	2	3,8

Discussion:-

Breast cancer is the most common cancer in women worldwide. It represents 1.7 million new cases per year and 522,000 deaths per year. "Triple negative" breast cancer represents 10 to 17% of breast cancers [4]. In our study the frequency of TNBC was 16.09% of the overall breast cancer count.

Age is one of the biggest risk factors for breast cancer. In American studies, TNBC are more common in African Americans, especially before menopause [5]. In our series, the mean age was 48.5 ± 11.1 years. O Al jarroudi found an average age of 46.5 years with extremes ranging from 26 to 87 years [6]

Menstruation before the age of 12 increases the risk of breast cancer [7], this being explained by more prolonged exposure to estrogen. In our series, the majority of our patients (36.7%) had had their first period at 12 years old, of which 50% had it at an age of more than 12 years, whereas in advanced age at menopause (after 55 years) Often also emerged as a risk factor for developing breast cancer. In our study, 51.9% of patients were postmenopausal.

The role of oral contraception in the onset of breast cancer appears to be more important in young women than in elderly women, where no increased risk has been reported. In our series, 66% of patients used oral contraceptives for an average duration of 8.16 years.

The risk of CS is high when the first pregnancy is late and it seems to decrease if this first is carried out before 30 years old [8]. In our study a single patient had her first pregnancy after 30 years, with an average of 22 years, and the risk associated with multiparity appears to be low since 10.4% of cases were nulliparous. Prolonged breastfeeding is associated with a reduced risk of invasive cancer.

Genetic factors are involved in 5 to 10% of breast cancers. They are mainly responsible for cancers that occur before the age of 40. The genes most involved are the BRCA1 and BRCA 2 genes.

O Al jarroudi reports a history of CS in 20.7% of cases[6], while Lahmadi reports 14 cases (15.7%) of patients with a family history of breast cancer [9]. For our study, a family history of breast cancer was reported in 7 cases, ie 13.5% of our patients. Unfortunately, the search for the BRCA1 / 2 mutation was not performed.

The time to diagnosis was over 3 months in 45% of cases, and over 1 year in 12% of cases for BLACK HOUSE [10]. In our series, the mean time between the appearance of the first clinical signs and the diagnosis was 3 months. This deadline is still late in developing countries due to a lack of resources and access to health facilities

TNBC are more often diagnosed at the 80% clinically detectable tumor stage. Our results are in line with those of the literature because consultation for breast nodules was 82.7 of the reasons: 52% of patients had a tumor of the left breast with a predominance in the upper outer quadrant: 51.9%

At the end of the clinical assessment, the tumors were classified according to the TNM classification.

Table N ° 4:- Comparison of TNM stages.

Stage Percentage%	O Al jarroudi et al [6].	Notre série
StageI	3.4	23,1
StageIIA	33.6	53,8
StageIIB	19.0	11 ,5
StageIIIA	12.1	1,9
StageIIIB	10.4	1,9
StageIIIC	6.0	1,9
StageIV	15.5	3,8

The role of mammography is essential in the conservative or radical surgical approach by assessing the extent of tumor images or microcalcifications. The codification of the radiological risk of carcinoma is assessed by the BI-RADS classification of the ACR (American College of Radiology) .

According to M Boissierie-Lacroix et al [11], the BI-RADS classification used was ACR 2 in 15.1% of cases, ACR 3 in 1.4% (one case), ACR 4 in 56.2% and ACR 5 in 27.4%. In our series, the tumors were classified as ACR4 in (75%) of cases and ACR5 in 25% of cases.

When the breasts are dense, especially in young women, the use of high-resolution ultrasound as an adjunct to mammography is of great help. In our series, ultrasound was used in addition to mammography as a means of diagnosis, but breast MRI was not used.

If most of the time, the TNBC are of the infiltrating ductal type without further specification, it is important to note that some TNBC correspond to special histological types, in our series, the histological type was dominated by the infiltrating ductal carcinoma found in 67, 3% of cases, followed by metaplastic carcinoma in 11.5% of cases.

Table N ° 05:- Comparison of histological types.

	LAHMADI[9]	O Al jarroudi et al	Notre serie
IDC	91,01%	75.9 %	67,3 %,
CM	---	6.9%	11,5 %
ILC	1,12%	6%	1,9 %
OTHER	7,89%	11.2%	19,3 %

More than half of breast cancers reach the lymph nodes at the time of diagnosis[12]; The prognosis is also linked to the number of lymph nodes invaded and more particularly the number of lymph nodes affected and the ratio of the number of lymph nodes reached to that of lymph nodes removed[12] .

O Al jarroudi found lymph node involvement in 56.2% of cases, while for Lahmadi[9] lymph node involvement was observed in 62.3% of cases, and in 39% of cases in Derkaoui et al [13]. In our series, lymph node invasion was found in 54% of cases, with less than 4 nodes in 17 cases, 4 or more nodes in 11 cases.

Regarding the SBR grade, it was in the majority of cases an SBR III, ie 56.8% of cases, which matches the results of the LAHMADI and AL literature 58.42% [9].

The most sensitive method for detecting bone metastases is bone scintigraphy, for our study, OS was performed in all patients; and showed metastasis in only one case.

Ultrasound is the first-line examination to check for liver metastases. It is performed systematically in the assessment of extension of breast cancer, and it was normal in the 49 patients, the same for the chest x-ray, whereas the TAP CT showed only metastases. in 2 cases: one hepatic and the other pulmonary and bonely.

The treatment of breast cancer is adapted to each case and decided within the framework of a multidisciplinary consultation between anatomical pathologist, surgeon, radiologist, radiotherapist and medical oncologist. Surgery remains the basic treatment, associated with a locoregional adjuvant treatment by radiotherapy, and a systemic treatment by chemotherapy, in order to obtain the greatest probability of cure or the longest survival without relapse, with aesthetic functional damage, quality of life, and at the lowest possible financial cost.

In our series, the indications for conservative treatment were mainly related to the following factors:

- tumor size in relation to the size of the breast,
- obtaining a carcinological result
- obtaining a satisfactory aesthetic result,
- the possibility of good monitoring in the medium and long term.

Conservative treatment was performed in 42.3% of patients. Radical mastectomy modified according to MADDEN includes mastectomy with axillary dissection. It is the most common procedure, especially for large tumors, mainly in our context where patients consult late. Especially in the case of multicentric tumors; and in cases of inflammatory carcinoma previously treated with chemotherapy.

All our patients underwent a classic lymph node dissection, with a sample of at least 10 lymph nodes, no sentinel lymph node case was performed for lack of technical means. (we started using the technique from 2017) With an invasion of 4 or more nodes in 11 patients, while in 17 cases this invasion was less than 4 nodes.

The objective of radiotherapy is to reduce the rate of locoregional relapse and to increase survival with a start-up time that should not exceed 8 weeks after surgery, in the case of adjuvant chemotherapy, the maximum time between surgery and radiotherapy is 20-24 weeks. 3 weeks after chemotherapy, which was not observed in all patients.

Despite a greater chemosensitivity of TNBC compared to luminal tumors, the rates of recurrence-free and overall survival are significantly lower.

The prognosis in patients less than 35 years old seems to be less favorable than that of older patients [14] In our series, only one 32-year-old woman presented with a cerebral metastasis during the course. It is well known that the prognosis of localized forms is better compared to that of advanced forms. Tumor size, the main parameter of the TNM classification, has a significance that is all the more pejorative as it is larger.

For our study, no patient with stage I presented metastases during the course, whereas we noted 3 metastases with stage II, 5 with stage III, 1 with stage IV.

Ductal, lobular and medullary carcinomas have the same prognosis, except for tubular or colloid carcinomas which have a slightly more favorable prognosis [15]. In our study, we found that CCI is the most metastatic with 6 cases.

The high grade SBR III represents a factor of poor prognosis; it correlates with a high risk of metastatic spread to sites of poor prognosis, such as the liver and lungs. In our study, 5 cases of metastasis in patients with grade SBR III.

Histological lymph node invasion is the best known and most important prognostic factor [16]. Most authors admit a threshold above 3 N + allowing us to classify patients with a poor prognosis [16]. In our series, 4 patients with systemic recurrence have lymph node invasion with 4 N + or more.

The presence of vascular emboli is a factor of poor prognosis in breast cancer. In our study 6 patients with recurrence had vascular emboli.

For immediate postoperative complications, Lymphorrhea is usual, and is only a complication when it is prolonged [17]. Nerve bundles may be injured during the operation, with tingling or numbness in the pectoral area, armpit, arm or shoulder. These disorders usually resolve after a few weeks, but localized insensitivity may be permanent [17]. In our series, 2 cases of wound infection were noted, or 3.8%.

Late in the day, lymphedema is more frequent in the event of radiosurgery on the hollow. Patients should be informed of any trauma (blood test, blood pressure, injury, sting) to the arm or hand on the treated side.

After a few sessions of radiotherapy, irritation of the skin (radiodermatitis) and mucous membranes (mucositis) appears [18]. KAHLAIN [18] estimated the rate of dermatitis induced by RTH at 6% and the rate of mucositis at 8%. In our study we noted: grade 1 radiodermatitis in 9 patients, grade 2 radiodermatitis in 5 patients, grade 3 radiodermatitis in 2 patients.

After chemotherapy the most frequent immediate consequences are digestive disorders: nausea and vomiting. After a few weeks, we have alopecia in 8% of cases. Given the great sensitivity of the bone marrow to chemotherapy, anemia is often found as well as an increased risk of infection due to neutropenia or even drug-induced aplasia. In our series, were reported: four cases of anemia, three cases of neutropenia, two cases of aplastic anemia and four cases of alopecia.

Locoregional surveillance is more useful because it is likely to improve survival, it is essentially based on clinical examination and mammography. Carrying out a clinical examination 3 to 4 times a year in the first year and every six months thereafter, the first mammogram to be performed six months after the end of treatment, it is then repeated every year, it must also concern the contralateral breast given the frequency of contralateral cancers in young women. The general purpose is to look for possible symptoms of metastases, more than half of metastases are discovered by clinical examination and questioning.

For BOUKERCHE [19] with a median follow-up of 61 months (14 to 116 months), 26 relapses (63%), 3 locoregional relapses (12%), 17 metastatic relapses (65%), 4 contralateral attacks were observed (15%), locoregional recurrence with metastatic relapse (6%) and contralateral involvement with metastatic relapse (4%). The 5-year survival rates without locoregional recurrence and without relapse were 88%, 45% and 73%, respectively. While in our series, 2 cases of locoregional relapse, 9 cases of metastatic relapse were recorded, i.e. 17.3% of the cases, no case of contralateral involvement.

Conclusion:-

TN tumors are defined in immunohistochemistry by the absence of expression of estrogen receptors, progesterone and HER2 receptors, given the unresponsiveness of TNBC to hormone therapy, chemotherapy remains the only systemic treatment for these tumors.

Through the analysis of the results of our study and data from the literature, we noted that the majority of TN tumors are characterized by a more unfavorable prognosis with a greater frequency of visceral metastases and a maximum risk of recurrence in the first two years after diagnosis.

The great heterogeneity of TN tumors and the absence of specific biomarkers predictive of efficacy for each of the therapies developed largely explain the impasse in which we find ourselves.

It now appears necessary to adopt more aggressive and above all more adequate therapeutic strategies and to develop predictive tools capable of guiding us in the choice of treatments: that this choice be oriented towards the chemotherapy molecule most suited to the treatment, tumor biology or towards new targeted therapies.

Such an approach cannot be carried out without an optimal biological characterization, making it possible to understand the complexity of this subgroup of tumors, and requires international collaboration in clinical trials involving pathologists, oncologists and fundamental researchers.

Competing interests:

The authors declare that they have no competing interests.

Authors contributions:

MB performed research; analyzed data statistically; AB, collected the clinical data; MB, SB, YB, HM, MABH and JK, designed and coordinated research and drafted the manuscript. All authors read and approved the final manuscript.

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