

Triple Negative Breast Cancer: Experience of the Obstetrics and Gynecology Department 2 Over A Period of 3 Years about 105 Cases at the Hassan II University Hospital in Fes

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Abstract

Original Research Article

Introduction: Breast cancer is the second leading cause of death worldwide and the leading cancer in women. It is both the most common and the leading cause of death in women from cancer, thus posing a real public health problem. It presents tumor heterogeneity on the histological and molecular levels, explaining the diversity of presentations, responses to treatments, and prognosis. Triple-negative breast cancer is defined by the absence of expression of hormone receptors: estrogen receptors (ER), progesterone receptors (PR) and by the absence of overexpression or amplification of genes encoding HER2 receptors (Human epidermal growth factor receptor 2) and representing only a minority of breast cancers (10-20%). The therapeutic choices for this type of breast cancer are limited because patients do not benefit from hormonal therapy or targeted therapies, which poses a real problem in therapeutic management. Our objective is to describe the epidemiological, clinical, anatomopathological characteristics, as well as the evolutionary profile after adequate management of triple-negative breast cancer through the analysis of a series of cases of triple-negative breast cancer collected at the gynecology-obstetrics department 2 at the Hassan II University Hospital in Fez. **Method:** This is a retrospective study of a series of triple negative breast cancer cases collected in the gynecology-obstetrics department II at the Hassan II University Hospital in Fez during the period between January 2020 and December 2023. Inclusion criteria: Histologically confirmed triple negative infiltrating breast cancer treated in the gynecology-obstetrics department 2 of the Hassan II University Hospital in Fez. IHC = ER = 0% RP = 0% HER2 negative Exclusion criteria: male sex and presence of distant metastases. **Results:** On the epidemio-clinical level: a peak in frequency between 31 and 42 years old, and 45.7% of patients still in genital activity. On the anatomic-pathological level: Infiltrating ductal carcinoma is the predominant type representing 100% of cases with an average tumor size of 4.4 cm. Histoprognostic grades II and III each represent 38% and 56% of cases. On the therapeutic level: 14% of patients benefited from conservative treatment and 85% underwent radical Patey-type (radical mastectomy with lymphadenectomy) surgery and finally 1% of patients did not undergo any surgical treatment. Adjuvant systemic chemotherapy was administered in 61.9% of cases and 73% benefited from neoadjuvant chemotherapy. On the evolutionary level: An unfavorable evolution was noted in 28% of cases, 19% developed systemic metastases with a predilection for the bone (40% of cases), lungs (32% of cases), brain (19%) and liver (13% of cases). **Conclusion:** Triple negative breast cancers (TNBC) represent a very heterogeneous subgroup of breast cancers in clinical, morphological, molecular and prognostic terms. The results of our study are consistent with the literature data regarding the epidemiological and clinicopathological characteristics of TNBC. Despite multiple efforts, there is still no established or clinically verified diagnostic test for the classification of TNBC and therefore a standardization of a clear therapeutic approach. This requires international collaboration involving pathologists, oncologists and basic researchers in order to validate these diagnostic tests based on molecular signatures and targeted therapies.

Keywords: Triple-negative breast cancer (TNBC), Epidemiology, Histopathology, Treatment, Prognosis.

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INTRODUCTION

Breast cancer is a real public health problem and represents the most common cancer in women worldwide and the leading cause of female cancer mortality [1]. In recent years, the classification and understanding of breast carcinogenesis have progressed

thanks to analyses of the transcriptomic expression profiles of invasive breast carcinomas, thus allowing effective adaptation of therapeutic approaches. In 2022, breast cancer caused 670,000 deaths worldwide according to the WHO. About half of breast cancers occur in women who have no specific risk factors other

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than sex and age. In 157 out of 185 countries, breast cancer was the leading cause of cancer in women in 2022. Breast cancer is present in all countries of the world. Men represent approximately 0.5% to 1% of people affected by breast cancer. In Morocco, breast cancer is the leading location of cancer (22.6% of breast cancer cases were recorded out of all cancers, both sexes combined, during the period from 2013 to 2017). In women, breast cancer represents 26% - 30% of cancers [2]. Triple negative breast cancer (TNBC) is a heterogeneous subgroup of breast cancers. It is defined by the absence of expression of hormone receptors (OR and PR) and overexpression of Her2 by immunohistochemistry, thus limiting targeted therapeutic options. It is a heterogeneous group of tumors with different molecular and prognostic portraits. Therapeutic choices for this type of breast cancer are reduced because patients do not benefit from hormone therapy or targeted therapies, which poses a real problem of therapeutic management. The objective of this work is to describe the epidemiological, clinical, anatomopathological and biological characteristics as well as the evolutionary profile of triple negative breast cancer through the analysis of a series of TNBC cases collected within the gynecology-obstetrics department 2 at the Hassan II University Hospital in Fez.

MATERIAL AND METHODS

This is a retrospective study of a series of 105 cases of triple-negative breast cancer collected in the

gynecology-obstetrics department 2 at the Hassan II University Hospital in Fez during the period between January 2020 and January 2023, describing the epidemiological, clinical, anatomo-pathological characteristics, as well as the evolutionary profile of triple-negative breast cancer in order to bring out histoprosthetic factors and compare them with those already described in the literature: patients were included in the study: Diagnosed with histologically confirmed breast cancer; treated in the department and having negative hormone receptors: ER - and RP -; absence of immunohistochemical expression or HER2 amplification. The following were excluded from the study: male sex; Metastatic breast cancer; The A and B lights. The data for the various study parameters come from the patients' source files, either from the paper files filed in the department's archives or from the electronic files of the Hosix.net system. An Excel database was created and analyzed.

RESULTS

Between 2020 and 2023, the gynecology-obstetrics department of the Hassan II University Hospital in Fez had recorded a total of 1012 new cases of patients with breast cancer, an average of 250 cases per year. According to our inclusion and exclusion criteria, 105 cases of non-metastatic triple negative breast cancer were included in our study, an average of 35 cases per year.

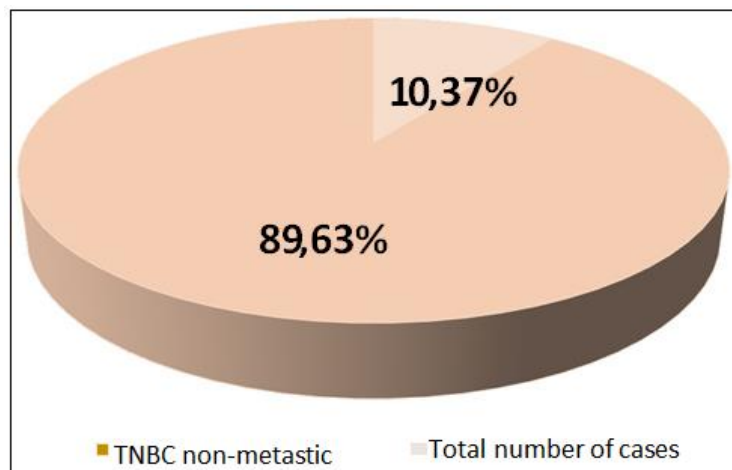


Figure 1: The frequency of non-metastatic triple negative breast cancer compared to all non-metastatic cases diagnosed

The average age of our patients was 48 years with extreme ages of 31 and 75 years. The most affected age group was between 31 and 42 years.

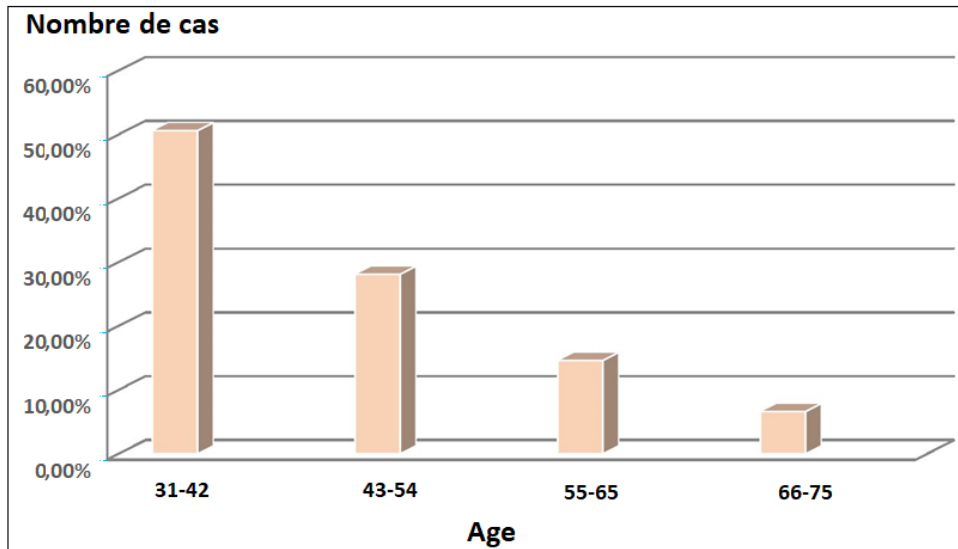


Figure 2:

The nodule was the revealing sign in 95 cases, or 90.5%, moreover, systematic screening by imaging did not allow the discovery of breast cancer in any case.

The average time of evolution is 06 months with extremes of 01 month and 04 years.

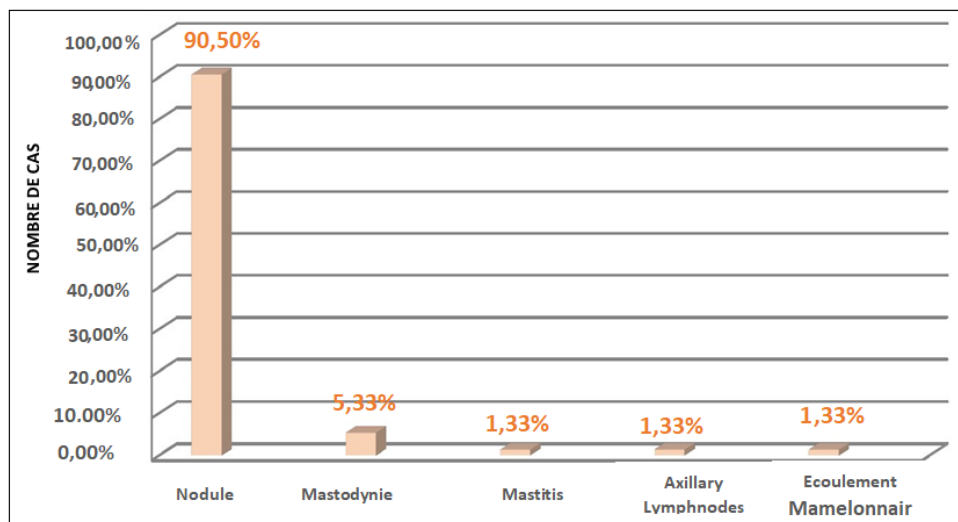


Figure 3: Percentage of clinical signs of TNBC discovery

The extension assessment is primarily clinical, bilateral mammography is the reference examination for breast cancers. This is associated with a bilateral breast ultrasound including examination of the axillary and supraclavicular areas given the high prevalence of asymptomatic metastases at diagnosis in patients with TNBC. It is recommended to perform a systematic assessment even in the absence of a clinical point of call. Indeed, ESO-ESMO international consensus guidelines (ABC2) recommends performing a thoraco-abdominopelvic CT scan and a bone scan (12). In our series, the remote extension assessment was performed in patients as follows: - A chest X-ray in 92 patients, i.e. a total of 87.6%; an abdominal ultrasound was performed in 86 patients or 81.9%; a thoraco-abdomino-pelvic CT scan in 100 patients or 95.2%; a bone scan in 74 patients or 70.4%.

Therapeutic management: 32 patients underwent primary surgery, i.e. a percentage of 30%. Surgery in 85% of cases consisted of a mastectomy using the Patey technique followed by axillary lymphadenectomy; conservative treatment was performed from the outset in 11.4% of patients (12 cases) and the Sentinel Node technique was performed in 2023 in 3 patients with non-metastatic triple-negative breast cancer, i.e. a total of 2.8%. Post-chemotherapy surgery: 72.3% or 76 patients underwent post-chemotherapy surgery. After neoadjuvant chemotherapy, 3.8% of patients (04 cases) did not respond, underwent no surgical treatment, and moved on to 2nd-line chemotherapy. In our study 61.9% (65 cases) received sequential adjuvant chemotherapy such as Anthracyclines followed by taxanes with a total of 6

courses versus 74.3% (78 cases) neoadjuvant chemotherapy.

The evolution of breast cancer in patients in our series

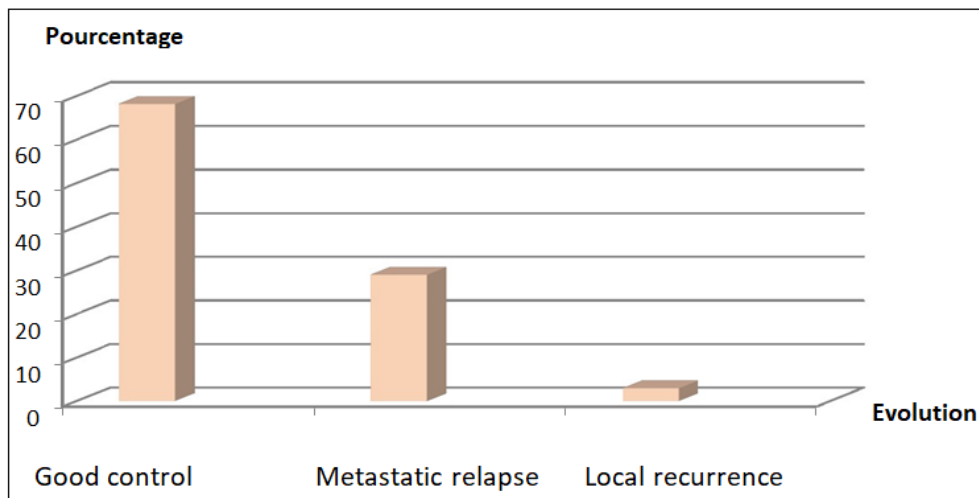


Figure 4: Evolution of triple negative breast cancer

In order to bring out the histo-prognostic factors of triple negative breast cancer, we studied the evolution of the latter according to age, hormonal status, tumor size, histological type, SBR grade, Ki67 proliferation index, lymph node invasion and the type of chemotherapy received. According to age, the evolution of the cancer was slightly more favorable for patients under 48 years old; according to hormonal status 77.4% of non-menopausal patients had good control versus 66.76% in menopausal patients; Tumor size was a criterion for evolution in our study. Tumors with a size ≤ 2 cm had good control. Infiltrating Ductal Carcinoma represented 100% of cases; SBR grade III is marked by an unfavorable evolution in 62.2% of cases versus 31.4% of grade II and 6.4% of grade I; 77.4% of cases with low Ki with an unfavorable evolution in 70.6% with a high Ki; The evolution was unfavorable in 66% of cases in the presence of lymph node involvement, on the other hand good control was objectified in 94% of patients who did not have lymph node invasion; our patients did not present vascular emboli; 79.5% of patients who received adjuvant chemotherapy were favorable on the other hand an unfavorable evolution was found in 56.2% of patients who received neoadjuvant chemotherapy.

DISCUSSION

Triple negative breast cancer accounts for 10–20% of all breast cancers [3, 5]. There are significant differences in the prevalence of TNBC in different countries around the world. Bauer KR et al reported that in California, USA, 51,007 new cases of breast cancer were diagnosed between 1999 and 2003, of which 6,370 (12.4%) were TNBC [9]. The College of American Pathologists states that an expression of 1% of HR by IHC classifies tumors as HR positive [4]. Mouh *et al.*, reported that 17% (85/500) of breast cancers registered at the National Institute of Oncology in Rabat (2009–

2014) were TNBC [8]. In our series, the prevalence of TNBC was 15.35% (105/1012).

Age is one of the most important risk factors for breast cancer. The incidence of breast cancer shows an age-dependent curve: as age increases, the risk increases. However, triple-negative breast cancer is common in younger women with premenopausal hormonal status. Bauer *et al.*, [5] confirmed that women younger than 40 years are more likely to develop triple-negative breast cancer. The median age at diagnosis of TNBC in the study by Rais *et al.*, was 46 years [6]. Furthermore, the mean age at diagnosis of TNBC in the study by Mouh *et al.*, was 47 years, with 54.7% of cases being younger than 50 years. Premenopausal women accounted for 48.6% of cases, while postmenopausal women accounted for 51.4% [8]. In our study, the mean age at diagnosis was 49 years, the most affected age range was 31–42 years, and 42.7% of patients were premenopausal, and postmenopausal patients represented 57.3% of our study sample.

Several studies suggest that parity is linked to an increase in the risk of triple negative breast cancer, paradoxically to luminal A tumors, for which multiparity reduces the risk of occurrence [10]. Indeed, a case-control study including 2616 women (1140 patients with breast cancer including 78 with a triple negative tumor and 1476 controls) was carried out by Phipps *et al.*, in 2008 and demonstrated that nulliparity compared to multiparity, led to a significant decrease in the risk of TNBC, while nulliparity increased the risk of HR positive tumors. In multiparous women, the increase in the number of pregnancies led to an increase in the risk of TNBC. Indeed, the authors demonstrated that women with 3 or more children are more likely to have a triple negative tumor compared to those with a single child [10]. On the other hand, this will reduce the risk of HR-positive tumors. Similarly, Millikan *et al.*, in their case-

control study carried out in the United States in 2008 and including 1424 patients with breast cancer and 2022 controls, found that the risk of TNBC increased significantly with the increase in the number of children, however this association was not observed for hormone-dependent tumors [11]. The retrospective study by MOUH *et al.*, including 905 patients with breast cancer, 85 of whom had TNBC, showed that at the time of diagnosis 80% of TNBC patients were multiparous women and only 20% of them were nulliparous [8]. However, other studies have not found a significant link between parity and triple negative tumors such as that of Dolle *et al.*, [12]. The results of our study are consistent with those in the literature, in fact, 67.2% of patients were multiparous, while 22.8% of patients were pauciparous and only 10% were nulliparous. Certainly several studies have shown that a late first pregnancy increases the risk of hormone-dependent breast cancers, but it is not associated with the risk of TNBC occurrence. In our series, we were not able to study this risk factor, given its absence in the majority of patients' medical records.

The discovery of a breast nodule during self-palpation remains the most common reason for consultation. However, in younger mutated women, it is essentially a cancer discovered during screening that should not be missed and should be characterized [16]. The study carried out by Ndounga *et al*, which included 34 patients with triple negative breast cancer, showed that the main reason for consultation was the discovery of a breast nodule in 79.4% of the sample studied, while bloody nipple discharge was found in 11.8% of cases, while 8.8% of patients reported the presence of mastodynia [13]. Similarly, the team of Benhmouda *et al* in Tunisia stated that self-palpation of a breast nodule was the first functional sign reported by almost all patients (55/56), it was found in 98.21% of TNBC patients, while only one patient presented for axillary adenopathy (1.97%) [8]. The results of our study are consistent with those of the literature, in fact self-palpation of a breast nodule was the first reason for consultation found in our series. It was present in 94.6% of patients.

It involves inspection and palpation of the breasts in a standing and then lying position and allows the characteristics of the breast tumor to be specified. It may be strictly normal when the tumor is small and/or the breast volume is large. Inspection: should look for breast asymmetry, an increase in breast volume, the existence or absence of cutaneous signs, retraction of the skin or the areola-nipple plate (examination carried out with the arms hanging then raised), the presence or absence of Paget's disease. Palpation: is carried out with the hands flat by gentle pressure using rotating movements rolling the gland on the costal grill, quadrant by quadrant (approximately 60% of cancers are located in the upper-outer quadrant). It must assess: the location, size, consistency and sensitivity, the clarity of the

contours, the mobility in relation to the skin by pinching the skin opposite the tumor in search of adhesion or even invasion) and at the deep level by the Tillaux maneuver (contrasted adduction of the arm allowing contraction of the pectoralis major muscle). Nipple pressure in search of discharge is necessary and can be considered as: Not suspicious if it is old and intermittent, provoked, bilateral, multi-ductal, white in color (lacteal, creamy, brown, or greenish appearance) Suspicious if it is of recent spontaneous appearance, unilateral, single duct, light translucent color, yellow (serous), red (bloody), or black. Breast cancer is generally unilateral and a little more often on the left side. Bilateral involvement is rare and is found in only 1%-2% of cases [17-19]. The location of triple negative breast cancer does not differ from other subtypes of breast cancer. Indeed, in the series of Mouh *et al.*, left-sided involvement was predominant with a percentage of 56% of cases studied, while the right side was affected in 44% of cases [8]. The study of Sanges *et al.*, in Italy demonstrated a predominance of left-sided involvement in 50.7% of cases compared to 48.6% of cases on the right, and bilateral location was found in 0.7% of cases [20]. Similarly, the left side was the most affected in our series. Indeed, the left location was present in 56% of cases, while in 44% of cases the lesions were located on the right, and in no case was the lesion bilateral. The usual location of breast cancers is the upper-outer quadrant in 38.5% of cases, followed by the central region, the other quadrants are less often affected. This topography is explained by the quantity of glandular tissue always more present in the central and upper-outer part [19]. In our series, all quadrants were involved with a predominance in the upper quadrant with a rate of 81.5% against 18.5% in the lower quadrant.

The upper outer quadrant was affected in 65.5% of cases. Triple negative breast cancer manifests as large palpable tumors of 30-40mm [16]. In our series, tumor size was specified in all patients, with a mean size of 4.4 cm (minimum size found was 1 cm and maximum size found was 15 cm). Our result is consistent with that published by Rais *et al*, the majority of their patients presented with tumors larger than 30mm [7]. The study by Vona Davis *et al.*, showed that triple negative tumors were larger than those in other receptor categories. The mean tumor size in the triple negative group was 3.01 ± 0.17 cm versus 2.27 ± 0.08 cm for the non-triple negative group ($P < 0.001$) [6]. Paradoxically, the study by Mouh *et al* did not find a significant association between tumor size and molecular subtypes of breast cancer, including TNBC and non-TNBC [8]. Dent *et al.*, concluded that there was no clinical correlation between TNBC and tumor size. Examination of lymph node areas is systematic in the presence of any breast symptomatology as well as in the context of clinical screening examination. It must be bilateral and comparative; it evaluates the axillary and supraclavicular areas; the internal mammary areas are not accessible to clinical examination. Signs of invasion are assessed on the volume, consistency, and mobility of the adenopathies.

The clinical examination must be finalized by a general examination that will target the main metastatic sites: lungs, abdomen (hepatomegaly, ascites), pelvis (ovaries) and skeleton. As well as a dated diagram including the results of this examination always remains desirable.

Mammography: the screening test par excellence, and the first diagnostic test in breast imaging, preferably performed in the first part of the cycle. A classic mammogram includes bilateral frontal and external oblique views. Sometimes, additional incidences will be performed: mediolateral, localized and enlarged localized views. The quality criteria are important, especially for the oblique incidence: visualization of the submammary fold and the pectoralis major muscle. Interpretation requires a comparison of the two breasts by opposing the images according to the same incidences [21]. Triple negative breast cancer presents in the majority of cases as a mass: round, oval or lobulated in 60 to 75% of cases, with an often circumscribed edge (24 to 43%) or indistinct (31.1%) [22-24]. This difference in description of the edges may be due to inter-observer variability.

Breast ultrasound plays an important role in the screening and diagnosis of breast cancer, its main indications are: the presence of a clinical abnormality, the detection of a mammographic abnormality, type 3 and 4 breast density and some type 2 density breasts with retro-areolar glandular grouping [21]. Axillary ultrasound is performed in cases of clinically suspicious adenopathy (INCa 2012 recommendations). This exploration is now part of the systematic preoperative assessment of breast cancer. It allows for the taking of ultrasound-guided cytological and anatomopathological samples. This examination is therefore of therapeutic interest in the event of a positive lymph node puncture. It makes it possible to avoid the practice of the sentinel lymph node in order to propose an axillary curettage from the outset. In the same way as in mammography, we find the predominance of the round-oval-lobulated shape: 65—70% of cases [16, 25]. The uncircumscribed or microlobulated contour appears evocative [13]. The tumor-parenchyma interface is more often abrupt in TN tumors [22] (84% of the series of Shin *et al.*, [26]). Rapid growth explains the lower frequency of the peripheral echogenic halo.

Breast MRI: This is a second-line examination that is very sensitive but not very specific, particularly in young women. MRI is only performed in certain indications: Additional assessment when standard imaging (mammography and/or ultrasound) does not allow a definitive conclusion on the absence of malignancy. Monitoring of patients undergoing neoadjuvant chemotherapy. Metastatic adenopathy of breast cancer and normal senological assessment. Search for local recurrence after conservative treatment (helps with diagnosis with a focus of cysto-steatonecrosis). Suspicion (clinical and/or ultrasound) of prosthetic

rupture in the event of breast reconstruction with prostheses. In our series, no patient benefited from a breast MRI.

Biopsy: Percutaneous biopsy techniques currently occupy a primordial place in the diagnostic approach in senology. They often constitute an excellent alternative to surgical biopsy [15]. In our series, the histological diagnosis of TNBC confirmation was documented in 100% of cases on percutaneous biopsies.

Anatomopathological study: Triple negative cancer is associated with a large tumor at the time of diagnosis, since only one third of the tumors were < 2 cm compared to 2/3 for other types of cancer. During our study, the results were in agreement with the literature since the tumor size was greater than 2 cm in 99 patients compared to only less than 2 cm in 6 patients. Infiltrating ductal carcinoma is the most predominant histological type followed by infiltrating lobular carcinoma (ILC). Other histological types were found at lower rates as demonstrated in the study by Lin *et al* (13) where infiltrating ductal carcinoma represented the most frequent histological type (93.2%). Similarly, the study by Rais *et al.*, showed that 86% of triple negative tumors were histologically classified as infiltrating ductal carcinoma. As well as medullary carcinoma was present in 9% of TNBC patients, other histological types represented 6% of the sample studied [6]. In our series, grade II or III in 94.4% of cases and the presence of tumor emboli was not found in any patient.

Surgical management of TNBC breast tumors should be comparable to that of other subtypes and follow the same rules of oncological surgery and involves surgical excision of the tumor mass by mastectomy or by breast-conserving surgery followed by radiotherapy.

Several studies have compared the therapeutic outcomes after surgical treatment in patients with TNBC versus other types of breast cancer. In a study by Parker *et al* the type of surgical therapy had an impact on the outcome of patients with TNBC breast cancer. The 5-year disease-free survival rates for breast-conserving surgery and mastectomy were 68% and 57%, respectively ($p = 0.14$). The 5-year overall survival was better for the breast-conserving surgery than for the mastectomy group (89% vs. 69%; $p = 0.018$). As well as no significant difference was found in local control rates [14]. In contrast, other studies have shown that the rate of locoregional recurrence after breast-conserving surgery was higher in patients with the TNBC subtype. These studies highlight the current lack of prospective clinical trials to evaluate the effect of treatment choice on locoregional recurrence in patients with TNBC breast cancer [27, 28]. In our series, unilateral mastectomy was performed in 85% of cases while 14.2% of our patients underwent lumpectomy with or without sentinel node technique. Similarly, the study by Mouh *et al.*, showed

that 70.6% of TNBC patients underwent mastectomy, and 29.4% of patients underwent lumpectomy [8].

RTH is an essential component of conservative breast cancer treatment and its importance for optimal long-term outcome has been established for breast cancer patients. Guidelines for adjuvant radiotherapy in TNBC do not differ from those for other breast cancer subtypes. In a study by Dragun *et al.*, 69% of patients with triple-negative breast cancer received RTH after conservative breast cancer surgery, and it was found that the 3-year locoregional relapse-free survival for patients who received RTH was 79.6% compared with 57.9% for those who did not receive RTH ($p = 0.049$), although patients who received RTH had a higher stage [29]. In our series, 82.6% of our patients received radiotherapy after surgical treatment. Since there is no target, chemotherapy is currently the only approved systemic treatment that improves outcomes in TNBC. In our series, 58 patients out of 105 patients or 67.3% of cases received neoadjuvant treatment. We were unable to calculate the RCP rate given the enormous lack of this information in patient records.

Prognostic factors can be defined by their ability to identify tumors at high risk of local or distant relapse in the absence of any treatment: age, tumor size, lymph node involvement, lymphovascular infiltration, degree of differentiation according to Scarff Bloom and Richardson (grades I to III), molecular profile, in particular hormone sensitivity and HER2 status of the tumor [14]. In our study, and contrary to literature data, the evolution of the cancer was slightly more favorable for patients under 54 years of age compared to patients over 54 years of age.

TNBC is generally more aggressive, with a poorer prognosis than other types of breast cancer, and is responsible for 5% of all cancer-related deaths each year. The median overall survival (OS) of the disease is 10.2 months with current therapies with a 5-year survival rate of 65% for local tumors and 11% for metastatic forms [32].

CONCLUSION

The clinical pathological heterogeneity of this pathology and the limited treatment options make management a challenge. Triple negative breast cancer is a subtype of breast cancer, characterized by clinical, prognostic and therapeutic polymorphism. Genetic and molecular studies have clarified the different subgroups of this type of breast cancer. TNBC generally occurs in young women, often associated with the BRCA 1/2 mutation. It manifests in the majority of cases by a palpable tumor, interval tumor (between two mammograms). In the absence of a therapeutic target, cytotoxic chemotherapy still maintains its formal indication for this type of breast cancer. Neoadjuvant chemotherapy with early response assessment is now the preferred approach for patients with TNBC [30]. TNBC

is very aggressive, with a high number of early relapses and a very poor overall prognosis. Patients who experience relapses of metastatic disease typically do so within 5 years of surgery. Metastatic survival is shorter than that of other subtypes. Treatment options are few and responses lack durability. Given that current therapeutic modalities for TNBC are needed to improve the prognosis of these patients [31]. A better understanding of the carcinogenesis and tumor progression of TNBC, as well as the cause of phenotypic heterogeneity, may help improve planning and design new individualized treatments for this type of breast cancer [32].

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