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BREAST CANCER UNDER 40: A STUDY OF 31 CASES

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ABSTRACT

Introduction: In Morocco, breast cancer is the most common cancer among women, with a rate of 36%. The occurrence of this cancer at a young age is often associated with anatomoclinical characteristics of poor prognosis. **Methods:** This is a retrospective study of a series of 31 cases of breast cancer in young women under the age of 40 who were admitted for treatment at the Moulay Ismail Military Hospital in Meknes between January 2019 and September 2023. **Results:** Breast cancer in women under 40 years old accounted for 11% of the total number of breast cancer cases diagnosed during this period, with an average age of 32 years and a peak frequency in the 31-35 age group (42%). Pauciparity and nulliparity were predominant (55% / 26%). A family history of breast cancer was reported in 31% of cases. Oral contraceptive use was noted in 72% of the patients. Clinically, the average consultation delay was three months. The most frequent mode of discovery was self-palpation of a breast lump, found in 82% of cases. The left breast was affected in 58% of patients. On the paraclinical level, among the patients who underwent ultrasound-mammography, 59% were classified as ACR4 and 41% as ACR5. Histologically, there was a clear predominance of infiltrating ductal carcinoma, accounting for 94% of cases, with an average tumor size of 3.5 cm. SBR grade II and III tumors were present in 100% of cases accompanied by vascular emboli in 34% of cases. Histological lymph node involvement was found in 71% of patients. Regarding molecular studies, HER2 overexpression was found in 22% of cases, and the triple-negative subtype in 26% of cases. Therapeutically, 67% of patients underwent radical surgery, 23% underwent conservative surgery, and 10% received palliative treatment. From a prognostic perspective, in our series, the overall survival rate for two years was 69%, while the five-year survival rate was 17%. **Conclusion:** A young age is often associated with unfavorable anatomo-clinical and prognostic characteristics. It is therefore essential to adopt a multidisciplinary approach aimed at diagnosing the disease earlier and tailoring treatments based on prognostic factors specific to young patients, to improve survival.

KEYWORDS: Breast cancer; Young woman; Prognostic factors.

INTRODUCTION

Breast cancer is the most common malignant disease among women worldwide. It accounts for approximately 2.3 million new cases and 670,000 deaths globally.[1] Due to screening efforts, its incidence has significantly increased in recent years. In Morocco, as in many parts of the world, this disease represents a major public health issue and is increasingly observed in the younger population. According to studies, breast cancer in young women presents distinct epidemiological, diagnostic and prognostic features, the latter being generally unfavorable. Awareness and early detection can increase the cure rate and make a significant difference in the management of this disease. The aim of our study is to analyze the various epidemiological, clinical, therapeutic, and prognostic aspects of breast cancer in young women under the age of 40.

METHODS

This is a retrospective study conducted over a 5-year period, focusing on cases of breast cancer in young women under the age of 40 who met the following criteria: women under 40 years old at the time of diagnosis, with histologically confirmed diagnosis. Excel software was used for statistical analysis. Data processing was carried out using percentages, means, or medians. Data collection was conducted with respect for patient anonymity and confidentiality of their information.

RESULTS

Among the 297 patients diagnosed with breast cancer during this period, 31 were under the age of 40, representing a frequency of 11%. The average age of the patients was 32 years, with extremes ranging from 24 to 39 years. The most affected age group was 31-35 years, accounting for 42% of the cases. A predominance of

pauciparity and nulliparity was observed, with rates of 55% and 26%, respectively. The average age at first pregnancy among non-nulliparous women was 23 years (ranging from 18 to 30 years). The average duration of breastfeeding was 19 months, with extremes ranging from one month to three years. A personal history of fibrocystic mastopathy was reported in only one patient (3.2% of cases).

A family history of breast cancer was found in 8 patients (31%), including 3 first-degree and 5 second-degree relatives. The average delay between the onset of symptoms and consultation was 2.6 months, ranging from 3 weeks to 6 months. Self-detection of a breast lump was the most common reason for consultation, observed in 82% of cases. Regarding tumor location, a slight predominance in the upper outer quadrant was noted (29%). Left breast involvement was found in 17 patients (54.8%), and bilateral involvement was noted in 2 patients (6.4%). The average tumor size was 3 cm, with a range from 1.5 to 6 cm. Tumors measuring 2–5 cm accounted for 58% of cases, while tumors smaller than 2 cm represented 12%. Inflammatory signs were present in 8 patients (27.6%). The tumor was mobile in 27 patients (87%), fixed to the superficial plane in 3 patients (9.6%), and fixed to the deep plane in one case (3.2%). Bilateral involvement was found in 2 patients (6.4%). In terms of body mass index, 45% of patients were overweight, 40% had a normal weight, and 15% were obese. Radiologically, a predominance of ACR4-classified lesions was observed, accounting for 44.82% of cases. Invasive ductal carcinoma was the most frequent histological type, representing 94% of cases. Other histological types (lobular, medullary, phyllodes sarcoma) were less frequent. Scarff-Bloom-Richardson (SBR) grade II was most common (52%), followed by grade III (48%). No cases of grade I were found. On immunohistochemy, both estrogen and progesterone receptors were positive in 15 patients (46.6%), dissociated in 3 (10%), and negative in 13 (43.3%). HER2 testing was performed using immunohistochemistry and confirmed by FISH in cases with a score of 2+. HER2-negative tumors were found in 21 patients (67.7%). The Ki-67 proliferation index was below 20% in 16.12% of cases and above 20% in 83.8%.

This immunohistochemical analysis revealed a predominance of Luminal A status (33%), followed by Luminal B (19%). Triple-negative status was found in 26% of patients, and HER2 enriched in 22%. For staging, axillary lymph node involvement was observed in 45.16% of cases, supraclavicular lymph node involvement in 3.22%, pulmonary metastases in 9.67%, hepatic metastases in 9.67%, vertebral metastases in 12.9%, and a single case of brain metastasis. In our series, 20 patients underwent surgical treatment: primary surgery in 12 cases and surgery following neoadjuvant chemotherapy in 8 cases. The remaining 11 patients received palliative treatment. Among the 20 patients who underwent axillary dissection, lymph node involvement was found in 71%, with capsular rupture in 35%. Vascular emboli were present in 10 patients (50%). The rate of tumor-infiltrating lymphocytes (TILs) was between 0–10% in 12 patients, 11–59% in 16 patients, and ≥60% in 2 patients. External radiotherapy was performed in all patients who had conservative surgery, and in other cases due to lymph node involvement and/or advanced tumor stage. The radiation protocol included:

- Breast + chest wall: 46–50 Gy in 23% of patients.
- Axillary areas + internal mammary chain: 46–50 Gy in 45.16% of patients.
- Tumor bed boost: 16 Gy in 23% of patients.

Radiotherapy-related complications were observed in 2 patients (8.69%) and consisted of simple radiodermatitis. A total of 28 patients received chemotherapy based on anthracyclines, taxanes, alkylating agents, and antimetabolites, with an average of 6 cycles. Chemotherapy-related toxicity was observed in 20 cases (71.4% of treated patients). Hormone therapy was prescribed in 52% of cases, and targeted therapy with Herceptin in 22%. In our series, the average follow-up duration was 24 months, ranging from 12 to 72 months. During this period, one patient (3.4%) experienced recurrence after conservative treatment, presenting as an ipsilateral breast nodule, which was managed by mastectomy and chemotherapy. The overall 5-year survival rate in our series was 88.2%.

DISCUSSION

Breast cancer in women has surpassed lung cancer as the most frequently diagnosed cancer, with approximately 2.3 million new cases and 670,000 deaths worldwide.[1] It has been reported that developed countries have the highest incidence of breast cancer both before menopause (30.6/100,000) and after menopause (253.6/100,000)[1], while developing countries show a lower incidence in both premenopausal (8.5/100,000) and postmenopausal women (53.3/100,000).[2] However, mortality rates are higher in low-income countries due to inadequate strategies for early diagnosis and effective treatment.[1] In young women, the frequency of breast cancer varies across studies. In the United Kingdom, this frequency is 4% according to Kollias[3], and 7.4% in France according to Fleurier[4], while in the United States, Anders[5] estimated it at 6.6%. In Asia, the frequency is estimated at 12.5% according to Wonshik in South Korea.[6] In our series, the frequency of breast cancer in women under 40 years of age was 11%, which is close to Wonshik's findings. The average age at diagnosis in young women varies according to the authors: in Tunisia, Khanfir reported an average of 31.5 years[7], Bouzid 31.3 years[8], and Chan 32.1 years.[9] The average age of onset among young women generally appears to be over 30 years, which is consistent with our findings, where the average was 32 years. An early menarche, before the age of 12, has a significant impact on breast cancer risk. Studies have shown that the risk increases by 3% for each year of delayed menopause, and conversely, each year of delayed menarche reduces

breast cancer risk by 5%. This is explained by prolonged exposure to estrogen.[10] In our series, 11 patients (44% of cases) had their menarche at age 12 or younger. A meta-analysis found that early pregnancy and longer breastfeeding durations reduce the risk of breast cancer.[11] According to most studies, the older a woman is at the time of her first childbirth, the less protected she is against the onset of breast cancer[12], and each full-term pregnancy decreases the risk by about 10%.[10] Nulliparity and late age at first pregnancy are associated with poor mammary tissue differentiation, greater exposure to non-estrogenic mutagens, and genotoxicity caused by estrogen.[13] In our series, pauciparity and nulliparity were predominant, with rates of 55% and 26% respectively, and the average age of the first pregnancy was 23 years. Women with atypical hyperplasia have a 3 to 5 times greater risk of developing breast cancer.[11] In our series, a history of benign breast disease was found in only one patient (3.2% of cases). Clinically, self-detection of a breast lump was the most common reason for consultation in our series, occurring in 82% of cases, consistent with data from the literature. According to Liukkonen[14], tumors were in the left breast in 59% of cases, the right breast in 40%, and were bilateral in 1%, with 56% involving the upper outer quadrant. According to Persand[7], tumors were in the left breast in 60.3% of cases, in the right breast in 37.9%, and were bilateral in 1.7%, with 37.6% involving the upper outer quadrant. In our series, the tumor was in the left breast in 54.8% of cases, in the right breast in 38.8%, and was bilateral in 6.4%. There was a slight predominance of involvement in the upper outer quadrant, with a frequency of 29.03%. Tumor size at diagnosis varies across studies. In our series, the average tumor size was 3 cm, which is smaller than that reported in other Maghreb series. In most cases, inflammatory breast cancers are considered among the most aggressive forms, with an often-poor prognosis due to their high metastatic potential and risk of locoregional recurrence.[15,16] According to Persand[7], the frequency of this form among young women is 28%, and 26.92% in the series by Lazreqh.[8] However, in Morgan's series[5], this frequency does not exceed 4%. In our series, inflammatory signs were observed in 27.6% of cases. Radiologically, mammographic lesions are more difficult to detect and classify due to the high density of breast tissue in young women. This density makes it challenging to distinguish between normal and malignant tissue, resulting in a higher rate of false-negative mammograms.[17,18] In our series, all patients underwent mammography, which revealed suspicious images classified as ACR 4 and 5 in 42% and 32.2% of cases, respectively. Stellate opacity was observed in 51.6% of cases, and suspicious microcalcifications in 12.9%. Breast ultrasound is particularly valuable for evaluating dense breasts in young women, as it can reveal abnormalities not seen on mammography.[19] According to Persand[3], suspicious lesions were detected by ultrasound in 75% of cases; 71% according to Znati[20], and 85% for Idmanga.[7] In our series, suspicious tissue lesions were observed in 90% of cases. Magnetic resonance imaging (MRI) is used as a second-line imaging modality after ultrasound and mammography. Despite its important indications, this exam remains expensive and not widely accessible. In our series, MRI was performed in 4 patients (12.9%) due to radio-clinical discordance. Tumor biopsy plays a crucial role in confirming the diagnosis and guiding treatment. It can be performed using specialized TRU-CUT needles, often under ultrasound guidance for small lesions, or using a large-gauge needle with a vacuum-assisted coaxial system in cases of suspicious microcalcifications seen on mammography but not detected on ultrasound. Research indicates that invasive ductal carcinoma (IDC) is the most frequently observed histological type, in both young and older women. In Paillocher et al.'s series, IDC accounted for 92.3% of cases[21], 95% in Bouzid's, 90% in Ben Ahmed's[22], and 68% in Khanfir's.[7] In our series, IDC accounted for 94% of tumors. Regarding the Scarff-Bloom-Richardson (SBR) histo-prognostic grading system, modified by Elston and Ellis, our findings are consistent with the literature, which shows that SBR grades II and III are common among young women.[23,24] The presence of vascular tumor emboli is a significant predictor of poor breast cancer prognosis. According to Bakkali[6], the frequency of tumor emboli was 26.6%, 60% according to Belhafiane[9], and 29% according to Fleurier.[4] In our series, emboli were found in 10 patients, representing 32.2% of cases. In the United States, Bhârat et al. observed that younger patients tend to have lower mRNA expression levels of estrogen and progesterone receptors, and higher expression of HER2, compared to their older counterparts.[25] According to Bouzid[8], hormone receptors were positive in 55.6% of cases, 76.8% according to Znati[25], and 54.8% according to Belhafiane.[22] In our series, both hormone receptors were positive in 46.6% of cases, discordant in 10%, and negative in 43.3%. As for HER2 gene amplification (C-erbB2): on the long arm of chromosome 17q21, there is an oncogene known as HER2. In about 20% of primary breast cancers, HER2 overexpression is observed. This overexpression is associated with a 50% to 80% increase in metastasis and relapse rates. It leads to hyperactivation of pro-oncogenic signaling pathways, resulting in uncontrolled cancer cell growth and poor clinical outcomes.[26] According to AGRUP[27], HER2 overexpression is a crucial prognostic factor in young women. This overexpression was detected in 27% of women under the age of 36 and was associated with a significant decrease in survival rates. In our series, HER2 overexpression was found in 22% of cases, consistent with the literature. Tumor-infiltrating lymphocytes (TILs): Within the tumor microenvironment, TILs play a key role as a major component of the immune infiltrate. They serve as indicators of the strength and effectiveness of the immune response against cancer. A TILs density of 50% or more is specifically associated with exceptionally high rates of pathologic complete response to neoadjuvant therapy in triple-negative and HER2+ breast cancers, as well as with significantly improved overall survival rates.[28] In our series, TIL levels ranged

between 0 and 10% in 58% of cases, between 11 and 59% in 32%, and ≥ 60% in 10% of cases. The Ki-67 proliferation index is a tumor proliferation marker with the potential to serve various purposes, such as prognostic assessment, evaluation of response or resistance to chemotherapy or hormone therapy, estimation of recurrence risk in patients undergoing standard treatment, and as a dynamic indicator of disease progression. It can also be used to assess treatment effectiveness using tissue samples collected before, during, and after neoadjuvant therapy.[26] A high Ki-67 index is considered a poor prognostic factor.[29] Axillary lymph node involvement is a key prognostic factor. It is important to note that axillary palpation does not reliably predict nodal involvement; instead, assessment relies on histological analysis. It is widely recognized in the literature that lymph node invasion is more frequent in young women. This has been supported by Cajdos[30], who reported a lymph node involvement rate of 37% in women under 40, compared to 25% in women over 40. Younger age and larger tumor size are two major factors associated with a higher incidence of lymph node metastasis, as demonstrated by Gann[31] and Kroman.[32] Studies have shown that nodal involvement significantly affects relapse-free and metastasis-free survival. The greater the number of affected nodes, the lower the overall survival rate. A threshold of more than three positive lymph nodes is generally used to identify patients with a poor prognosis.[33] Node size and capsular rupture are also important in increasing the risk. In our series, 20 patients (71%) had positive lymph node involvement, and capsular rupture was observed in 7 of these cases (35%). BRCA1 and BRCA2 are tumor suppressor genes, and mutations in these genes are responsible for 95% of hereditary breast and ovarian cancers, and 65% of breast cancer cases alone.[34] A study focusing on young women showed that those with BRCA1 or BRCA2 mutations had a cumulative local recurrence risk at 12 years of 49%, compared to 21% for sporadic breast cancers.[35] According to DELALOGE, breast tumors associated with germline BRCA mutations typically appear 10 to 15 years earlier than sporadic cancers/[36] Unfortunately, due to limited resources, BRCA mutation testing was not performed for the patients in our series. After histological diagnosis, a metastatic workup is systematically performed regardless of tumor size. However, the new INCa recommendations advise against performing a metastatic workup in the absence of clinical signs for patients with breast tumors classified as T1 or T2 and without lymph node involvement.[24] Nevertheless, in clinical practice, a metastatic workup is often carried out prior to initiating adjuvant chemotherapy, regardless of tumor stage. In such cases, it routinely includes a thoraco-abdominal CT scan and a whole-body bone scintigraphy. Additional investigations are ordered depending on the clinical context. In the literature, the metastasis rate was reported as 6.7% by Bakkal[37], 7% by Khanfir[7], and 6% by Persand.[9] In our series, the metastatic workup revealed 11 cases of metastases, primarily in the bones. Each patient diagnosed with breast cancer must be discussed in a multidisciplinary tumor board in order to decide on the most appropriate therapeutic strategy. When the tumor-related parameters allow, the decision between breast-conserving surgery or radical surgery is made in coordination with the patient, after providing comprehensive information on the benefits and risks of each option. Following breast-conserving surgery, the local recurrence rate ranges between 2 and 10% at five years. It also represents a predictive factor for the development of metastases.[38] Currently, thanks to the widespread use of screening programs, a growing number of patients are now eligible for breast-conserving surgery. In addition, neoadjuvant treatments such as chemotherapy or hormone therapy make it possible to extend the indication of this approach to larger tumors.[39] According to Boufettal's series[40], 18% of patients received breast-conserving treatment; this rate was 14% in Guendouz's series[41], 30% for Bouzid[8], and 32% for Liukkonen.[14] In our series, 7 patients underwent breast-conserving surgery, representing 23% of cases, which is consistent with findings in other North African studies. Mastectomy for invasive carcinoma is indicated in the following situations: patient's expressed preference, inability to undergo radiotherapy, inflammatory breast cancer after neoadjuvant chemotherapy, positive surgical margins after multiple interventions, technical impossibility to perform en bloc resection, or when the expected aesthetic outcome is deemed unsatisfactory.[42] According to Znati's series[18], the mastectomy rate was 71%, 74% in Darwich's series, and 54% in Fleurier's series.[4] In our series, 21 patients underwent radical surgery, representing 67% of cases. Axillary lymph node surgery has traditionally involved complete and extensive axillary dissection. However, the morbidity associated with this technique including upper limb lymphedema, pain, dysaesthesia and sometimes even limited arm abduction has led to the development of less invasive axillary techniques.[39] Currently, the main objective of axillary lymph node assessment is to establish prognosis to guide the therapeutic strategy.[26] In 1994, Giuliano et al. were the first to describe the sentinel lymph node procedure, which allows the identification of the first lymph node in the chain where metastases are likely to spread. This node is then removed and examined histologically to determine whether it contains cancer cells.[39] Unfortunately, this technique is still not available in our hospital due to the absence of a nuclear medicine department. In 2005, the Early Breast Cancer Trialists' Collaborative Group demonstrated that chemotherapy reduced the risk of recurrence by an average of 40 ± 6% in patients under 40 years of age, compared to a 23 ± 3% reduction in those aged 50 to 59 years.[43] The main indications for neoadjuvant chemotherapy in the treatment of breast cancer include tumors not amenable to immediate conservative surgery, initially unresectable or locally advanced tumors requiring oncologically satisfactory resection, and inflammatory breast cancers. Patients with triple-negative or HER2-positive breast cancer may also

benefit from neoadjuvant treatment.[44] In our series, neoadjuvant chemotherapy was indicated in 12 women, accounting for 42.8% of cases. In the adjuvant setting, Kroman et al. highlighted an increased risk of cancer-related death among women under 35 years with favorable-prognosis breast cancer, if they did not receive adjuvant chemotherapy.[45] In our series, adjuvant chemotherapy was indicated in 25 patients, representing 89.2% of cases. Radiotherapy is a treatment technique using ionizing radiation. Numerous studies have demonstrated its benefit as an adjuvant therapy for localized breast cancer following breast-conserving surgery. It is also used palliatively to treat metastatic sites. Various randomized trials compiled in the meta-analysis by the Early Breast Cancer Trialists Collaborative Group have shown that radiotherapy improves not only local control but also overall survival, both after conservative surgery and mastectomy in patients with lymph node involvement.[46] In our series, radiotherapy was performed in 22 patients, accounting for 70.9% of cases. Tamoxifen remains the standard hormonal treatment for women under 50 years with estrogen receptor-positive breast cancer. Aromatase inhibitors alone are not indicated before this age, as they only inhibit the biosynthesis of estrogens from adrenal androgens, without affecting ovarian production. Successive meta-analyses in 1998[47], 2005[48], and 2011[49] have progressively clarified the extent of its benefits. In ER+ patients, 5 years of tamoxifen therapy improves recurrence-free survival by 13% at 15 years and overall survival by 9%. This benefit persists for at least 10 years after treatment cessation, and is largely independent of menopausal status, progesterone receptor status, nodal status, and the use of chemotherapy. Tamoxifen is strictly indicated in ER+ patients only. No benefit is observed in patients who are PR+ only. Moreover, in patients who are ER- or have <10% ER expression, hormone therapy offers little to no benefit in terms of reducing recurrence or mortality.[50] Hormone therapy was prescribed in 23% of cases in Znati's series[6], 41% in Khanfir's series[13] and 30% in Ndounga's series.[14] In our study, this rate was 54%. The HER2 receptor, a transmembrane tyrosine kinase encoded by the HER2/neu proto-oncogene located on chromosome 17, plays a key role in the regulation of cell proliferation. When this receptor undergoes gene amplification or overexpression, it endows cancer cells with a more aggressive phenotype. This anomaly is present in 15 to 20% of breast cancers. Due to its unfavorable prognostic impact, targeted therapies such as trastuzumab and lapatinib have been developed to block HER2 activity and improve clinical outcomes.[51] As for follow-up, young women are more likely to develop aggressive forms of breast cancer, increasing the risk of recurrence. According to Roche Fordière et al., after five years, the decrease in relative recurrence risk is slower in younger women.[51] In our series, follow-up was conducted through clinical breast examinations and mammography. During follow-up, only one patient (3.4% of cases) experienced a locoregional recurrence. In young women, breast cancer often displays more aggressive characteristics, which negatively influence prognosis and survival. While localized forms of the disease have high survival rates, metastatic breast cancer remains a major clinical challenge.[41,40] In Boufettal's series[5], the 3-year overall survival rate was 56.4%, with relapse-free survival at 48.4%. In Bouzid's series[8], the 3-year overall survival was 67.7%, and relapse-free survival was 58%. Meanwhile, in Fleurier's study[4], the 3-year overall survival reached 87.7%. In our series, the 3-year overall survival rate was 88.2%, aligning with the results of Fleurier's study. The 3-year relapse-free survival rate was 93.4%.

CONCLUSION

Breast cancer remains the most common malignancy among young women. In recent years, a significant increase in its incidence has been observed in this population, requiring special attention due to its specific morphological and prognostic features, as well as its unique challenges particularly regarding fertility preservation. A young age is often associated with unfavorable anatomo-clinical and prognostic characteristics. These include delayed diagnosis, a higher prevalence of advanced forms with larger tumors, more frequent histological lymph node involvement, higher histological grade, lower expression of estrogen receptors, increased HER2 overexpression, a greater risk of both locoregional and distant recurrences, and reduced overall survival. It is therefore essential to adopt a multidisciplinary approach, aiming for earlier diagnosis, promoting genetic counseling in women at risk, and tailoring treatments according to the specific prognostic factors found in young patients, to improve their outcomes.

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