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## Breast cancer in women under the age of 35: About 21 cases

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### Abstract

**Background:** Breast cancer is a serious disease. Its incidence in young women is constantly increasing. The objective of the study is to analyze the epidemiological, clinical, therapeutic and prognostic characteristics of breast cancer in young women under 35 years-old.

**Method:** This is a retrospective study about 21 cases of patients aged less than 35 years treated in the gynecology and obstetrics department of the university hospital Mohammed VI of Oujda, Morocco between January 2015 and December 2018.

**Results:** The frequency of breast cancer in young women under 35 was 12.7% in our center. The age average was 31.5 years. 38% had a family history of cancer and among them, 28% had a family history of breast cancer, 5% of endometrial cancer and 5% of colon cancer. The self-examination of a nodule was predominant (57.1%). T3 tumors were the most common (43%), followed by T4 tumors (33%). 24% were immediately metastatic with predominantly pulmonary locations (48%). It was invasive carcinoma of non-special type in 43% of cases, with predominance of SBR grade II and III (84%). Hormone receptors were positive in 57% of cases and no overexpression of HER2 was found. 18 patients underwent surgery, radical in 61% of cases. 18 had a locoregional irradiation, 58.8% received adjuvant chemotherapy. Hormonal therapy was prescribed in 66.6% of cases. After an average follow-up of 14.7 months, 40% presented relapses. The overall 3-years survival was 38% and the relapse-free survival 40%.

**Conclusion:** Our series joins the data of the literature pleading in favor of the more advanced forms and the more unfavorable prognosis of breast cancer in young patients.

**Keywords:** Cancer, breast, young age, prognostic factors, survival

### Introduction

Breast cancer is the most common cancer in the world. It is the second leading cause of death from cancer. The average age is between 50 and 70 years, its frequency in young women aged less than 35 varies from 2 to 24% [1].

Compared to older women, breast cancer in women aged under 35 is often linked to a genetic predisposition and seems more aggressive with poorer prognosis and higher recurrence rate. Around 10% of cancer patients aged less than 40 had a BRCA1 or BRCA2 mutation [2].

According to the majority of authors, breast cancer in this age group has its own epidemiological, diagnostic and also prognostic characteristics, going so far as to consider youth as a poor prognostic factor [3-5].

### Methods

This is a retrospective study carried out for 4 years covering all patients aged less than 35 years old and treated for breast cancer by the obstetrics and gynecology department of the University Hospital Mohammed VI of Oujda. Data processing was done as a percentage, on average or as a median. Survival was calculated using the Kaplan-Meier method.

### Results

During 4 years, 165 cases of breast cancer were admitted to the Obstetrics and Gynecology department of the Mohammed IV university hospital of Oujda, Morocco.

Among the patients, 21 were aged less than 35 years old, representing a rate of 12.7% of the overall breast cancer patients treated during this period in our center.

The average age of the patients was  $31.5 \pm 4.04$  years with extremes of 18 and 35 years. The 31-35 age group was the most affected with a rate of 71.40%.

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The average menarche age was  $12.76 \pm 1.8$  years. It was before 12 years-old in 11 patients (52.4%). Oral contraception was taken by 13 patients (61.9%) with an average duration of  $4.3 \pm 5.6$  years.

In our series, we note a predominance of multiparity and pauciparity, and their rates are respectively 38.1% and 33.3%; while nulliparous women represent only 28.6%. The age of the first pregnancy was 21.7 years-old with extremes of 19 and 29 years. The notion of breastfeeding was confirmed in 12 patients (57.2%) with an average duration of 14.5 months with extremes of 6 months and 2 years. Personal history of fibrocystic mastopathy was recorded in 3 patients (14.3%).

Body mass index was calculated and a slight predominance of overweight was observed in 38% of women, followed by 33% of patients with a normal build, while obesity was noted in one patient (5%).

In our series, only one smoking patient was found, no history of mediastinal radiation was reported.

A family history of breast cancer was found in 6 patients (28.6%); 4 in a first-degree parent and 2 in a second-degree parent. One case of endometrial cancer was noted in a first-degree relative and one case of colon cancer.

Concerning clinical characteristics, the average time between the onset of symptoms and the consultation was 8.3 months with extremes of 15 days and 3 years. Among these women, 38% consulted within less than 3 months.

Overall, the most frequent reason for consultation (57.14%) was represented by the self-examination of a breast tumor.

Breast examination revealed a slight predominance of involvement of the right breast in 14 patients (67% of the cases). The mean tumor size was 5.2 cm with extremes of 3 and 10 cm. 54% of the patients had a tumor size between 2 and 5 cm. The inflammatory signs were found in 2 patients (9.5%). These signs were dominated by redness and local heat.

Palpation of the lymphatic areas found a homolateral axillary lymphadenopathy in 5 patients (23.8%), and supraclavicular lymphadenopathy in 3 patients (14.3%); 5 of the lymphadenopathies were mobile and 3 fixed.

All of our patients underwent mammography: we noted a predominance of tumors classified ACR5 with a rate of 57%. All our patients have benefited from a breast ultrasound. In the majority of cases, the anomaly looked hypoechoic and/or heterogeneous in 10 patients (48%).

Carried out in 2 patients, breast MRI objectified in the one case a sarcomatous breast image and in the other one a spiculated image with metastatic axillary lymphadenopathy.

The diagnosis was confirmed by percutaneous micro biopsy in 18 cases and by surgical biopsies in 3 cases: Invasive ductal carcinoma (IDC) was the most prevalent with a rate of 43%, followed by invasive lobular carcinoma (ILC) with a rate of 29%. In the majority of cases, it is an SBR II grade noted in 11 cases or 57%, followed by SBR III grade in 5 cases or 26%, while SBR I grade was only found in 3 cases or 16%. The search for hormone receptors was carried out in all the patients. These estrogen and progesterone receptors were both positive in 57%, dissociated in 10% and negative in 33% of the cases. The Hercept test was performed on 17 patients using the immunohistochemistry techniques, supplemented by the Fluorescence in situ hybridation (FISH) or Chromogenic in situ hybridation (CISH) method in case HER2 (2+) score was found. Thus, none of the patients had overexpression of HER2.

The determination of the hormonal status and HER2 status of infiltrating carcinomas showed a predominance of RH + / HER2- status with a rate of 71%. Patients with "triple-negative"

status were 29%.

At the end of this extension assessment: thoracoabdominal and cerebral CT scans; 5 patients were immediately metastatic (24%): 3 cases with a single metastatic location (pulmonary metastasis in 2 cases and bone metastases in one case), 2 cases with double metastatic localizations (1 case of hepatic metastasis associated with pulmonary metastasis and 1 case of pulmonary metastasis associated with bone metastasis)

The main site of metastasis was the lung (48%) followed by the bone (32%), then the liver (20%).

After the examination and the extension assessment, the cTNM clinical classification could be established based on the TNM 7th edition 2010 classification: A predominance of the T3 forms was observed with a rate of 43%, followed by the T2 forms with a rate of 33%. The clinical study of lymph node involvement has shown that the N0 forms are frequent with a rate of 62% followed by the N1 forms at a rate of 24%. 17% of all patients were immediately metastatic.

The patients were divided into different stages of the Union for International Cancer Control (UICC). In our series, stages IIA and IV were the most frequent with rates of 25% and 24% respectively.

Molecular classification was established in 17 patients from hormone receptors and HER2 status data. In our series, the Luminal A and B subtypes were the most frequent with respective rates of 43% and 41%, while the Basal subtype called "triple-negative" is 16%.

In our series, 18 patients (86%) underwent surgical treatment on the breast or axillary lymphadenopathy. It was primary surgery in 13 patients, and post neoadjuvant chemotherapy surgery in 5.

The radical mastectomy associated with homolateral axillary lymph node dissection (Patey procedure) was performed in 11 patients (61%). Conservative surgery was performed in 7 patients (39%).

Regarding the 3 remaining patients, one patient was lost to follow-up after diagnosis; the 3 patients were metastatic and received palliative treatment.

In our series, 18 patients (86%) benefited from external radiotherapy by linear accelerator. Only one patient was lost to follow-up after surgery, while 2 were diagnosed as metastatic before the start of radiotherapy. Radiation therapy was used curatively in 17 patients (94.4%), and as a palliative treatment in only one patient or 5.6%.

The time between surgery and radiotherapy varied between 3.5 months and 10 months with an average of 5.7 months.

This chemotherapy was indicated as an adjuvant treatment in 10 patients (58.8%) while 5 cases (29.5%) received it in neoadjuvant and 2 cases as palliative treatment.

The time between surgery and adjuvant chemotherapy varied between 1 month and 3 months with a median of 1.72 months.

Hormonal therapy of the tamoxifen type (Nolvadex) at a dose of 20 mg/day was received by 14 patients or 66.6% of the cases with an expression of hormone receptors.

The average duration of taking it was 18.5 months with extremes of 1 month and 5 years. In our series, no patient benefited from targeted therapy with Trastuzumab.

During follow-up, 8 patients or 40% had a relapse of their disease with a locoregional recurrence (60%), a metastatic spread or both. The mean time to relapse was 7.8 months.

Metastatic relapse was observed in 5 patients (25%) (Table 1). Note that in 3 patients, metastatic relapse was associated with a locoregional relapse. The most common metastatic site was the lung (40%).

**Table 1:** Distribution of locoregional and metastatic relapses based on prognostic and therapeutic factors

Pronostic factor		Locoregional relapse (%) (n=6)	Metastatic relapse (%) (n=5)
Tumor size	T ≤ 2cm	16.6	0
	2 < T ≤ 5cm	50.1	60
	T > 5cm	33.3	40
Age	≤ 20	0	0
	21-25	0	0
	26-30	16.6	40
	31-35	83.3	60
SBR Grade	Grade I	16.6	0
	Grade II	61.1	80
	Grade III	22.3	20
Histological type	IDC	50	60
	ILC	33.3	20
	phylode Sarcoma	16.7	20
Lymph node metastasis	N0	16.6	20
	N+	83.4	80
Tumoral emboli	Yes	66.7	50
	No	33.3	50
Hormone's receptors	Positive	50	80
	Negative	50	20
Molecular subtype	Basal	66.7	20
	Luminal A	0	20
	Luminal B	33.3	60
Surgery	Conservative	66.7	60
	Radical	33.3	40
Adjuvant chemotherapy	Yes	66.7	60
	No	33.3	40
Radiotherapy	Yes	83.4	100
	No	16.6	0
Hormonothérapie	Yes	50	80
	No	50	20

61.9% of the patients are alive, while 28.6% are deceased. Survival was calculated using the Kaplan-Meier method. The overall survival time was calculated between the date of diagnosis of breast cancer and the date of death or last consultation. The rate of OS at 3 years was 38%. The period of survival without relapse was calculated from the date of the first therapeutic intervention (surgery or neoadjuvant chemotherapy) until the date of the occurrence of the relapse or the date of the last consultation. The 3-year recurrence-free survival rate was 40%.

### Discussion

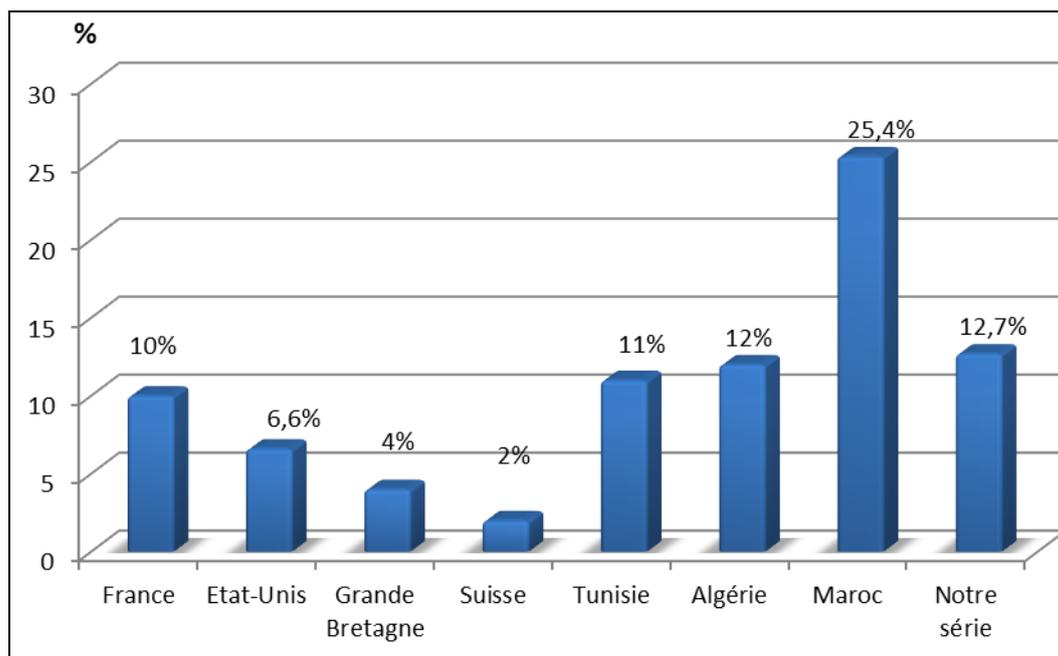
The frequency of breast cancer in young women varies according to the authors. In Morocco, breast cancer mainly affects middle-aged women between 50 and 70 years-old; its frequency in young women aged less than 35 varies from 2 to 24%, according to a study done at the Casablanca University Hospital, Boufettal estimates this frequency at 25.4% [3].

It is estimated at 10% in France according to Molinié [6], at 6.6% in the United States (USA) according to Anders [7], at 4% in Great Britain according to KOLLIAS [8], and 2% in Switzerland according to ZAMN [9].

In Asian countries, this frequency is estimated at 9.6% according to WONSHIK in South Korea [10].

In the Maghreb, this frequency is 11% according to Bouzid in Tunisia [11], and 12% according to Guendouz in Algeria [12].

In our series, the frequency of breast cancer was 12.7% in patients aged less than 35 years, thus exceeding the frequency of the Western series and consistent with the Maghreb ones. (Figure 1).

**Fig 1:** Young women breast cancer frequency according to different studies

However, the incidence of breast cancer in young women is on the rise worldwide. This would be explained by changes in eating habits, exposure to more toxins and hormones and a decrease in physical activity.

The definition of breast cancer in young women is not unequivocal. Different studies have defined a “young” woman as corresponding to a woman under 30, 35, 40, 45 years or

simply not menopausal [13].

In our study, we opted for an age limit below 35 years. Thus, was considered young, any patient who did not exceed this age at the time of diagnosis.

Age is the most important risk factor. Indeed, between 20 and 50 years old, the risk of breast cancer increases very quickly, then more slowly after menopause (50 years) to stabilize after 80.

The average age of onset of breast cancer in young women in the literature is often after 30 years-old [2, 11, 12], which agrees with our series whose average was 31.5 years-old.

Numerous studies show that the first menstrual period before the age of 12, as well as menopause after the age of 50, increases the risk of breast cancer. This is explained by longer exposure to estrogens [14]. In our series, the early menarche was found in 52.4% of the patients, while all the patients were in genital activity during the diagnosis.

Epidemiological data indicate that the risk of breast cancer increases with nulliparity and the late age of first pregnancy (after 30 years) [14]. The meta-analysis of Ewertz *et al* [15] also goes in this direction, since it concludes that a first pregnancy before 30 years-old reduces the risk by 25% compared to a nulliparous woman, and the first pregnancy before 20 years-old reduces the risk by 30% compared to a woman who had her first pregnancy after 35 years.

On the other hand, women who gave birth to eight to nine births have a reduced risk of about 30%, compared to those who have had five deliveries (Hinkula *et al.*, 2001).

Unlike our series, multiparity was predominant (38.1%) while nulliparity was reported in 28.6% of the patients, only 4.8% had their first pregnancy after 30 years and 95.2% before 20 years. The average age of the first pregnancy is 21.7 years.

Regarding breastfeeding, data from 47 studies carried out in 30 different countries including 50,302 women who had breast cancer and 96,973 women without disease, highlighted that the more a woman breastfeeds, the more she is protected against breast cancer, regardless the age, the country, the menopausal status, the ethnic origin and the age of the first pregnancy. This is inconsistent with our series, where breastfeeding was practiced in 12 patients (57.2%) and the average duration of breastfeeding was 14.5 months.

Taking oral contraception leads to a minimal increase in risk in young women after prolonged use. In our series, 61.9% of patients used oral contraceptives for an average duration of 4.3 years.

Menopausal hormone therapy (THM) can increase the risk of breast cancer in certain circumstances: synthetic hormones taken for more than 7 years. In our series, none of the patients were postmenopausal.

According to several authors, a personal history of benign mastopathies does not increase the risk of developing breast cancer. On the other hand, proliferative lesions without atypia multiply the risk by 2 and hyperplastic lesions with atypia

increase this risk by at least 4 times [16]. In our series, a history of fibrocystic mastopathy was found in 3 patients (14.3%).

A family history of breast cancer appears to be the essential risk factor for developing breast cancer at an early age [11].

According to the combined data of 52 epidemiological studies, 20 to 30% of women with breast cancer have a family history [17], but only 5 to 10% of cancers have their origin in genetic mutations.

This is consistent with our series where family history of breast cancer was found in 28% of patients, 66.6% of whom had a family history of first-degree parents diagnosed with breast cancer.

The link between ionizing radiation and breast cancer in women is established. The risk of breast cancer increases in women who have been exposed to strong ionizing radiation (> 100-200cGy) in the chest. In our series, no cases of irradiation were noted.

Obesity increases the risk of postmenopausal breast cancer. However, this does not increase the risk in women during genital activity [18]. In our series, overweight and obesity were noted in 43% of patients.

Regular physical activity at an early age appears to reduce the risk of developing breast cancer. A sedentary lifestyle is responsible for 11% of breast cancers. Regular physical activity reduces this risk by 20 to 30%. In our series, physical activity could not be assessed.

This delay is still late in developing countries due to a lack of means and access to health facilities. In developed countries, a long delay would be due to an insufficiency of awareness of the young population against this cancer and a high frequency of other benign breast diseases. This period is 6 months on average for Boufettal [13], 4 months for Bouzid [11], and 3.5 months for CHAN [21], 4 months for KOLLIAS [8].

In our series, the average consultation time was 8.3 months with a rate of 38% of patients who consulted within less than 3 months. By comparing our results with those in the literature, we see that our patients consulted more quickly than the patients in other series.

Concerning circumstances of discovery, our series joins the literature data, since self-palpation of a tumor was the mode of discovery in 57.14% of cases.

The size of the tumor at the time of diagnosis varies according to the authors. In our series, the average tumor size was greater than that of the Western and Maghreb series but joined that of the Boufettal series [13] (Figure 2).

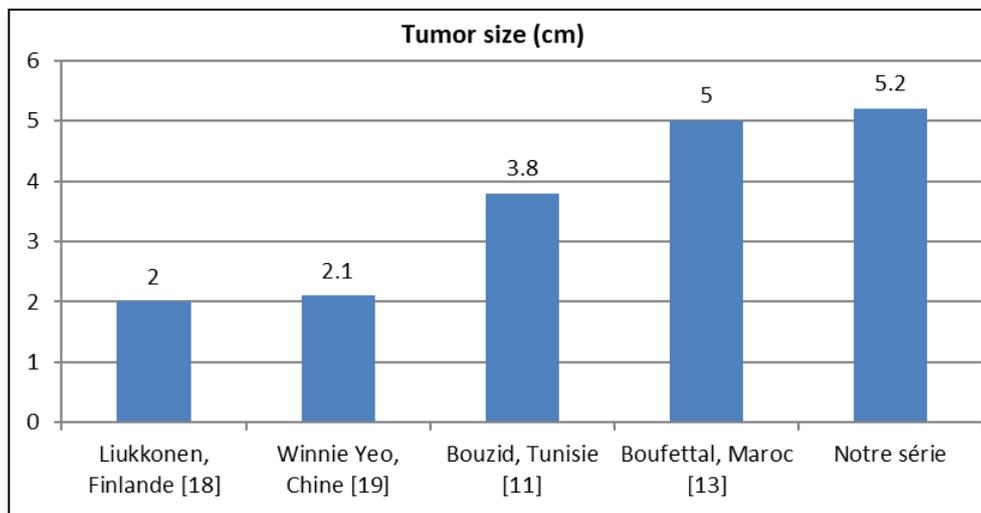


Fig 2: Comparison of tumor size according to different studies

Inflammatory forms of breast cancer account for 2.5% of all breast cancers worldwide [21]. In our series, inflammatory signs were found in 9.8% of patients, which could be explained by a long consultation delay or a long diagnostic time.

Concerning pathological and prognostic factors, most authors [22] agree on the predominance of invasive carcinomas in young women as well as in elderly women. According to several authors, IDC represents more than 90% of breast carcinomas. Jmor S. [22] estimates the frequency of IDC in young women to 94% and Bouamama [6] to 83%. On the other hand, Chan [21] shows, in a multicenter study, that women under aged 35 years-old have a significantly higher rate of spinal cord carcinoma (8%) and lobular carcinoma (7.5%) compared with 4.9% and 4.4% respectively found in older women. In our series, the rate was 42% for IDC, followed by 28% for ILC.

The prognosis is established to define the appropriate treatment depending on the degree of severity of the disease.

The prognostic factors for breast cancer are:

- Age: Analysis of certain series does not show a significant difference in terms of overall survival or survival without recurrence between young women aged under 35 or 40 compared to older women in both single-factor and multi-factor analysis [25]. However, according to several other

authors, age under 35 was an independent negative prognostic factor [13]. Young age is correlated with faster tumor proliferation, higher histological grade, more frequent lymph node invasion and vascular emboli, and negative estrogen receptors.

- Inflammatory signs: The existence of diffuse or localized inflammatory signs has a very marked negative significance. Thus the inflammatory form of breast cancer represents a significant prognostic factor. In our series, inflammatory signs were present in only one patient (4.8%).
- Histological tumor size and tumor stage: It is well known that the prognosis of localized forms is better compared to advanced ones. The tumor size is conventionally correlated with the prognosis, the risk of metastases increases proportionally with the tumor size. The 10-year survival is 75% for tumors sized less than 2cm and increases to 41% when the tumor size is more than 6cm [26] (Figure 3). In our series, tumors classified T1, T2 and T3 were 10%, 57%, and 33% respectively. T2 and T3 tumors were the most associated with locoregional relapses with rates of 50.1% and 33.3% respectively.

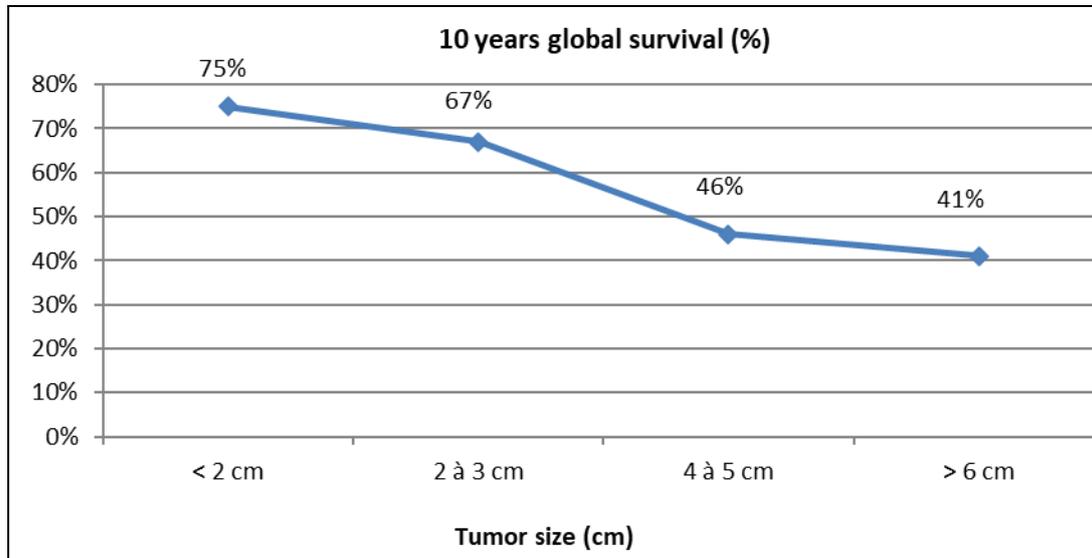


Fig 3: Overall survival at 10 years according to tumor size [26].

- Histological factors: The difference in prognosis between invasive and non-invasive histological forms is clear. In young women, invasive carcinoma is the most frequent, which makes the prognosis worse in this age group. In our series, invasive ductal carcinoma represents 42% of tumors.
- SBR grade: All studies show that metastatic risk and survival are strongly determined by grade; the higher the grade is, the worse the prognosis would be. Thus, the histoprognostic grade constitutes an independent prognostic factor and significantly influences overall survival. The frequency of high SBR grades in young women is a source of aggressiveness of these tumors in this age group [25]. In young women, the literature reports a greater frequency of SBR II and III grades, which agrees with our series.
- Lymph node invasion: It is one of the most important prognostic factors; the number of metastatic nodes has an essential role in the evaluation of the prognosis and the choice of the therapeutic attitude. Many authors agree that lymph node involvement is more common in young women.

According to Foxcort [25], 45.1% of young women have lymph node invasion versus 38.2% in older women. Cajdos [27] found this rate at 37% for women under 40 years-old compared to 25% for those over 40. He also found that the percentage of lymph nodes invaded increases with younger age and bigger tumors. In our series, 68.8% of the patients had a lymph node invasion. This invasion was found associated with 83.4% of locoregional relapses and 80% of metastatic relapses.

- Vascular emboli: The presence of vascular emboli constitutes a factor of poor prognosis in breast cancer, their positivity is an independent risk factor in patients without lymph node invasion, and their presence promotes metastasis and decreases the survival rates [8]. It constitutes a risk factor for local recurrence. In our series, the presence of tumor emboli was found in 42.9% of patients and was associated with locoregional relapse in 66.7% and metastases in 50% of cases.
- Hormone receptors: Several retrospective studies have

shown that overexpression of hormone receptors is considered to have a good prognosis and a better response to hormonal therapy. According to Mousseau, this response is 30% if estrogen receptors are positive and reaches 75% if both estrogen and progesterone receptors are positive [25]. In our series, the estrogen and progesterone receptors were both positive in 57% of the cases, dissociated in 10% and negative in 30%.

- Amplification of the HER2 gene (C-erb-2): Her2 overexpression is associated with higher frequencies of liver, lung and brain metastases. In our series, no HER2 overexpression was noted.

Several studies have shown that conservative treatments (coupled with radiotherapy) have an overall survival rate identical to mastectomies for tumors less than 5 cm. This percentage is 84.6% after five years for mastectomies and 82.3% for conservative treatments in IDC stage I and II.

Also, Fleurier [28] found that the age below 40 years is associated with a more pejorative presentation of breast cancer. Age below 40 was also an independent factor associated with shorter relapse-free survival. Breast cancers diagnosed in young women have different characteristics and often appear more aggressive in their histological characteristics. Overall survival and survival without local or long-term recurrence are at a disadvantage in this population.

### Conclusion

Breast cancer in young women has an unfavorable prognosis; they have more aggressive biological characteristics, greater genetic predisposition and often a delayed diagnosis. Many authors agree about more advanced forms and worse prognosis of this tumor in this age group than in older women.

An improvement in prognosis could be made by setting up a screening program in women before 40 with a risk factor for breast cancer and by therapeutic management adapted to different prognostic factors as well as local control of the disease.

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