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RESEARCH

OM.Breast Cancer in Very Young Women Aged 25 Year-Old or Below in the Center of Tunisia and Review of the Literature

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Abstract Breast cancer in very young women under 40 or 35 years attracted a widespread attention. Few studies have focused on women aged below 25 years. The aim of this study was to evaluate the situation of breast cancer in women ≤25 years in the center of Tunisia. Retrospective review from 1993 to 2013. Clinical, histopathological, therapeutic and outcome data were recorded. Cases were classified into different molecular subtypes based on the immunohistochemistry-based definitions. The series included 25 patients. The mean duration of symptoms was 7.5 months. The most common presenting symptom was a palpable mass. Four patients had at least one relative diagnosed with breast cancer. Mammography combined with ultrasound was suggestive of malignancy in 60 % of cases. Curative surgical treatment could be offered in 19 cases. The mean tumor size was 39 mm. Nodal metastases were detected in 9/18 cases. Twenty cases could be classified into: luminal A (5 cases), luminal B (6 cases), Her-2 (1 case), triple negative (6 cases) and unclassified (2 cases). Two women experienced locoregional recurrence and 6 had distant recurrence. Asynchronous contralateral breast cancer occurred in one case. The overall survival at 5 and 10 years was 85 and 75 % respectively. The survival was significantly lower in grade III tumors (p=0.04) and triple negative tumors (p= 0.03). Breast cancer in women ≤25 years is uncommon. An adequate medical education of young women and physicians is necessary.

Keywords Breast cancer · Young women · Tunisia · 25 years-old

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Introduction

Breast cancer in Tunisia is less frequent compared to western countries; however, it remains the most frequently diagnosed cancer among women with an age-standardized incidence rate of 29.2 per 100,000, significant increasing trends of the incidence and a relatively young age at diagnosis [1, 2]. According to data from cancer registry of the center of Tunisia, about 11 % of breast cancer cases occurred in women under 35 years old [2]. Despite variances in risk factors, Age Standardized Incidence Rates of early onset breast cancer vary little between populations and generally remain low [3]. Breast cancer in young women is an issue that has received a particular attention in the recent literature. It has been identified as a risk factor for recurrence and death from breast cancer and correlates with a worse clinical outcome in comparison to breast cancer in older premenopausal women [4]. In a Tunisian series of 72 young patients aged less than 35 years, the 5 years overall survival was 57 % [5]. Nevertheless, whether age per se is an independent risk factor for worse prognosis is still controversial. The cut off age limit to designate the patient as young is different and most of the series treating this subject have examined breast carcinoma in young women under 35 [4]. Few series [4, 6–9] have addressed the topic of breast cancer occurring in women in their teens or early 20s. These studies have revolved around limited number of cases with the largest series to date by Alipour S et al. [9] in which 55 women were evaluated. No Tunisian series of breast

cancer before 25 years-old are available, which inspired the current retrospective study of a series including 25 patients of early onset breast cancer diagnosed under the age of 25 years over a period of 21 years. The aim of this study was to evaluate the frequency, the clinicopathological and biological characteristics of breast cancer in this age group in order to make a current situation in the center of Tunisia.

Methods

A retrospective analysis was carried out, including all cases of primary and histologically confirmed breast cancer diagnosed in women aged less than 25 years-old at the department of pathology, Farhat Hached hospital, Sousse, Tunisia over a period of 21 years, from January 1993 to September 2013. This study was approved by the research ethics committee of the hospital. Data were recorded from medical files and pathological reports. The collected data included age at the time of diagnosis, the duration of the illness, personal and family history, presenting symptoms, tumor size, tumor localization, mammography findings, ultrasound findings, results of staging procedures (bone scintigraphy, chest film and upper abdominal ultrasound examination), treatment, pathological findings (primary tumor size, histological subtype, grade, multifocality, lymphovascular invasion, lymph nodes' status, immunohistochemical results) and outcome. Locoregional recurrence was defined as a tumor arising in the treated breast or ipsilateral chest wall or the ipsilateral axillary nodes. Data on mortality were obtained at the time of study from medical files and from death certificates for patients lost to follow-up. Overall survival was defined as the time from first diagnosis of primary breast cancer to death from any cause. Histological typing was performed on hematoxylin and eosin stained sections, using the 2012 WHO classification of breast tumors [10]. Grading was performed following the modified Scarff-Bloom-Richardson (SBR) histological grading system [11]. Grading was provided only in the primary tumor not submitted to preoperative chemotherapy. TNM classification was made according to the American Joint Committee on Cancer (AJCC) staging system [12]. Estrogen receptors (ER) and progesterone receptors (PR) status (referred to jointly as hormone receptor (HR) status) were performed at the time of the original diagnosis by immunohistochemistry, HER2 was routinely assessed in our institution only since 2007 and Ki67 was already performed at the time of the original diagnosis for some cases. Archival tissue blocks were available for 15 cases and were used to determine, with immunohistochemical techniques, p53 status as well as Ki67 and HER2 status for the cases lacking these two latter antibodies. CK5/6 was assessed only for the triple negative cases. Tumors were grouped according to their immunohistochemical status into five intrinsic subtypes according to the definitions used in prior studies [13]: luminal A (ER+ and/or PR+, and HER2−), luminal B (ER+ and/or PR+, and HER2+), HER2 over-expressing (HER2+, and ER− PR−), triple negative/basal-like (ER−, PR−, HER2−, CK5/6 +) and unclassified (ER−, PR−, HER2−, CK5/6−).

Immunohistochemistry Tissue sections (4 μm thick) of 10 % formalin-fixed, paraffin-embedded specimens were deparaffinized in toluene, rehydrated in graded alcohol and then washed in distilled water. Antigen retrieval was achieved by treatment in citrate buffer (pH=6) at 98 °C for 40 min. Endogenous peroxidase activity was removed by dipping the sections in 3 % hydrogen peroxide for 7 min at room temperature. Tissue sections were then incubated at room temperature for 30 min with the following primary antibodies: anti-ER (DAKO, Glostrup, Denmark; clone 1D5; code M7047; 1:40 dilution), anti-PR (DAKO, Glostrup, Denmark; clone PgR636; code M3569; 1:40 dilution), anti-HER2 (DAKO, Glostrup, Denmark; clone polyrb; code A0485; 1:300 dilution), anti-CK5/6 (DAKO, Glostrup, Denmark; clone D5/16B4; code M7237; 1:50 dilution), anti-Ki67 (DAKO, Glostrup, Denmark; clone mib1; code M7001; 1:50 dilution) and anti-p53 (DAKO, Glostrup, Denmark; clone DO7; code M7240; 1:100 dilution). Positive controls for HER2 were included. The slides were then rinsed 2 times with washing buffer. Immunohistochemical staining was performed using the highly sensitive polymer based EnVision+Dual Link system-HRP (DakoCytomation). The reaction was visualized with diaminobenzidine as chromogen substrate solution for 15 min at room temperature. Hematoxylin was used as a counterstain. Finally, sections were dehydrated through alcohol and mounted using a standard procedure.

Interpretation of the staining was carried out according to the usual criteria by the same experienced pathologist (SH). This immunohistochemical analysis was performed in a blind fashion, without knowledge of the clinical data. Only nuclear immunoreactivity was evaluated for ER, PR, p53 and Ki67 and was distinguished as positive or negative. The results were determined semi quantitatively as a percentage of positive staining of all cells included in the microscopic fields. For Ki67, the staining was considered as positive if the percentage of nuclear staining was more than 15 % of cells examined at the high power (40x) objective. The expression of p53 was assessed as positive if there were any immunostained tumor cells. Allred scoring system was used to evaluate the HR status [14]. CK5/6 was scored positive if any cytoplasmic and/or membranous staining was seen in the tumor cells [13]. The 0–3 scale DAKO classification system was used to interpret HER expression. Staining was scored as 1+, 2+, or 3+ when limited to a membrane staining of more than 10 % of tumor cells and according to intensity and partial/complete staining. Tumors with intermediate immunohistochemical score (2+) were tested for gene amplification by chromogenic in situ

hybridization (CISH) (visualization with the ZytoVision detection kit C-3003). HER positivity was defined as either immunohistochemistry 3+ or 2+ staining intensity with gene amplification detected by CISH.

Statistical Analysis Analyses were done with SPSS 11.0 for windows software. Overall survival was calculated according to Kaplan-Meier method. The comparison of survival curves was performed according to the log rank test.

Results

The series included 25 patients, representing 0.5 % of the 4566 cases of breast cancer diagnosed at the period of the study. The patients were ranging in age from 19 to 25 years (mean age: 23.7 years). The mean age of occurrence of menarche was 13.5 years (range: 12–16 years), it was >15 years in 20 cases. At the time of diagnosis, 76 % (19 cases) of patients were nulliparous. For the six remaining patients, mean age of first pregnancy was 20.6 years (range: 16–23 years). Breastfeeding was noticed in all patients who had children with a mean duration of 15 months (range: 7–24 months). Only one patient was breastfeeding at the time of diagnosis. Four patients used oral contraceptive agents with a mean duration of 1.4 year (range: 9 months-2 years). Three patients (12 %) had a personal history of benign breast disease: fibroadenoma in one case, abscess in one case and fibrocystic disease in one case, while four patients (16 %) had a family history of breast cancer: one patient reported that her mother and sister were diagnosed with breast cancer respectively at 30 and 25 years; another patient had two sisters diagnosed with breast cancer at 45 and 38 years and the two remaining patients had a second degree family history of breast cancer with a cousin treated for breast cancer at the age of 35 years for one patient and two aunts deceased from breast cancer at the age of 35 and 40 years for the other patient. Four other patients had a family history of other neoplasms: ovarian cancer (grandmother) in one case, large bowel cancer (brother) in one case and lung cancer (father and uncle) in 2 cases.

The time from onset of the first symptom and the first consultation ranged from 1 to 24 months (mean 7.5 months) and was ≥6 months in 13 cases (52 %).

Patients presented with a self-detected breast mass in 20 cases (80 %), pain was experienced by eight women (32 %), and cutaneous signs (skin inflammation, nipple retraction) were seen in 3 cases (12 %); three patients complained from nipple discharge.

On examination, a palpable mass was present in all cases. The tumors occurred in the left breast in 12 cases (48 %), and in the right one in 13 cases (52 %). The upper outer quadrant was involved in 11 cases (44 %). The mean clinical tumor size was 6.5 cm (range 1 to 25 cm) and tumors greater than 2 and 5 cm accounted for 80 and 40 % of cases respectively (20 cases and 10 cases). Tumors were classified as follows: 5 T1, 7 T2, 3 T3, 10 T4 (1 T4a, 2 T4b, 2 T4c and 5 T4d). Examination of the contralateral breast was normal in all patients. Palpated ipsilateral axillary lymph nodes were found in 9 cases and were fixed in one case. There were no palpated contralateral lymph nodes. Two patients (8 %) had ipsilateral supraclavicular lymph node and one patient (4 %) had contralateral supraclavicular lymph node. Mammography was performed in all cases and showed an ill-defined stellate opacity in 15 cases and a well-defined opacity in 5 cases (20 %). It showed asymmetry of density in 2 cases and was inconclusive in 2 cases. Microcalcifications were seen in 7 (28 %) cases (pure in one case).

Ultrasound, performed in all cases, showed a heterogeneous, hypoechoic, ill defined mass, suggestive of malignancy in 15 cases (60 %). In 6 cases (24 %), it was suggestive of a benign lesion. Echographic size was specified in 23 cases (mean 37 mm, range: 10–70.5 mm).

Fine needle aspiration was performed in 10 cases and suggested the diagnosis of malignancy in 7 cases. Core biopsy was performed in 4 cases (all cases diagnosed after 2009, core biopsy was carried out on a routine basis only starting from 2009 in our institution) and showed atypical hyperplasia in 3 cases and low grade ductal carcinoma in situ (DCIS) in one case. Incisional biopsy was made in 10 cases. Ten patients were diagnosed on the basis of lumpectomy with frozen section analysis and four patients had lumpectomy at presentation -without frozen section analysis- for a non suspicious breast mass.

A complete clinical examination, chest radiography, abdominal ultrasound, bone scintigraphy and serum CA15-3 measurement were performed for all the patients and revealed metastatic disease at presentation in 2 cases (8 %): one case with osseous localization and another case with osseous and contralateral supraclavicular lymph node metastases.

Treatment

Surgical treatment was applied in 21 cases. One patient refused curative surgery. The 3 remaining patients were lost to follow-up after neoadjuvant chemotherapy, 2 of them presented again with locally advanced disease and were deemed inoperable at that time. The surgical procedures performed consisted of palliative simple mastectomy for the 2 cases who were metastatic at presentation, total mastectomy plus axillary dissection in 13 cases and breast conserving therapy for 6 women, one of whom was treated by wide excision only, for pure ductal carcinoma in situ (DCIS), without axillary surgery.

Neoadjuvant chemotherapy was done in 9 cases (3 with inflammatory breast and 6 with a tumor >= 5 cm); among these 9 women, 5 were treated with radical surgery, 1 refused

surgery and 3 were lost to follow-up. Fourteen patients received adjuvant chemotherapy (5 cases after conservative surgery and 9 cases after radical surgery). Palliative chemotherapy was done in two patients at first presentation.

Sixteen patients underwent post-operative radiation: the two patients treated by breast conservation, nine after radical surgery and one after palliative mastectomy; the patient who refused curative surgery and one patient lost initially to follow-up and presenting later in an inoperable condition received also radiation.

Two patients received ovarian irradiation; chemical ovarian suppression was performed in 8 cases. Five patients received Trastuzumab.

Pathology

Pathologic findings revealed a mean tumor size of 3.9 cm ranging from 0.2 to 14 cm. Multifocality was noticed in 4 cases. Invasive carcinoma of no special type was the most common histological subtype seen in 84 % (21 cases). DCIS was present in 14 cases (56 %) among which one case of pure DCIS and 5 cases with high grade DCIS with comedonecrosis >50 % of the tumor. Lymphatic vessel invasion was seen in 4 cases. Pathologic nodal status, known in 18 cases, revealed metastases in 9 cases (≥4 N+ in 4 cases). Pathologic findings and results of immunohistochemical stains are shown in Table 1 and Fig. 1. HR status was known in all cases. The 2 cases having an intermediate HER2 score didn't show HER2 gene amplification with the CISH technique. For the Ki67 positive group, 54 % (7/13) were triple negative. The mean percentage of positive Ki67 labeled tumor cells was 43.8 %. Positivity for the p53 antigen was noticed in 9 cases among which 8 were triple negative. Only 20 tumors could be classified (all were invasive carcinoma of no special type): 5 luminal A (25 %), 6 luminal B (30 %), 1 HER2 (5 %), 6 triple negative/basal-like (30 %) and 2 triple negative/unclassified (10 %). Two out of the 6 basal-like tumors were grade III and 4 were N+.

Table 1 Pathological and immunohistochemical characteristics of the tumors

Tumor grade	
1	3 (12 %)
2	11 (44 %)
3	11 (44 %)
Lymph nodes	
No axillary dissection	7
Negative	9 (50 %)
Positive	9 (50 %)
1–3	5
4–9	4
Histological subtype	
Invasive carcinoma of no special type ± DCIS	21 (84 %)
Infiltrating lobular carcinoma ± DCIS	2 (8 %)
Pure DCIS	1 (4 %)
Mucinous carcinoma	1 (4 %)
HR status (25 cases)	
ER+/PR+	12 (48 %)
ER-/PR-	12 (48 %)
ER+/PR-	1 (4 %)
ER-/PR+	0
HER2 status (20 cases)	
0	5 (25 %)
1	6 (30 %)
2	2 (10 %)
3	7 (35 %)
Ki67 (17 cases)	
Positive	13 (76.5 %)
Negative	4 (23.5 %)
p53 (15 cases)	
Positive	9 (60 %)
Negative	6 (40 %)
CK5/6 (8 triple negative cases)	
Positive	6 (75 %)
Negative	2 (25 %)

Outcome

The follow-up period ranged from 1 month to 12 years. Twelve patients were completely lost to follow-up after the initial treatment. Two patients experienced locoregional recurrences (in an average period of 6 months each one) in the ipsilateral chest wall (mastectomy scar), one of whom had also a contralateral breast cancer treated by radical surgery (Patey). Except for the two women who were metastatic at presentation and the 12 patients lost-to follow-up, distant metastases occurred in 6 out of 11 patients (54.5 %) during follow-up, in an average period of 39 months. All these cases were N+, 3 were classified T4d, 4 were grade III, 3 were ER and PR-, 3 were HER2+, 3 were Ki67+ and 4/5 were p53+, the 6 cases were classified into 1 luminal A, 2 luminal B, 1 HER2, 1 basal-like and 1 unclassified.

Twelve patients were dead at the time of study (six patients with metastatic disease among the 13 for whom we have follow-up data and six patients among the 12 patients lost to follow-up (data recorded from death certificates but we don't know if these 6 patients died from disease progression). The overall survival at 3, 5 and 10 years was respectively 95, 85 and 75 %. These rates did not vary significantly with the tumor size, the surgical procedure, the nodal status, the HR status neither with the HER2 status. The survival was significantly lower in the grade III tumors (p=0.04) (Fig. 2) and the triple negative tumors (p=0.03) (Fig. 3). Disease specific

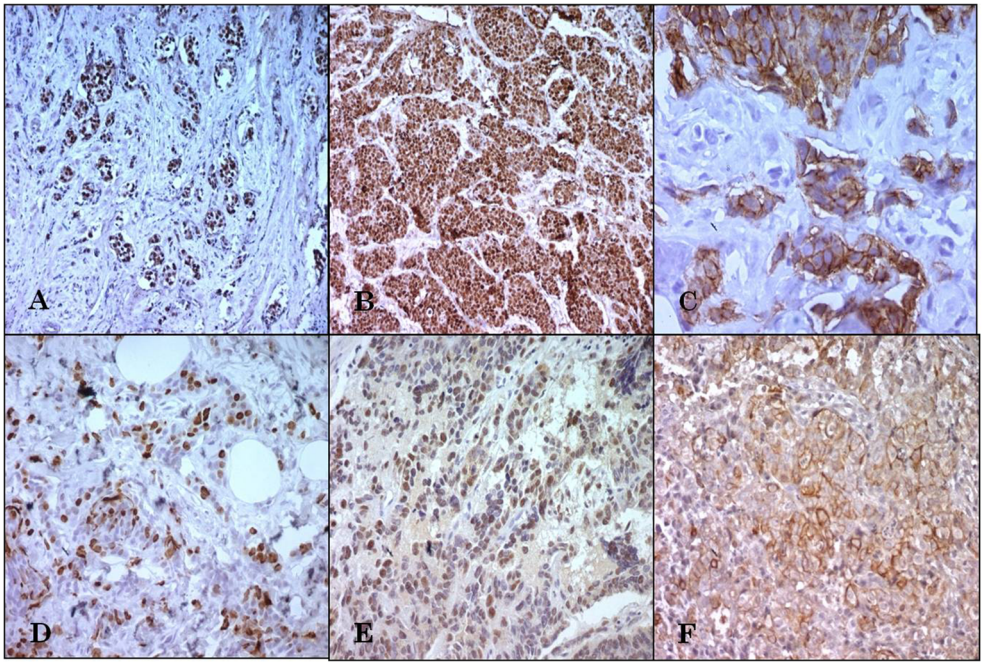

Fig. 1 Immunohistochemical expression of ER (A, 4x), PR (B, 4x), HER2 (C, 20x), Ki67 (D, 10x), p53 (E, 10x) and CK5/6 (F, 10x)

overall survival was not recorded seeing that almost half of the patients were lost to follow-up and that the cause of death is usually not mentioned on the death certificate.

Three patients had a successful pregnancy after curative treatment. Three patients suffered from reactive depression at the follow-up period.

Discussion

Breast cancer occurring in young women is uncommon in the absence of family history or genetic predisposition. The proportion of women diagnosed with breast cancer aged 25 years or below over the 21 years period compared to all women with breast cancer seen at our institution during that time was 0.5 %. In a Pakistani series, among all patients with breast lump up to the age of 25 years, 1.9 % were diagnosed with carcinoma [15]. This proportion was 1.7 % in a Nigerian series [16] and another recent study [17]. Age Standardized Incidence Rates of early onset breast cancer vary little between populations and the rates have been more or less stable in most countries in the past 20 years and generally remain low [3].

The incidence of a positive family history of breast cancer in the current series was 16 % which may reflect the presence of a breast cancer susceptibility gene. This parameter could be underestimated, as a detailed family history of breast cancer may not have been documented in all cases. Hereditary breast

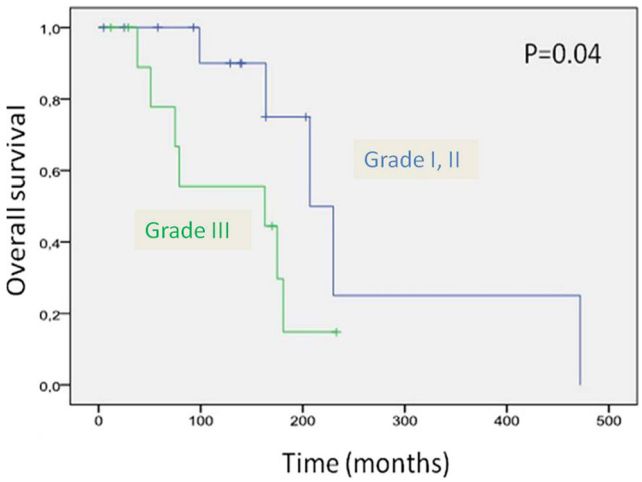

Fig. 2 Kaplan-Meier survival curves showing overall survival in grade I/II and grade III breast cancer groups

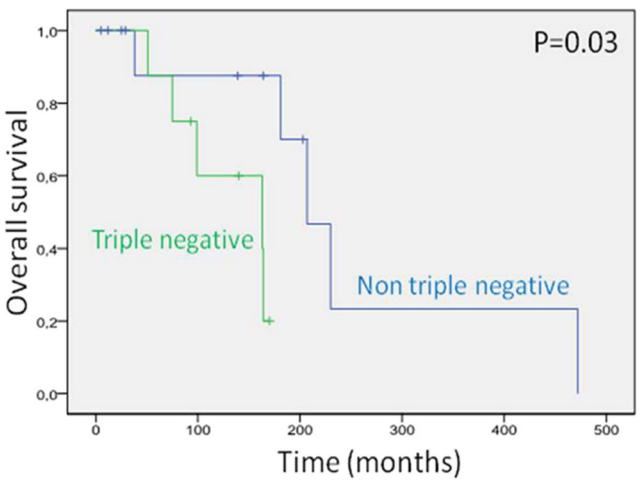

Fig. 3 Kaplan-Meier survival curves showing overall survival in triple negative breast cancer and non triple negative breast cancer groups

cancer accounts for 5-10 % of all breast carcinomas and most are attributed to autosomal dominant germline mutations in breast cancer susceptibility gene 1 (BRCA1) and breast cancer susceptibility gene 2 (BRCA2), these women are at an increasing risk of developing breast cancer at a young age [18, 19]. The Li-Fraumeni syndrome caused by germline mutations in the p53 gene and Cowden syndrome caused by a mutation in the PTEN gene are rare syndromes accounting also for hereditary breast cancers [19]. In one series of 28 patients aged less than 25, genetic testing for BRCA1 and BRCA2 mutations was performed in 12 patients and mutations were found in 25 % of them [6]. The positive family history of breast and/or ovarian cancer is the most important predictor of increased likelihood to be carrier of BRCA mutation especially if the affected family member is a first degree relative, diagnosed less than 50 years or had bilateral breast cancer [19, 20]. However, Yao S et al. [8] in their series of 54 patients aged less than 25 didn't noticed any case of familial history of breast or ovarian cancer. Our patients had not genetic testing for BRCA1 and BRCA2 mutations which is not routinely available at our institution.

Classic risk factors for breast cancer are increasing age, family history, early menarche, late menopause, estrogen use, nulliparity, late age at first full-term pregnancy, absence of breastfeeding and dietary factors such as alcohol [21]. Risk factors of early-onset breast cancer are not very clear [22]. Early childbearing, seen in 24 % of our patients, seems to be a risk factor for developing breast cancer before the age of 35 or 40 [1, 23]. Long duration of lactation seems also to be associated with early onset breast cancer [23]. Other reported risk factors of breast cancer in young women include multiparity, prior mantle radiation for Hodgkin lymphoma and oral contraceptive use [17]. Developmental factors such as very high birth weight (of the patient) or very high maternal age (of the patient's mother), growth rate in childhood, and attained height have been reported as potential risk factors as well [19, 22].

Breast cancer in adolescents and young women tend to be larger when diagnosed and to have a longer history of a palpable mass than tumors diagnosed in older women [24]. All our patients presented with breast complaints, and even women with a first degree history of breast cancer didn't undergo breast cancer screening. In our study, average tumor size was 3.9 cm with 80 % of patients classified >= T2 and mean time to consultation was 7.5 months. As we reported recently, breast cancer remains diagnosed at advanced stages in Tunisia [1]. In another Tunisian series of 72 young patients aged less than 35 years, mean tumor size was 5.2 cm and time to diagnosis was 5 months [5]. In fact, young women are often less likely to seek early medical advice, leading to later detection often at more advanced stages [23]. However, in two series of women younger than 25 years with breast cancer [4, 7], T1 tumors accounted for 46 and 58 % respectively with an average and median tumor size of 28.78 and 20 mm respectively and an average and a median duration of symptoms of 6.6 months and 4 weeks respectively. Population education and increasing breast cancer awareness play most probably a great role in prompt diagnosis of early onset breast cancer. Other factors that contribute to the diagnosis delay in young women are the unexpectedness of breast malignancy within this age group leading to the lack of screening mammography advisement [4] and the limited accuracy of physical examination and imaging studies in young women; mammography is in fact less sensitive in very young women due to the increased density of breast [19, 23]. Diagnostic delay of >3 months have been shown to be a poor prognostic factor [8]. Finally, the severity of the disease (adverse pathological and biological findings) in young women plays also a great role in advanced stage at diagnosis. For all these reasons, it is unusual for breast cancer in young women to be detected on screening mammography and the diagnosis tends to follow identification of a palpable mass.

In our study, pathologic findings were comparable to those of previous series. Invasive carcinoma of no special type was the most common histological subtype and only one patient had pure DCIS. No cases of secretory breast carcinoma, typical of children and teenagers or medullary carcinoma typical of BRCA mutations were recorded. The proportions of node positive cases and grade II/III tumors were 50 and 88 % respectively. In the literature, breast cancer in very young women has distinct and adverse histopathological characteristics in comparison to less young premenopausal women, showing higher proportions of histological high grade, advanced stage and node positive tumors, vascular or lymphatic invasion as well as a more aggressive biological phenotype with a lower HR positivity and a higher overexpression of HER2 [4–7, 18, 20, 22, 24–26]. Other factors that occur more frequently in young women include overexpression of p53 and high tumor proliferation rate which are associated with more aggressive tumors [20, 25, 27]. In our study, the mean tumor proliferation rate as determined by Ki67 was 43.8 % in the 76.5 % cases of Ki67 positive cases and p53 was positive in 60 % of tested cases.

Breast cancer is nowadays considered as a heterogeneous disease based on different molecular subgroups and this molecular subclassification could exhibit a prognostic value [28]. Some studies have shown that the aggressive nature of breast cancer in young women is the result of higher frequencies of aggressive breast cancer molecular subtypes among younger patients [26]. Sorlie and Perou identified 5 categories of breast cancer based on different patterns of gene expression: luminal A, luminal B, basal-like, HER2-positive and normal breast-like [29, 30]. To approximate this genetic profiling and facilitate the classification into subtypes, these subgroups were defined according to routinely assessed immunohistochemical markers as follows: luminal A (ER+ or PR+ and HER2−),

luminal B (ER+ or PR+ and HER2+), HER2 overexpressing (ER− and PR− and HER2+), basal-like (ER, PR-, HER2-, CK5/6+, and/or EGFR+) and unclassified (negative for all five markers) [13]. In 2011, the St Gallen International Breast Cancer Conference suggested a surrogate definition of intrinsic subtypes of breast cancer: luminal A (ER + and/or PR+, Ki67 low and HER2-), luminal B (ER + and/or PR+, Ki67 high and/or HER2+), HER2-positive (ER-, PR- and HER2+) and triple negative (ER-, PR-, HER2-) [31]. It has been shown that basal-like and HER2 overexpressing subtypes are the most aggressive subtypes of breast cancer and that they are over-represented among young women, which could partly account for the worse outcome of young age [17, 18, 22, 28, 32]. In our study, the Kaplan-Meier method showed that triple negative subtype was significantly associated with poor overall survival. We have previously shown that according to immunohistochemical-based molecular subclassification, the proportions of luminal A, luminal B, HER2 and triple negative subtypes in a Tunisian population were 51.5, 16, 14.5 and 18 % respectively [33]. In this small series of women aged less than 25, 20 cases were classified into 25 % luminal A, 30 % luminal B, 5 % HER2 overexpressing and 40 % triple negative. Few data with conflicting results are available in the literature about molecular breast cancer subtypes among young women; a probable reason could be the difference in definitions of the surrogate subtypes. In a large population-based American series of 5605 women aged 15 to 39 years, luminal A was the most commonly diagnosed subtype (41.1 %) as for older women, followed by triple-negative (19.1 %), luminal B (15 %) and HER2 overexpressing (8.7 %); however, compared with older women, young women had higher proportions of luminal B, triple- negative, and HER2 breast cancer subtypes [17]. In contrast to young breast cancer patients in western countries, Taiwanese patients have a higher prevalence of luminal A and a lower prevalence of basal-like subtype, compared with older (>50 years) patients and the reasons remain unclear [13].

Distribution of molecular subtypes among young women is still poorly understood, BRCA1 mutations were reported to be associated with triple negative breast cancer, which may contribute to the early age distribution of this subtype [17]. Our data are too limited to indicate distribution of molecular subtypes in women under 25, but triple negative tumors seem to be overrepresented in this very young population.

Very young women with breast cancer are faced with unique and specific medical and quality-of-life issues including concern over loss of fertility, contraception after cancer, cancer during pregnancy, sexuality and body image, emotional distress, family and professional problems, anxiety, depression and genetic issues. All these special considerations complicate treatment decision-making. When diagnosed with breast cancer at such a young age, these women should benefit then from coordinated multidisciplinary care including psychological support [18, 23].

Table 2 Comparison between different series of breast cancer in women aged less than 25 years

Reference	[4]	[7]	[8]	[9]	Our series
Number of cases	15	13	54	55	25
Duration of study	26 years (1970–1995)	29 years (1977–2005)	26 years (1980–2005)	33 years (1979–2012)	21 years (1993–2013)
Country	United Kingdom	France	China	Iran	Tunisia
Incidence among all breast cancers	NS	0.13 %	0.48 %	1.17 %	0.5 %
Mean/median duration of symptoms	4 weeks	6.6 months	4 months	NS	7.5 months
Family history of breast cancer	13 %	23 %	0 %	2 %	4 (16 %)
Bilateral breast cancer	NS	7.7 %	NS	10 %	1 (4 %)
Breast cancer during pregnancy and/or lactation	NS	7.7 %	22 %	10 %	1 (4 %)
Mean/median size	20 mm	28.78 mm	NS	57 mm	39 mm
Grade III	69 %	53.8 %	NS	7.1 %	11 (44 %)
Pure DCIS	13 %	0 %	NS	1.9 %	1 (4 %)
Nodal involvement	33 %	23 %	NS	63.2 %	9/18 (50 %)
ER	62 %	61.5 % (hormone receptors)	29.6 %	42.1 %	13/25 (52 %) (ER and/or PR +)
PR	NS		36 %	40 %	
HER2	18 %	1/3 (33.3 %)	22.2 %	12.5 %	7/20 (35 %)
5 years overall survival	≈70 %	91 %	55.5 %	NS	85 %

NS not specified

The optimal treatment strategy of breast cancer in young women is subject to debate. Breast conserving surgery produces an acceptable cosmetic appearance and less psychological impact when compared with mastectomy but is associated with an increased risk of local recurrence; nevertheless, different studies failed to demonstrate that conservative surgery in young women has a negative impact on survival [24]. Young patients should receive adequate counseling so that they can make an informed choice regarding treatment [19].

Pathological and biological characteristics of breast cancer in young women have negative impact on the rate of local recurrence and overall survival. Very young women are more likely to have local recurrences, higher failure rates both with mastectomy and breast conservation and to have a poorer overall survival compared to their older premenopausal counterparts [6, 18, 19]. A high mortality rate is observed among women aged less than 25 years: 69 % experienced recurrence and died of their disease in a series including 15 women [4] and 5-year disease-free survival was 66.5 % in another study of 13 women [7]. In a series of 54 patients ≤25 [8], 48.1 % out of all patients were dead by the end of the study and the 5-year overall survival was 55.5 %. In our series, at the time of study, 12 patients (48 %) were dead.

Table 2 shows a comparison between the clinicopathological features of breast cancer in women aged less than 25 years in different series.

Previous reports have shown that the very rare breast cancer occurring before 25 years-old doesn't differ from young women aged less than 35 or 40 in terms of family history, pathology and prognosis [4, 7] and that there are no significant differences regarding histological subtype and HR status in comparison to premenopausal women older than 25 [6]; but whether patients in their early twenties are special cases remains unclear given the rarity of studies and the small number of specimens.

In addition to the inherent weakness present in any retrospective study, this analysis had multiple limitations. First of all, it would have been more interesting to have a direct comparison group of patients older than 25 years of age. The major limitation of this study is the small number of specimen such that a relatively low number of events could have an impact on our results and may account for the high recurrence rate. The incidence of the disease was truly low since breast cancer in women less than 25 is an uncommon condition in a single institution. Moreover, since we analyze data over a 21-year period, improvements in treatment approaches and chemotherapy regimens which differed over the years would have an impact on overall survival. In the present study, the St Gallen categories were not used for subtyping breast carcinomas as we have a small series with ER, PR and HER2 available for only 20 tumors and Ki67 was not known for all these 20 tumors. The immunohistochemical classification we have been using ignores the Luminal B proliferative subgroup and most likely, some HR positive cases with high Ki67 labeling index were classified as Luminal A cancers (being ER+/PR+/Her2-). For instance, in a Hungarian study investigating 41 breast cancer patients under the age of 35, the following ratios were found: Luminal A: 10/41, Luminal B HER2+: 8/41, Luminal B HER2-: 7/41, HER2+: 8/41, Triple negative: 8/41 [34]. Finally, the follow-up period, although relatively long, is not likely adequate and nearly half of the patients were lost to follow-up.

Conclusion

Breast cancer diagnosis in women aged 25 years and younger is uncommon and accounted for 0.5 % of all invasive cancers seen at our institution over a 21-year period. In agreement with previous studies, we found that these patients have high proportion of large, node positive, high grade and advanced stage tumors.

The major facts disclosed by the study of this small series is the advanced stage at clinical presentation and the high proportion of patients lost to follow-up. We emphasize then the importance of medical education of the Tunisian population including awareness of risk factors, early signs and self-examination technique as well as the importance of physician education regarding the importance of eliciting a family history and risk factors of breast cancer, screening advisements for appropriately selected young women, prompt diagnosis, the importance of obtaining a tissue diagnosis on all palpable lumps in women of any age and early referral to psychological support.

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