Journal Homepage: -www.journalijar.com
INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)
Article DOI:10.21474/IJAR01/9266
DOI URL: http://dx.doi.org/10.21474/IJAR01/9266

RESEARCH ARTICLE

BREAST CANCER IN YOUNG MOROCCAN WOMEN UNDER AGE OF 40 YEARS, A RETROSPECTIVE STUDY.

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Manuscript Info

Manuscript History
Received: 12 April 2019
Final Accepted: 14 May 2019
Published: June 2019

Key words:-
Breast cancer; Epidemiological; Retrospective study; Cancer incidence; Treatment; Prognostic factors.

Abstract

Purpose: This study aimed at evaluating the epidemiological, clinical, pathological and therapeutic characteristics of breast cancer in young Moroccan women.

Patients and methods: About 60 cases of breast cancer in young women under the age of forty, haves been admitted at the radiation service of the military hospital Mohammed V of Rabat for the period starting from 01 January 2010 and ending at 31 December 2015.

Results: The frequency of breast cancer in young women who were under 40 years old was about 18.5%. The average age was 35 years. About 25% of theme had a family history of breast cancer. Tumors classified T2 were the most frequent (numerically 45%), followed by T1 tumors (31.7%). N0 forms were the most common (76.6%) followed by N1 forms (18.3%). Regarding anatomopathological aspect, the invasive ductal carcinoma has been the most frequently, noticed in 90.1%, SBR II in 57% and SBR III in 34%. Hormone receptors were positive in 66.6% of cases and HER2 over-expressed in 35% of cases. In regard to therapeutic plan, all patients had undergone surgical treatment, which was identified as radical in about 66.7% of cases and conservative in 33.3%. The radiotherapy has been delivered to 59 patients and the chemotherapy has been prescribed for 57 patients. The hormonotherapy has been prescribed for 40 patients and monoclonal antibody trastuzumab for only 19 patients. The overall 3-years survival rate was found to be 92.1%.

Conclusion: The incidence of breast cancer in young Moroccan women is so high; this could be explained by the existence of familial medical history and genetic forms. Our study confirms the data found in the literature advocating more advanced forms and worse prognosis of breast cancer in young patients. An improvement of this prognosis could be obtained after the implementation of a cancer screening program, in young women having a potential risk factor to suffer a breast cancer, followed by a well-adapted medical care taking into account the known prognostic factors.

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Introduction:-

As it is well-known, the breast cancer (BC) represents the most common cancer among women around the world. Its incidence don't stop elevating even though the many progress of science in terms of both diagnosis and treatment. Indeed, the risk for a woman to be affected by a BC over her life, is about one in 10 women [16]. Collected data notifying that BC increases with age but doesn't spare young women. Indeed, in young women, the diagnosis of BC is often unexpected and therefore delayed. It has particular epidemiological aspects, and confronts difficulties diagnosis by the usual means of investigation, mainly mammography, given the increased density of the breasts at this age.

Depending on conclusion delivered by almost authors, BC of young women has epidemiological, diagnostic and prognostic characteristics going up together to consider the youth as a pejorative prognostic factor. Indeed, it is often, at these young women, a greater genetic predisposition is found, that is mostly correlated to a low-survival and high-recidivism rates compared to their more aged peers. Culturally, the breast organ, as a major symbol of the femininity, making a treatment, particularly surgery, in these young women hardly acceptable or even strongly rejected.

The principal goal of this work is to make a deep analysis of the epidemiological, clinical, therapeutic and prognostic characteristics related to BC suffered by Moroccan young women aged under 40 years, this, through a retrospective study that were established at the radiotherapy department of Military Hospital of Instruction Mohammed V of Rabat (MHIMV-Rabat).

Patients and Methods:

This is about a retrospective study spanning in a period of 6 years (from 1 January 2010 to 31 December 2015) and concerning 60 cases of BC in young women aged under 40 years, those who were taken medical care at oncology-radiotherapy service of MHIMV-Rabat.

In a first step, we have proceeded to sort concerned treated patient dossiers in order to highlight only those related to a BC regardless of their age (325 cases were found). Then, we selected the dossiers of young patients who don't exceed an age of 40 years (60 cases were found). A farm return has been punctually completed for each case.

In a second step, the SPSS software was used in order to perform a statistical analysis on the collected data. The data processing was done in percentage, average or mean. Survival quantity has been calculated according to the Kaplan-Meier method, the date of origin is the date of histological diagnosis of a BC.

All patients had undergone both mammography and ultrasound medical examinations and the concerned diagnosis has always been confirmed by an anatomy-pathological examination. Possible metastatic spread has been investigated by an X-ray chest examination, hepatic ultrasonography and bone scintigraphy or TAP-CT scan. The relevant cure was a function of the clinical stage, it included a surgery, most often radical associated with radiotherapy, with or without chemotherapy or hormone therapy. Post-therapeutic surveillance was both clinical and radiological. Patient follow-up has been extended until April 2018. Tumor classification has been done using the TNM classification of the 7th edition publish on 2010. The collection of data has been done with the respect of the anonymity of patients and a strict confidentiality of their information.

Results:

Thought the period in which the study has been performed, about 325 women with BC were treated at radiotherapy department of MHIMV-Rabat. Among of them, 60 were aged equal or less than 40 years; which represents, statistically, a frequency of 18.5%. The epidemiological and anatomy clinical characteristics of the concerned patients are well-summarized in Table.1.

The average age of our patients was about 35 years with extremities of 22 and 40. The most affected age group was between 36 and 40 years old (numerically, 53.3% of cases). With the regards to risk factors, the average age of menarche was about 13 years (11-17). The average age of the first pregnancy (specified in 18 women) was about 22.3 years (17-34). In our series, we signal a predominance of pauciparity (1 to 2 children) and multiparity (3 to 4 children), and their rates are,

Table 1: Epidemiological and anatomoclinical characteristics of patients.

Characteristics	number	Percentage (%)
Family history of breast cancer	15	25
Tumor size		
T1	19	31.7
T2	27	45
T3	9	15
T4	5	8.3
Histology		
DCI	54	90.1
Others	6	9.9
Grade		
I	5	9
II	32	57.1
III	19	33.9
Invasive ganglion		
Curage -	22	36.7
Curage +	38	63.3
< 4 N+	19	31.6
≥4 N+	19	31.6
Hormonal receptors		
RE+RP+	40	66.6
RE-RP-	15	25
Dissociated	4	6.8
Unknown	1	1.6
HER2 study		
HER2+	21	35
HER2-	39	65

respectively, of 44.2% and 42.3%; while large multiparas (≥ 5 children) represent only 2%. Oral contraception was used in 27 women (45%). The mean duration of it intake was 78 months (ranging between 6 and 216). The hormonal state has been identified in all patients whom were still under genital activity. The family history of a BC was found in 15 patients, so representing about 25% of cases.

The mean consultation time was about 5 months (1- 24). The revealing symptomatology has been specified in 58 patients. Overall, the most frequent reason for consultation was represented by the self-examination of a breast nodule, since we found it in about 81.1% of cases. Our study showed that the left breast was affected in 35 patients, or 58.3%. right breast in 24 patients or 40% and bilateral has been suffered by a single patient. The nodule localization was identified in 50 patients, statistically, with a rate of 83.3%. This nodule, mostly, sat at the supra-external quadrant in 54% of cases. Mammography-ultrasound examination was performed in the 60 patients. Various mamography aspects were classified according to the ACR classification; we noted predominance of tumors classified as ACR4 with a rate of 35% and as ACR5 with a rate of 35%. Histopathological examination was performed in all patients to confirm the malignant nature of the tumor, with 23 biopsies (38.3%) and 37 extemporaneous examinations (61.7%).

The extension rapport was normal for all patients. X-ray chest and AP ultrasound were performed in 50 patients, the remaining patient were benefited from a TAP-CT scan. Bone scintigraphy was performed in 57 of them.

Following clinical examination and the extension rapport, we note a predominance of patients with a T1 or T2 lesions with rates of 31.7% and 45%, respectively. N0 forms were the most common with a rate of 76.6% followed by N1 forms (18.3%). Any of known metastasis case wasn't observed in all of them.

The patients were regrouped according to the various stages defined by the international union against cancer (UICC). Thus, stages I, IIA and IIB seem to be the most frequent with 30%, 35% and 21.7%, respectively. Regarding the therapeutic care, all of the patients have benefited from a surgical cure. It is about a primary surgery for 54 patients and neo-adjuvant chemotherapy post-surgery for 3 of them. The three remaining patients were benefited only from surgery cure. Breast surgery was performed in all patients, it was identified as radical (radical mastectomy) in 40 of them so 66.7%, conservative in 20 of them (33.3%). Axillary surgery consisted of a dissection lymph node in all patients who have undergone breast surgery cure. The sentinel lymph node technique was not performed in any of the concerned patients. The histological type was identified in all of them. The ductal carcinoma infiltrant (DCI), currently called non-specific infiltrative carcinoma, was the more predominant at 90.1%, whereas other histological types were found at lower rates. Tumor size was determined in 54 patients; mean height was 3 cm with extreme values of 0.5 and 21 cm. The histopronotic grade of Scarff-Bloom and Richardson (SBR) was reported in 56 patients. The SBR II grade was the most frequent at a rate of 57.1%, followed by grade SBR III at a rate of 33.9%. The search of emboli tumors were reported in 56 patients, 26 of whom were positive, representing a rate of 43.3%. The intraductal quota was present in 24 patients at a rate of 40%. All of them had healthy margins of excision. Ganglion dissection was sufficient (greater than or equal to 10) in 51 patients. The mean value of the removed ganglions was 13 lymph nodes. The cure was positive in 38 patients at a rate of 63.3% of which 50% had an invasion of 4 ganglions or more. The proliferation index Ki 67 has been researched by immunohistochemical technique in only 10 patients, 2 of whom had a rate of between 10% and 20% while the remaining 8 had a rate> 20%.

The search for hormone receptors (HR) was performed in 59 patients. These receptors of estrogen (ER) and progesterone (PR) were both positive in 66.6% of cases, dissociated in 6.8% and negative in 25%.

The hercept test was carried out in all patients by immunohistochemistry technique, complemented by the FISH or CISH method in case of HER2 score (2+), 35% of patients had an over-expression of HER2.

Of all of the examined patients, 57 had received chemotherapy, where 54 of them (90%) as adjuvant while 2 cases had received neo-adjuvant and a case before and after surgery. The delay between surgery and adjuvant chemotherapy varied between 1 and 5 months with a mean of 2 months. The patients had benefited from different protocols of chemotherapy based on anthracyclines, taxanes or both. The number of cures ranged from 6 to 8. About 44 patients (77.2%) had received FEC plus Docetaxel.

In our series, that consists of the 60 patients who had undergone oncologic surgery, 59 of them had benefited from external radiotherapy. Only one patient had lost it live after surgery. The average time between surgery and radiation therapy for patients who had received chemotherapy was (5 +/- 1.8) months, whereas it was 1.7 months (1 - 2), among those who didn’t receive chemotherapy. The mean time between chemotherapy and radiotherapy was about 1 month (1 – 2.75).

Target volume shapes change from one case to another and were represented by the tumor bed (breast or chest wall) associated or not with one or more ganglionic areas (the area clavicular, subclavicular and internal mammary chain). About 34% of patients were irradiated only on the tumor bed and 66% of them on the tumor bed and ganglionic areas together. A dose of 50 Gy was given at a rate of 2Gy per treatment sit, 5 sits per week. A boost of 16 Gy on the tumor bed was administered to 15 patients. The staggering was (35 +/- 2) days (31-45). Radiotherapy complications were reported in 17 patients, or 28.8% of cases, and consisted of radiodermatitis grade I in 9 patients, grade II radiodermatitis in 5 patients, grade III in 2 patients and one case of dysphagia. Hormone therapy was prescribed in 42 patients who had positive hormone receptors. It consisted of administering anti-estrogens such as tamoxifen 20mg/day in 38 patients and tamoxifen with "SWITCH" to an antiaromatase in 4 patients. The mean time of taken those medical drugs was 5 years (2 – 10). The targeted therapy used was trastuzumab in patients overexpressing HER2.

In our series, patients were medically followed until April 2018. The mean of the concerned follow-up was 46 (27-62) months with extremes of 3 and 99 months. 75% of patients had stayed alive, 8.3% had died, while 16.7% were

lost of their sight. No locoregional relapse was reported in our series. However, 13 cases of relapse metastatic infections were recorded (ie 21.7% of cases). The most common metastatic site was the bone (61.5%). The mean time to oncoming of metastatic relapse was 12 (6-29) months. 53.8% of relapsed patients aged of 35 years or less with preponderance of tumor size greater than 2 cm (84.6%), 69.2% of patients were SBR II with tumoral emboli, 50% had 4 positive lymph nodes or more and 76.9% of relapsed patients had a negative hercept test. The 3-year overall survival rate was 92.1% whereas the 5-year overall survival rate was 88.9% (Figure 1). The rate of 3-year overall survival was 87% in women aged 35 and less whereas it was 96.4% among women aged 36 to 40 (Figure 2). The survival rate without relapse was 94.2% at 3 years and 91% at 5 years (Figure 3). The survival rate without relapse was better for women aged 36 to 40 compared to less-aged ones (Figure 4).

Discussion:-

The age limit for defining BC in young women is controversial subject. In the literature, some authors set it to 30 years old others to 35, 40 or 45 years [8, 7, 3]. In our study, an age limit of 40 years old has been set.

BC remains a disease of the menopausal woman, it is uncommon in the young woman. In our series, the observed frequency was 18.5% in patients aged less than 40 years and 8.75% for the ones under 35 years, which exceeding by 2 to 3 times the frequency claimed by the occidental series and concordant with the frequency showed in the Maghreb series [18]. This difference in frequency could be explained by the discrepancy in age pyramids between populations. Indeed, more than half of the age pyramid in Morocco is represented by a young people under 40 years old [22]. The

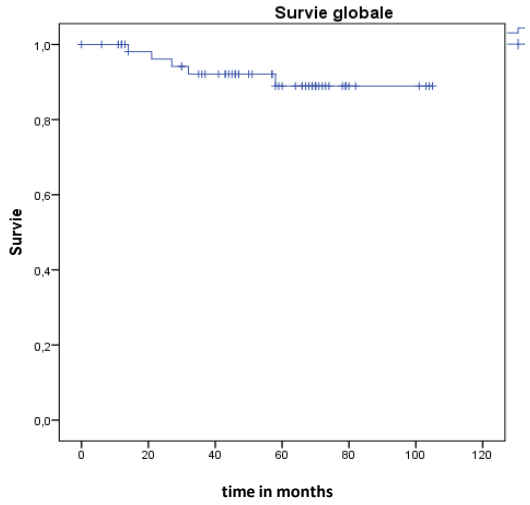

Figure1: Kaplan-Meier overall survival curve.

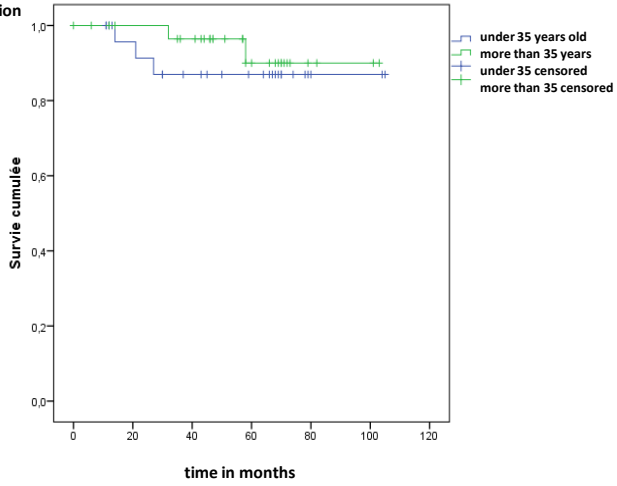

Figure 2: Overall survival curve according to age.

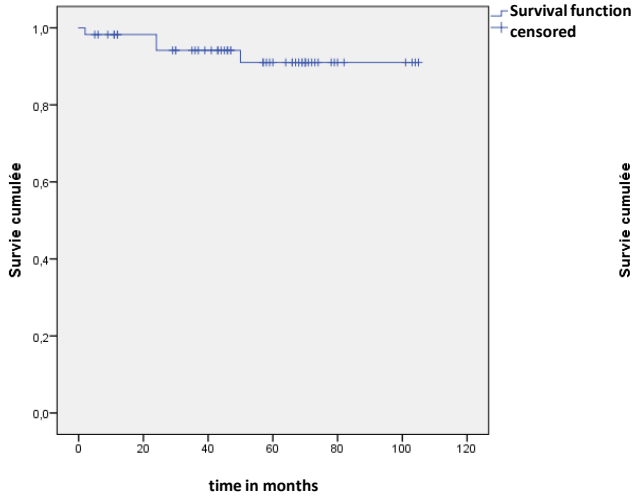

Figure 3: Kaplan-Meier Relapse-Free Survival Curve.

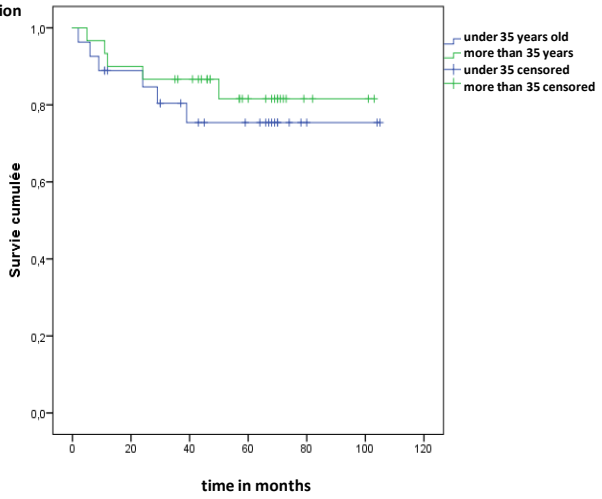

Figure 4: Relapse-Free Survival Curve according to age.

average age of oncoming of BC in young women in the literature is often after 30 years [18], which is in good agreement with our series where the average was 34.9 years.

The results of most epidemiological studies are consistent in impact of the age of the first completed pregnancy and parity on the occurrence of a BC. The meta-analysis of Ewertz et al [15] also goes in this path, since it concludes that a first pregnancy before age 30 reduces the risk by 25% compared to woman who has not had a child, and a first pregnancy before the age of 20 decreases the risk of 30% compared to a woman who had her first pregnancy after 35 years. In our series, the average age of first pregnancy was 22.3 years with a predominance of pauciparity and multiparity with respective rates of 44.2% and 42.3% while nulliparity were accounted for only 11.5%.

The influence of oral contraception in the happening of BC seems to be greater in the young woman than in the aged one where no elevation of the risk was found [3]. Another study in a population of young women (aged between 24 and 43 years) had shown that oral contraception would slightly increase the risk of BC. However, this increase had been linked to a specific type of estrogen-progestin (namely the tri-phasic pill) [22]. It remains to be noted here, that, the risk of BC occurring in women using oral contraception is even higher when the woman having the BRCA1 and BRCA2 gene [28]. In our series, about 45% of patients had used oral contraceptives, averagely, for a duration of 78 months.

With the regard to the combined data from 52 epidemiological studies, it seems that, 20 to 30% of women with BC have a family cancer background [10], but only 5 to 10% of cancers had been find their origin in genetic mutations [32]. The risk of developing cancer is so more important that the family cancer history has appeared young, that it is bilateral or that is figured in a first-degree relative (sister, mother and daughter). The risk of developing a BC called penetrative, is estimated according to the series between 60 and 85% before 70 years for BRCA1 and BRCA2 versus 10% in the general population [2]. Before 45 years old, this risk would be lower for BRCA2 around 7% versus 25% for BRCA1. Hence, the great interest of oncogenetic consultations allowing the search for mutation of these genes in

individuals having a personal (and/or) family history of breast and ovarian cancer, implicative of a genetic predisposition. It should be emphasized here, that, in our series, 25% of cases had family history of BC.

The delay between the oncoming of the first clinical symptoms and the first consultation may be longer or shorter and different depending on a given case. Indeed, this period is still late in the under-developing countries, because of the lack of means and access to health facilities, without trim the developed countries where the delay would be due to insufficient awareness of the young population against this cancer as well as a high frequency of other benign breast diseases [14]. In our series, the mean time to have consultation was of 5 months and the self-examination of a nodule was the mode of discovery of breast cancer in 81.1% of the cases which is in line with the data of provided by the literature.

Given the fact that a high density of the young woman's breasts, several authors [4, 23] report high false negative mammography, and all of them point out on the poor performance of this diagnostic procedure when it is performed at a young age. According to conclusions in the study reported by Kolb et al, the sensitivity of mammography significantly decreases with increasing density. Therefore, this sensitivity is about 98% for breast density type I, 83% for type II, 64% for type II and only 48% for type IV [26]. For some authors, this weakened sensitivity is responsible for late diagnosis for this portion of age [24].

Breast ultrasound is the essential complementary examination as soon as there is a anomalous of clinical aspect, radiological or suspected cancer. It allows a better definition in the young woman with high-dense breasts. Advantageously, it has the same sensitivity and specificity at the young woman as well as at the older one [5].

With regard to the pathological examination, and as for the elderly woman, the most frequent histology type is the invasive ductal carcinoma [27, 13], found in 90.1% of patients showed in our series. But what makes the specialness and explains the aggressiveness of the cancer suffered by young women is the frequency of the forms of grade SBR III and tumors not expressing hormone receptors. In comparative studies conducted by Colleoni et al. and Khotari et al. Tumors that do not express hormone receptors significantly were higher in the group of young patients compared to aged ones. They reported the rates of tumor characterized by negative hormone receptors of 49.1% and 70%, respectively [27, 13]. It was 25% in our series. A recent study conducted by Cancello et al. also showed a higher frequency of triple negative forms in young women compared to older ones [9].

The determination of ganglionic invasion is an indispensable prognostic factor. As the number of lymph nodes affected increases advantageously, the risk of recidivism turns more significant [1]. The rate of histological involvement of lymph nodes reported in the literature in young women is 50%. It is not constantly superior to that of the aged woman [6]. In our series, we found a rate of 63.3% of which 50% had 4 or more lymph nodes.

The treatment of BC in young women follows the same recommendations as in the aged woman with some peculiarities, it is a multidisciplinary treatment that often founded on a strategy associating locoregional and systemic treatments.

Surgical care should be done not according to age, but according to clinical features of the tumor and the relationship between tumor size and breast volume. The important aesthetic involvement in the young woman explains the conservative treatment which could be expanded with oncoplasty and neoadjuvant chemotherapy. This treatment involves a tumorectomy allowing wide and complete excision of the tumor in order to decrease the risk of a local recidivism. It must be guided a priori by an interest carcinological rather than aesthetic concern [34]. However, the risk of a local recidivism after conservative surgery is nine times greater in the 35-year-old woman and less compared to the older ones [35]. Nevertheless, many authors [21] have confirmed that the conservative treatment is a perfect therapy which is adapted to young patients if the selection criteria are well respected. So, even though Mathews et al. also have reported greater frequency of local relapse in younger women after conservative treatment, the risk of a local relapse was the same for all women under 35 years, whether or not they had followed by a conservative treatment [31]; this advises unfavorable differences in stage and tumor biology, would be responsible for a high level of local relapse among young women and also that there is no additional risk may be affect the conservation of the breast at this age [3]. In our series, 20 patients (33.3%) had benefited conservative treatment, and 40 patients (66.7%) of radical surgery, these rates join the Maghreb series.

Radiation therapy is an essential weapon for BC treatment. She decreases the rate of local relapse by a factor of 70%. An additional benefit can be provided by a boost of 16 Gy which reduces by a factor of two the rate of local recidivism (20% without boost against 10% with boost) [8, 3].

In our series, 34% patients were irradiated on the tumor bed and 66% of them on the tumor bed and ganglion areas together, the boost was administered in 15 patients. The benefit of chemotherapy in young women has been proven regardless of the status of ganglion and the stage of the disease. Chemotherapy seems to deliver better results in young women. The Oxford's meta-analysis showed an annual reduction in risk of general mortality by chemotherapy by a factor of 29% for patients under 40 years, 26% for patients between 40 and 50, and only 7% for those over 60 years old. [11]

In our series, adjuvant chemotherapy was indicated in 54 patients (90%), 77.2% of them were FEC plus Docetaxel. Two patients (T4b) benefited from neoadjuvant chemotherapy. The used protocol was FEC plus Docetaxel in 6 to 8 courses.

Regarding hormone therapy, in premenopausal women, expressing estrogens, tamoxifen remains the standard of care. Meta-analyzes has defined the extent of the benefit: in patients with RE +, tamoxifen hormone therapy for a duration of 5 years allows a gain in survival without recidivism at 15 years of 13% (versus observation), and 9% in overall survival. This gain, extending at least 10 years after stopping treatment (carry-over effect), is practically independent of menopause, HR status, lymph node status, and possible association with chemotherapy [19]. Hormonal therapy was prescribed in 42 patients, or 70% of the cases, consisted of administering anti-estrogens such as tamoxifen in 38 patients and a "SWITCH" in 4 patients. The average duration of their taking was 5 years (2-10).

The prognosis of BC in young women is generally considered less favorable. According to Chung et al. [12], survival without recidivism significantly appeared more low to five years for women under 40 compared to other age groups (60.8% versus 73.2% for the 41 to 50 age group). For Lee et al. [29], the survival of women under 30 years of age was 10 to 20% lower compared to ones over 30 years. However, the analysis of the largest series did not show a significant difference in overall survival or survival without recidivism between women aged 30 or 40 and those aged ones [17,25] while age under 35 years was a independent pejorative prognostic cause according to several authors [30,33].

In our series, no locoregional relapse was identified. 13 cases of relapse metastatic infections were recorded (21.7% of cases). The most common metastatic site was bone (61.5%), these relapses were predominant in patients with tumor size greater than 2 cm, of SBR grade greater than or equal to II, presence of tumor emboli, (and/or) with 4 or more positive lymph nodes. The rate of 3-year SG was 87% for women aged 35 years and under, whereas it was 96.4% for women aged 36 to 40 years.

Conclusion:-

The incidence of BC in young Moroccan women is so high; exceeding 2 to 3 times the frequency of occidental series, this deviation in terms of frequency could be explained by the difference of age pyramids between populations, by the existence of family cancer background and genetic forms. In our context, there is a delay in diagnosis explaining the advanced stage at the instance of diagnosis, biological characteristics often more aggressive and the prognosis more unfavorable. An improvement of this prognosis could be obtained after the introduction of a cancer screening program, among young women with a risk factor for BC, followed by an adequate cure to the identified prognostic factors.

Competing interests:
The authors declare that they have no competing interests.

Authors' contributions:
KAS, performed research; AM and ME, analyzed data statistically; AB, collected the clinical data; KAS, ME, KH, HS and HM, designed and coordinated research and drafted the manuscript. All authors read and approved the final manuscript.

Acknowledgement:-
All the authors are thankful for providing the necessary facilities for the preparation the manuscript. Special thanks are due to the Faculty of Medicine and Pharmacy of Rabat; the source(s) of funding for all authors.

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