



RESEARCH ARTICLE

RISK FACTORS FOR BREAST CANCER RECURRENCE : ABOUT 310 CASES

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Abstract

Purpose: To retrospectively study our risk factors for breast cancer recurrence and compare them with data from the literature.

Materials and Methods: Through the analysis of 310 patients admitted to the radiotherapy department of the Mohammed V Military Teaching Hospital in Rabat between January 2009 and December 2015, we identified local, locoregional and / or systemic recurrence factors.

Results: The mean age was 49.15 ± 10.37 years, the mean parity was 3.3 ± 2 , 43.5% were postmenopausal, 18.3% had a family history of breast cancer, and 41.3% used oral contraception. According to the TNM classification, 49.8% were classified as stage IIA. Invasive ductal carcinoma was predominant (82.6%). For the histo-prognosis grade of Scarf-Bloom and Richardson (SBR), 91% of patients were classified as SBR II and III. Lymphovascular invasion (LVI) were positive in 44.2%, and hormone receptors (HR) were positive in 75.8%. Lymph node involvement ≥ 4 nodes was noted in 28.5% of patients. In univariate analysis, the presence of LVI ($p < 0.001$), $N \geq 4$ ($p < 0.025$) and RH negative ($p < 0.021$) were statistically significant risk factors for recurrence. While in multivariate analysis, only EV ($p < 0.035$) and HR negativity ($p < 0.012$) were statistically significant.

Conclusion: Our study highlights known risk factors; namely massive ganglionic invasion, lymphovascular invasion and hormone receptors. Other factors must be studied to improve the future management of our patients.

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Introduction:-

According to GLOBOCAN 2018, breast cancer in women is one of the leading cancer in the world in terms of the number of new cases; approximately 2.1 million diagnoses are estimated in 2018 [1]. In Morocco, its frequency is constantly increasing to become the most common cancer in women, its incidence is estimated at 43.4 new cases per 100 000 women per year, and therefore constitutes a real public health problem [2].

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Breast cancer is a multifactorial disease, and several factors influence the risk of its occurrence. There are many prognostic factors, and each year new ones appear and others disappear. These same factors have been analyzed in several studies for their potential roles in local and systemic recurrence of breast cancer after treatment. Some have been the subject of a consensus about their contribution in relapse, such as age, Lymphovascular invasion (LVI), and surgical excision margins. Although, some factors are still controversial, such as the histological type, The Scarff-Bloom-Richardson (SBR) grade, initial tumor size, the presence of hormone receptor (HR) status, the presence of intraductal carcinoma, and the C-erbB-2 oncogene amplification[3].

In light of these data, and given the high frequency of breast cancer in our hospital, it was essential to think about studying these factors in relation to the risk of recurrence after treatment.

The aim of this work is to study the respective weight of each factor, in relation to the risk of recurrence and their effects in the recurrence of breast cancer, through a retrospective study of 310 patients in the department of radiotherapy in Mohammed V Military Teaching Hospital in Rabat.

Material and Method:-

Study population:-

This is a retrospective study conducted in Mohammed V Military Teaching Hospital in Rabat and included 310 patients admitted and regularly monitored by the department of radiotherapy-oncology from January 2010 to December 2015, of which 48 patients developed a local, locoregional and / or metastatic recurrence during their follow-up.

Data for each patient in the study were obtained from the medical records completed during their first admission. All clinical, paraclinical, anatomopathological, therapeutic and prognostic information has been collected by qualified professionals. These informations have been listed on an exploitation sheet.

Statistical analysis:-

Statistical analysis of the data was performed by SPSS 20 for Windows (SPSS, Inc., Chicago, IL, USA). Qualitative variables are presented in number and percentage. Quantitative variables are presented as mean \pm standard deviation for normal and median and interquartile range (IQR) for asymmetric distribution variables. To determine the risk factors, we applied regression analysis to determine the odds ratio and the p value for each factor in univariate and multivariate analysis. The test was considered significant when the p value <0.05 .

Results:-

The average age of breast cancer reveal in our patients was 49.15 ± 10.37 years (2 - 84 years). The average age of menarche was 13.64 ± 1.58 years (10 - 18 years). The average age of first pregnancy was 21.78 ± 5.44 years (15 - 41 years). The average parity was 3.3 with (0 – 13). In this population, 124 (43.5%) patients were postmenopausal at the time of diagnosis. Oral contraception was noted in 128 (41.3%) patients. A family history of breast cancer was recorded in 55 (18.3%) patients. The median time to diagnosis of breast cancer was 3 [1-12] months, with extremes of 1 and 72 months. The median tumor size in the mammogram was 25 mm [19-33] with extremes of 15 and 70mm. Invasive ductal carcinoma was the most common histologic type since it was found in 251 (82.6%) cases, followed by infiltrating lobular carcinoma in 12 (3.9%) cases, and for the Scarff-Bloom-Richardson (SBR) histoprognostic grading, 63.8% of patients were classified SBR II, 27.2% SBR III, and 8.7% were classified SBR I. Breast tumors were classified stage I in 27.1%, stage IIA in 49.8% and stage IIB in 14.4%. Hormonal receptors (HR) and HER2 status were investigated in all patients in our serie. HR was positive in 227 (73.2%) patients, while HER2 was positive in 86 (28.5%) patients. The median of Ki67 was 20 [10 - 38.75]. LVI were present in 126 (44.2%) patients.

All patients underwent surgery (breast surgery + axillary dissection). The surgical margins were negatives in 301 (98.7%) patients. The average number of lymph nodes (LN) removed was 15 ± 5.5 . Lymph node dissection was negative in 116 (39.6%) patients, whereas node involvement of more than 4 lymph nodes ($> \text{or} = 4N+$) was noted in 84 (28.5%) patients, and less than 4 ($<4N+$) lymph nodes, in 95 (32.2%) patients.

As adjuvant therapy: 268 (86.7%) patients received adjuvant chemotherapy, 77 (26.6%) patients received Trastuzumab treatment, and 298 (95.8%) patients received local radiotherapy.

Hormonal therapy was indicated in 227 (73.2%) patients: it was Tamoxifen hormone therapy in 114 (50.2%) patients, aromatases inhibitors in 80 (35.2%) patients or switch protocol in the remaining 33 (14.5%) patients. The median follow-up was 34 months [22; 48] with extremes of 1 and 97 months. All these descriptive results are reported in Table 1.

During the follow-up, 48 (15.5%) patients developed local, locoregional and / or metastatic recurrence. Local and locoregional relapses were noted in 7 (2.4%) patients, while 41 (15.2%) patients had a distant relapse. The median time to relapse was 14 months [8-25], with extremes of 2 and 50 months.

The results of our analytical study of various risk factors for recurrence are reported in Tables 2 and 3. The univariate analysis (Table 2) indicated that the presence of LVI, lymph node involvement ≥ 4 and negative HR were statistically significant parameters influencing the occurrence of relapse in our serie. Moreover, multivariate analysis (Table 3) showed that absence of LVI and positive HR were associated with a lower risk of recurrence.

Discussion:-

Through this study, we tried to highlight the risk factors that seemed to influence local, locoregional and metastatic recurrence in our department. We noted that our relapse rate was a little higher than reported in the literature (15.5% versus 8 to 9%) [4,5]. We found a many common risk factors with those found in the literature, such as massive node invasion, the presence of LVI and the HR status. But other decisive factors do not emerge from our analysis.

Massive axillary lymph node involvement is often found as a risk factor for locoregional recurrence [6-9]. When the axillary or supraclavicular lymph nodes are invaded, the risk of relapse is greater than when the disease is localized to the breast. The risk increases with the number of lymph nodes affected. The absolute number of invading axillary lymph nodes is considered the most important prognostic factor in breast cancer. An accurate assessment of the axillary region is the basis of adjuvant treatment decision and prognostic assessment. Over the past decade, several studies have been published indicating that LNR (Lymph Node Ratio) may be a superior indicator of axillary tumor invasion and predict the outcome better than the number of positive LN. In the Van der Waal study [10], the 10-year survival of patients with LNR greater than or equal to 0.2 was 52%, compared to 73% of patients with LNR less than 0.2 ($p = 0.0001$). In the Kim.J study [11], the prognostic value of the LNR was evaluated in 144 patients, 130 of whom had a low LNR (0.01-0.15), and 14 patients had a high LNR (> 0.15). The 5-year survival was 93.5% and 85.7% in the patients with low and high LNR respectively. A high LNR was associated with a poor prognosis in the univariate analysis ($p < 0.004$) and the multivariate analysis ($OR = 3.453$ [1.273-9.361], $p < 0.015$). The results of our work are consistent with these studies since LN involvement was a statistically significant factor of relapse, with $OR = 0.420$ [0.197-0.896] and $p < 0.025$ for $< 4N+$ and $OR = 0.223$ [0.097-0.513] and $p < 0.0004$ for $\geq 4N+$ invasion.

The presence of LVI is also found to be a risk factor for locoregional recurrence by many authors [7,12-16]. This factor is particularly important in patients without lymph node involvement. It is reasonable to assume that the worst prognosis of LVI is related to the high level of tumor cell dissemination (metastasis). Young Du Song [17] demonstrated, through a retrospective study of 967 patients, that lymphovascular invasion (LVI) was a significant independent prognostic factor of disease-free survival (DFS) and overall survival (OS). In univariate analysis, 5-year OS and 5-year DFS were significantly different in patients with and without LVI: 88.8% vs. 94.1% ($p = 0.007$) for OS and 76.4% vs. 90.9% ($p < 0.001$) for DFS. In addition, survival without metastasis at 5 years was shorter in patients with LVI: 80.1% versus 91.5% compared to patients without LVI ($p < 0.001$). In our serie, the presence of LVI had a significant effect on relapse with $OR = 0.343$ [0.17-0.66] and $p < 0.001$. This factor is noted in 66% of patients who had a recurrence.

The value of HR status for predicting the hormone sensitivity of tumors is no longer in doubt. On the other hand, their independent predictive value of relapse is variously appreciated in the literature. Patients with triple-negative breast cancer have an increased likelihood of distant recurrence and death compared to other profiles, and the difference persists after control with established prognostic factors. However, the recurrence patterns in both subgroups are qualitatively different. Patients with triple-negative breast cancer had high recurrence rates only 1 to 4 years after diagnosis. The risk then decreased rapidly and no recurrence occurred after 8 years of follow-up. In the other group, the risk of recurrence and death was stable and continued for 17 years after diagnosis [18]. The presence of hormone receptors was a significant factor in the multivariate analysis in our serie. The odds ratio was $OR = 2.525$ [1.223-5.217], and $p < 0.012$. Only 28 patients with positive hormone receptor relapses, compared to 199 without local or systemic recurrence.

The age of patient, the histological SBR grading, the size of the tumor and the quality of margins are often associated with the risk of locoregional and distant recurrence according to several authors [19-22]. But, our numbers did not allow us to highlight this difference. Thus, all these factors were not identified in the univariate and multivariate analysis of our study.

Table 1:- Patient Characteristics.

Patient Characteristics		
Age (years)		49,15 ±10,37
Menarche (years)		13,64±1,58
Average age of first pregnancy (years)		21,78±5,44
Number of pregnant		3,9 ± 2,34
Parity		3,3 ± 2
Contraception	No	55 (17.7%)
	Yes	128 (41.3 %)
Menopause	No	161 (56.5%)
	Yes	124 (43.5 %)
Family history		55 (18.3%)
Diagnostic delay (month)		3 [1-12]
Tumor size in the mammogram (mm)		25 [19-33]
TNM Stage	Tis	3 (1%)
	I	81(27.1 %)
	IIA	149(49.8 %)
	IIB	43(14.4 %)
	IIIA	5(1.7 %)
	IIIB	8(2.7%)
	IIIC	2(0.7%)
	IV	8(2.7%)
Histologic type	Invasive ductal carcinoma	251 (82.6 %)
	Others	53 (18.4%)
SBR	I	25 (8.7 %)
	II	183 (63.8 %)
	III	78 (27.2 %)
LVI	No	159 (55.8%)
	Yes	126 (44.2%)
LNR	N0	116 (39.6 %)
	<4N+	95 (32.2%)
	>or= 4N+	84 (28.5%)
Margins	Negatives	301 (98.7%)
	Positives	.
HR	No	83 (26.8%)
	Yes	227 (73.2 %)
HER	No	216 (71.5%)
	Yes	86 (28.5%)
Ki67	<20%	34 (44.7%)
	>or= 20%	42 (55.3%)
Chemotherapy		268 (86.7 %)
Hormonotherapy		227 (73.2 %)
Type of HTH	Tamoxifen	114 (50.2 %)
	Aromatases inhibitors	80 (35.2 %)
	Switch	33 (14.5 %)
HERCEPTIN		77 (26.6%)

1. OR : Odds Ratio
2. CI : confidence interval
3. LNR : Lymph Node Ratio
4. HR: Hormone receptor
5. HTH : hormonal therapy

Table 2:- Univariate analysis of the different risk factors for breast cancer recurrence.

Factor of relapse		Relapse		UnivariateAnalysis		
		Oui	Non	OR	95% CI	p Value
Age (years)		47,8±10,25	49,36 ± 10,36	0,987	0,985-1,017	0,404
Menarche (years)		13,58±1,89	13,65 ± 1,55	0,980	0,729-1,317	0,894
Average age of first pregnancy (years)		23±5,96	22,03 ± 5,00	0,953	0,824-1,060	0,294
Number of pregnant		3,95± 2,59	3,91 ± 2,31	0,999	0,870-1,147	0,990
Parity		3,3 ± 2,16	3,31 ± 2,01	0,996	0,850-1,168	0,965
Contraception	No	32 (64,4%)	43 (16,4%)	1	-	-
	Yes	16 (35,6%)	112 (42,7%)	1,493	0,672-3,317	0,325
Menopause	No	28 (62,2%)	137 (52,3%)	1	-	-
	Yes	17 (37,8%)	106 (40,5%)	1,032	0,532-1,999	0,927
Diagnosticdelay (month)		2,50 [1-12]	7,67 ± 11,28	1,002	0,974-1,032	0,875
Tumor size in the mammogram) (mm)		30[20-48,5]	23 [18-31]	1,005	0,992-1,017	0,451
TNM Stage	Tis	0 (0%)	3 (1,1%)	1	-	-
	I	6(13,3%)	75 (28,6%)	1,29.10 ⁸	0-0,001	0,999
	IIA	23(51,1%)	126 (48,1%)	2,84.10 ⁸	0-0,001	0,999
	IIB	11(24,4%)	32 (12,2%)	5,55.10 ⁸	0-0,001	0,999
	IIIA	2(4,4%)	3 (1,1%)	1,09.10 ⁹	0-0,001	0,999
	IIIB	3(6,7%)	5 (1,9%)	9,69.10 ⁸	0-0,001	0,999
	IIIC	0(0%)	2 (0,8%)	9,69.10 ⁸	0-0,001	0,999
	IV	0(0%)	5 (1,9%)	0,001	0-0,001	0,999
Histologic Type	Invasive ductal carcinoma	36 (81,8%)	212 (80,9%)	1,157	0,585-2,288	0,676
	Others	8 (18,2%)	45 (17,2%)	1	-	-
SBR	I	4 (9,5%)	21 (8,0%)	1	-	-
	II	24 (57,1%)	157 (59,9%)	0,750	0,225-2,495	0,639
	III	14 (33,3%)	63 (24,0%)	0,652	0,328-1,297	0,223
LVI	No	16 (36,4%)	143 (54,6%)	1	-	-
	yes	28 (63,6%)	95 (36,3%)	0,343	0,178-0,661	0,001
LNR	N0	8(17,8%)	107 (40,8%)	1	-	-
	<4N+	12 (26,7%)	82 (31,3%)	0,223	0,097-0,513	0,0004
	>or= 4N+	21 (46,7%)	61 (23,3%)	0,420	0,197-0,896	0,025

Margins	Negatives	43(95,6%)	255 (97,3%)	1	-	-
	Positives	.	4 (1,5%)	2,91.10 ⁸	0,0001	0,999
HR	No	17 (37,8%)	55 (21,0%)	1	-	-
	Yes	28 (62,2%)	199 (76,0%)	2,171	1,126-4,184	0,021
HER	No	32 (71,1%)	181 (69,1%)	1	-	-
	Yes	13 (28,9 %)	73 (27,9%)	1,086	0,543-2,170	0,816
Ki67	<20%	4 (40%)	30 (45,45%)	1	-	-
	>or= 20%	6 (60%)	36 (54,55%)	1,005	0,972-1,040	0,762
Chemotherapy		43 (95,6%)	222 (84,7%)	0,247	0,058-1,061	0,060
Hormonotherapy		26 (57,8%)	198 (75,6%)	2,655	1,399-5,040	0,003
Type of HTH	Tamoxifen	19 (67,9 %)	90 (34,4%)	1	-	-
	Aromatases inhibitors	7 (25 %)	64 (24,4%)	3,100	0,680-14,129	0,144
	Switch	2 (7,1 %)	31 (11,8%)	1,453	0,277-7,618	0,658
HERCEPTIN		12 (27,9%)	65 (24,8%)	0,993	0,484-2,038	0,985

Table 3:-Multivariate study of different risk factors for breast cancer recurrence.

Factor		Multivariate Analysis		
		Odds Ratio	CI 95%	p Value
LVI		0,451	0,216-0,944	0,035
LNR	<4N+	0,604	0,183-1,997	0,409
	>/=4N+	0,609	0,267-1,388	0,238
HR		2,525	1,223-5,217	0,012

Conclusion:-

In total, the analysis of the risk factors of 310 breast cancer cases treated in the Mohamed V Military Teaching Hospital in Rabat, highlights known risk factors consistent with the data from the literature; such as; massive node invasion, presence of LVI and HR status. These factors are well used in the various current algorithms of adjuvant treatment decision in order to build a better therapeutic strategy of breast cancer management more and more targeted.

Ethics approval and consent to participate:-

Informed consent (verbal) was obtained from all participants. This study was submitted to and approved by research and ethics committee of military teaching hospital Mohamed V

Competing interests:-

We (authors) declare that we have no conflict of interest.

Authors' Contribution:-

Abdelhak Maghous and Mohamed Elmarjany, performed research and share the first position in this manuscript; A.M and M.E analyzed data statistically and drafted the manuscript; E.M, K.A, K.H, H.S, N.Z, J.H, B.H and H.M, designed and coordinated research and drafted the manuscript. All authors read and approved the final manuscript.

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