

## Oncology

**Study of survival without progression local of non-metastatic breast cancer****Messid Bouziane Meflah H. , Daoud S., Terki Kh., Besbes FZ, Benrabah L., Mokhtari L.**

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**Abstract**

**Introduction:** Breast cancer is a real public health problem. The objective of this work was to estimate the survival without progression local at 10 years of non-metastatic female breast cancer and to determine the main prognostic factors, which condition this survival in the wilaya of Oran-Algeria.

**Method:** we carried out a retrospective study on 247 incident cases of non-metastatic female breast cancer diagnosed between January 1st, 2007 and December 31st, 2009. The patients included in the study were residents of the province of Oran and had a clinical record at the University Hospital Center of Oran. The survival without progression local analysis was carried out according to the Kaplan Meier Method. To study the characteristics of the prognostic factors, the survival of patients was calculated in univariate analysis by the Log-rank test; in multivariate analysis by the Cox model.

**Résultats :** At the point date, December 31st, 2018, we noted rates of survival without progression local at 10 years of 90 %. In the univariate analysis, survival without progression local was affected ( $p < 0.05$ ) by tumor size, lymph node involvement, Molecular Classes and loco-regional Radiotherapy. In the multivariate analysis, Luminal class B her2 positive (HR : 4,27 ; IC à 95% [1,11-16,36] ;  $p = 0,03$ ) and the absence of loco-regional Radiotherapy had an adverse effect on survival without progression local at 10 years.

**Conclusion:** Luminal class B her2 positive and the absence of loco-regional Radiotherapy were associated with significantly higher risk local relapse of breast cancer.

**Keywords:** *Survival without progression local at 10 years, Prognostic factors, Non-metastatic female breast cancer*

**Introduction**

Breast cancer is a major public health concern worldwide, its incidence reached 2.261419 million new cases, and an estimated mortality of 684996 in 2020 [1]. It ranks first among female cancers, ahead of colorectal cancer and lung cancer [2]. Its incidence is low before the age of 25 (less than 10 new cases per 100,000 women), and increases from the age of 45 years to reach its maximum between 65 and 75 years [3].

In Algeria, breast cancer represents 53.8% of malignant tumors in women with a standardized incidence rate estimated at 76/100,000 women per year, it is therefore considered

to be the first cancer in women with the particularity to frequently affect young women (median age 50 years) [4].

Many clinicopathologic factors are used to determine whether breast cancer has a good or bad prognosis, and determine whether a complementary systemic treatment should be administered, in order to reduce the risk of progression (local or remote) and death, among others: young age less than 35 years [5], size of the tumor, grade histology of Scarff-Bloom and Richardson (SBR), lymph node invasion, presence of vascular and lymphatic emboli, molecular classes and limits of surgical excision.

In Algeria, few studies focus on the prognostic factors that condition survival without long-term local progression of breast cancer.

The objective of this work was to estimate the 10-year local progression-free survival (PFS) of non-metastatic female breast cancer and to study the main prognostic factors that condition it.

## Materials and methods

This is a descriptive retrospective prognostic study conducted among 247 incident cases of non-metastatic female breast cancer diagnosed between January 1, 2007 and December 31, 2009. The women included in the study were residents of the wilaya of 'Oran and had a medical clinical record at the University Hospital Center of Oran-Algeria.

## Data Collection

The variables studied were: Age ( $\leq 35$  years,  $> 35$  years), tumor size, SBR histo-prognostic grade, lymph node invasion, presence of vascular and lymphatic emboli, Molecular classes, exeresis limits, locoregional radiotherapy, concept and date of diagnosis of local progression. The original date was the date the breast cancer was diagnosed (January 1, 2007 through December 31, 2009). of points were censored as well as the data of the lost sight.

## Data Analysis

We carried out a descriptive analysis of the study population, where the quantitative variables were represented by mean and standard deviation and the qualitative variables by number and percentage per class.

Local progression-free survival was estimated using the Kaplan Meier method. For the study of the characteristics of the prognostic factors, the local progression-free survival of the patients was calculated in univariate analysis by the log-rank test and in multivariate analysis by the Cox model and the adjusted Hazard Ratios (HR) which were reported with their 95% confidence interval [95% CI]. All the variables with a p-value  $p < 0.05$  in univariate analysis were implemented in a multivariate Cox model. Some parameters were found in previous studies to influence metastatic progression-free survival rates and were not significant in the univariate model such as age, so they were forced into the multivariate model. The survival curves were constructed by the Kaplan-Meier method.

The significance threshold of the tests used is the classic threshold of 5%, the confidence intervals of the means or percentages are at 95% (95% CI). Statistical analysis of the data was performed using SPSS.20.0 software.

## Results

A total of 247 cases of non-metastatic female breast cancer were collected. The study population was aged under 35 in 12.6% of cases. The size of the tumor was classified as T1 in only 51 patients (20.6%). Lymph node dissection was performed for 236 patients and the result was positive in 142 cases (61.8%). Vascular emboli were found in 17.4% of patients. The resection limits were healthy in 97.5% of the patients. More than 95% of the tumors had a poor prognosis criterion (SBR II or III). Thirty-two percent of the tumors were of the “Luminal A” molecular type and 197 patients had received locoregional radiotherapy (Table 1).

**Table 1:** epidemiological, histo-pathological and therapeutic characteristics of non-metastatic female breast cancer

Variable	Number of cases	%
<b>Age of diagnosis</b>		
≤35 years	31	12,6
> 35 years	216	87,4
Total	247	100
<b>Tumor size</b>		
T1	51	20,6
T2	107	43,3
T3	17	6,8
T4	72	29,1
Total	247	100
<b>Positive lymph node removal</b>		
Positive	142	61,8
Negative	94	38,8
Total	236	100
<b>Lymph node involvement</b>		
N0	94	39,8
N1	66	27,9
N2	58	24,5
N3	18	7,6
Total	236	100
<b>SBR Grade</b>		
I	12	4,9
II	77	31,7
III	154	63,4
Total	243	100
<b>Vascular embols</b>		
Yes	25	17,4
No	117	82,6
Total	142	100
<b>Molecular Classes</b>		

Luminal A	79	32
Luminal B HER2 negative	5	2
Luminal B HER2 positive	27	10,5
Overexpression Erb-B2	18	7,3
Basal-Like	113	46,2
Total	242	100
excision limits		
Reached	6	2,5
not reached	241	97,5
Total	247	100
loco-regional Radiotherapy		
Yes	198	80,1
No	49	19,9
Total	247	100,0

Local relapses occurred in 16 patients, i.e. 6.5% of cases, and the rate of loss of follow-up at the point date was 9.7% (n=24).

The local PFS rate at 10 years was 90% (95% CI [88.2% - 91.8%]) (Figure 1).

The group of women aged under 35 had a low local PFS (82.3%). Patients with a tumor classified as T4 and an N3 status had a low survival rate (59% and 74%). Local PFS according to the limits of surgical excision of the tumor did not show any significant difference (p= 0.49). Survival was low for SBR grade III (85.3). Patients with peritumoral vascular and lymphatic emboli had lower local PFS (86.7%). women in class (Luminal A-Luminal B HER2 negative - Basal-Like - Erb-B2 overexpression) had better survival than in class (Luminal B her2 positive) (Figure 2) and The use of loco-regional radiotherapy showed significantly higher local PFS (92.5%) (Figure 3) (Table 2).

In univariate analysis, tumor size, lymph node involvement, molecular classes and loco-regional radiotherapy were associated with a significantly higher risk of local relapse at 10 years (Table 2).

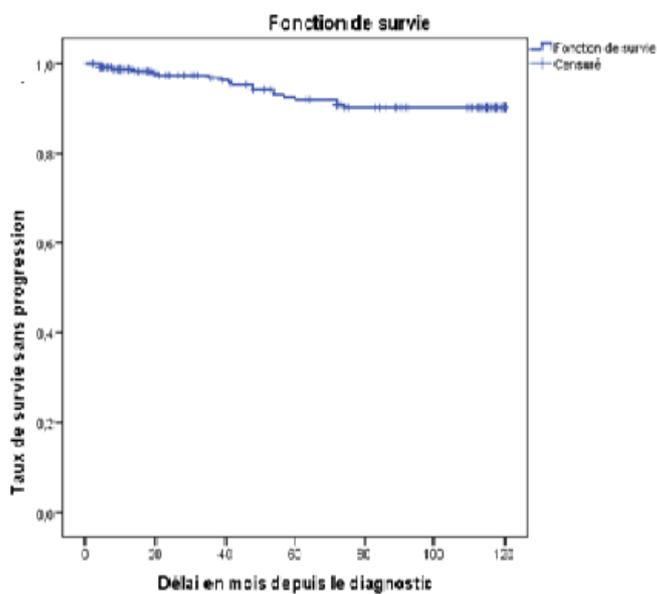


Figure 1: Local PFS rate at 10 years in patients with non-metastatic breast cancer

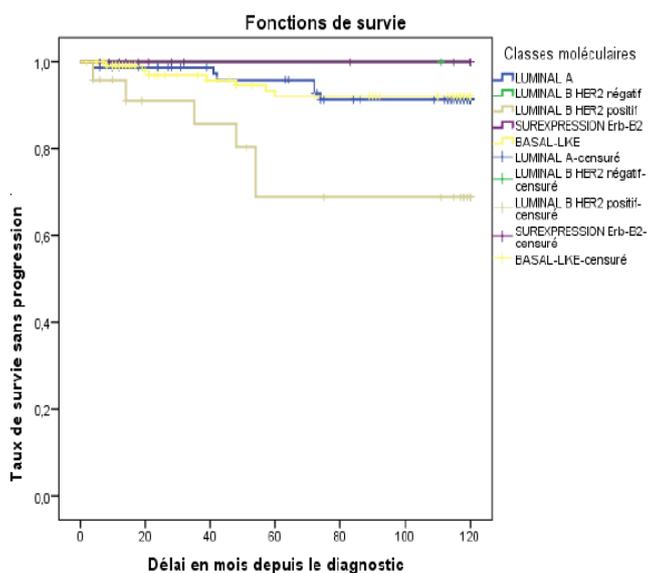


Figure 2: 10-year local PFS rate of patients with non-metastatic breast cancer according to molecular classes.

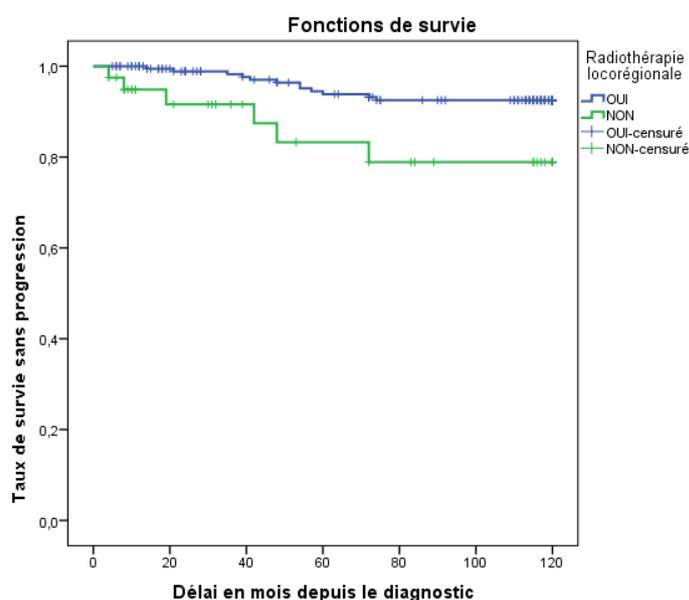


Figure 3: local PFS rate at 10 years of patients with non-metastatic breast cancer according to the notion of radiotherapy.

Table 2: Local PFS at 10 years of patients with non-metastatic breast cancer

Variable	10-years Local PFS rate (%)	p
<b>Age of diagnosis</b>		
≤35 years	82,3	0,27
> 35 years	91,9	
<b>Tumor size</b>		
T1	97,6	0,00
T2	93,6	
T3	75,3	
T4	59	
<b>Lymph node involvement</b>		
N0	92,1	0,00
N1	92,2	
N2	89,2	
N3	74	
<b>SBR Grade</b>		
I	100	0,00
II	91,7	
III	85,3	
<b>Vascular embols</b>		
Yes	86,7	0,34

No	91,8	
<b>Molecular Classes</b>		
Luminal A	91,3	
Luminal B HER2 negative	100	
Luminal B HER2 positive	68,9	0,01
Overexpression Erb-B2	100	
Basal-Like	92,1	
<b>excision limits</b>		
reached	97	
not reached	93,3	0,49
<b>loco-regional Radiotherapy</b>		
Yes	92,5	
No	78,9	0,00

Multivariate analysis shows that there is an association between local PFS at 10 years and Luminal class B HER2 positive (HR: 4.27; 95% CI [1.11-16.36]; p=0.03) and loco regional radiotherapy (HR: 0.29; 95% CI [0.09-0.85]; p=0.02) (Table 3).

Table 3: Local PFS at 10 years according to the multivariate Cox model.

Variable	multivariate analysis		
	p	HR	[IC à 95%]
<b>Tumor size</b>		<i>Réfé</i>	
T1		-	
T2	0,95	-	-
T3	0,94	-	-
T4	0,94	-	-
<b>Lymph node involvement</b>			
N0		<i>Réfé</i>	0,32-0,18
N1	0,80	1,17	0,10-0,01
N2	0,30	0,46	-
N3	0,95	0,00	
<b>SBR Grade</b>			
I		<i>Réfé</i>	
II	0,76	0,00	-
III	0,96	-	-

Molecular Classes			
Luminal A	0,97	Réfé 0,00	-
Luminal B HER2 négative	0,03	4,27	1,11-16,36
Luminal B HER2 positive	0,94	0,00	-
Overexpression Erb-B2 Basal-like	0,05	1,42	0,42-4,78
loco -regional Radiotherapy			
Yes		Réfé	0,09-0,85
No	0,02	0,29	

## Discussion

Our series showed a 10-year local PFS rate of 90%. This result is similar to the data from the study by Bhatti ABH et al. [6], where they reported a rate of 88%, and results from the study by Zhang WW et al. [7] who also reported a 10-year local PFS survival rate of 86.3% through a study published in 2018 analyzing the impact of the delay between surgery and radiotherapy on local cancer relapse-free survival long-term breast cancer.

A very high rate has been reported in Germany, by Kümmel A et al. [8] where they determined, through a study on the prognostic factors for relapse of non-metastatic breast cancer, carried out on a cohort of 3054 women diagnosed between 1998 and 2011, a local PFS at 10 years of 98%.

Some studies have described age as a prognostic factor for local relapse after breast cancer. In our series, local PFS at 10 years was significantly better in elderly patients (91.9%) than in young patients (82.3%), but this did not conclude that there was a significant difference between the two groups. ( $p=0.27$ ). These results are consistent with those reported by the study by Bhatti ABH et al.[6], which reported a rate of local PFS at 10 years of 86% for young patients and a rate of 91% for elderly patients with no statistical significance.

Tumor size is an independent prognostic factor, regardless of tumor status. lymph nodes [9]. In our series, patients with T4 size breast cancer at diagnosis showed a markedly low 10-year local PFS rate.

Bhatti ABH et al. [6] demonstrated that T4 size tumors had a poor prognosis with a very low local PFS rate at 10 years (77%) compared to other tumor sizes with a statistically significant difference ( $p<0.00$ ). The team of Kümmel A et al. [8] also confirmed the relationship between the increase

tumor size and decrease in local PFS, but with better rates compared to our results (93% for T4).

Nodal invasion is the major prognostic factor. The number of lymph nodes invaded is decisive for the prognosis of breast cancer. Most authors admit a threshold beyond three invaded lymph nodes. The more the number of lymph nodes affected increases, the higher the risk of relapse [10, 11]. Our series showed better local PFS for the N0 status (92.1%) associated with a highly significant difference ( $p < 0.00$ ). These results are consistent with those described in the study by Kümmel A et al. [8], and Bhatti ABH et al. [6] where they reported local PFS rates at 10 years ranging from 92% to 99% respectively in the absence of lymph node involvement, with a very high significance level.

The lack of significance between the presence and absence of vascular emboli in our series can be explained by the high frequency of patients who had received radiotherapy after surgery. These results are consistent with those of the study by Kümmel S et al. [8] who reported excellent local PFS rates at 10 years (99% and 98% in the presence and absence of vascular emboli) but without statistical significance.

All studies show that survival is strongly determined by grade: the higher the grade higher, the worse the prognosis. Our study demonstrated that there was statistical significance between local PFS and SBR grade ( $p < 0.00$ ) with a markedly low survival for SBR III grade (85%). These results are consistent with those of the study by Kümmel A et al. [8] where they revealed almost equal local PFS rates between SBR grades (95% for the SBR I and II and 96% for SBR III) with a statistical difference ( $p < 0.05$ ).

Historically, overexpression of Her2 has been associated with a higher frequency of local relapse. In our series, Luminal B her2 positive patients had the lowest 10-year local PFS rate (68%) associated with statistical significance ( $p < 0.00$ ).

Our series revealed excellent survival rates for positive or negative surgical resection limits and without statistical significance ( $p = 0.49$ ), this can be explained by the high frequency of patients having benefited from radiotherapy.

In our series, the use of radiotherapy showed local PFS at 10 years clearly superior with a statistically significant difference ( $p < 0.00$ ). These results are comparable to those of the study by Kümmel A et al. [8] who demonstrated a very high rate of 99% for women receiving radiotherapy with a statistically significant difference.

## Conclusion

the data presented in our study conclude that her2 positive molecular class, tumor size, lymph node involvement, SBR grade and locoregional radiotherapy were associated with a significantly higher risk of local relapse.

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