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Identification of predictive factors of recurrence of hormone receptor positive breast cancer after completion of 5 years of aromatase inhibitor and development of prognostic tool. An analysis of 1496 women of the ICO database.

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SUMMARY

Abstract.

INTRODUCTION: Women with hormone receptor positive early breast cancer receive generally adjuvant endocrine therapy (ET) for 5 years including tamoxifen and aromatase inhibitors (AI) for pre and post-menopausal women respectively. However, more than half of recurrences occurred after that time and extension of ET is an option. The identification of patients who could benefit the most of extended ET is major issue. We aimed to develop a simple prognostic tool to estimate the risk of late recurrence of patients who had completed 5 years of AI, in order to help the decision making process of extending AI. We hypothesized that late recurrence including metastatic disease, contralateral disease, and ipsilateral recurrences after completing 5 years of AI in may be associated with initial clinical and pathological prognostic factors.

METHODS: In this monocentric, retrospective and descriptive analysis from the database BERENIS we included all postmenopausal women diagnosed for early breast cancer and who completed 54 months of endocrine therapy.

RESULTS: Between January 2003 and December 2011, 1107 post-menopausal women were included. After a median duration of follow-up of 32.6 months [1-132], the recurrence rate was 8% including 60 metastatic relapses, and 8 and 21 homolateral and controlateral recurrences respectively. Multivariate analysis showed the pathological tumour size (continuous) (HR = 1.02; p = 0.035), the number of macro-metastases (continuous) (HR = 1.17; p = 0.001) and age (HR = 1.04; p = 0.012) were independent prognostic factors of relapse free survival. We designed a prognostic score of late relapse corresponding to: 10*(tumour size (mm)) +79*(number of macrometastases) +14*(years old) with a cut-off at 1200 points. In our patients, 78.8% were categorized as low risk, 21.2% as high risk for late recurrence. Those categorized as low risk had a mean 5- to 10-year local or distant recurrence risk of 9.8% (95% CI, 7.1% to 13.5%) as compared with 38.3% (95% CI, 27.6% to 50.9%) for high-risk groups.

CONCLUSION: This score predicts the risk of recurrence after 5 years of aromatase inhibitor and can be a simple tool to help clinicians to select patients who could derive the most benefit of extending adjuvant AI above 5 years.

KEY WORDS:
EARLY BREAST CANCER - HORMONAL POSITIVE RECEPTORS - LATE RECURRENCE - ENDOCRINE THERAPY EXTENSION - PROGNOSTIC SCORE

Abreviation

AI: Aromatase inhibitor

AIC: Akaike Information Criteria

ATAC: Arimidex, Tamoxifen, Alone or in Combination

BC: Breast cancer

BERENIS: Base d'Evaluation et de Recherche des Néoplasmes Infiltrants et in Situ

CI: confidence interval

CTC: circulating tumoral cells

DFS : Disease free survival

ER: oestrogen receptor

ET: endocrine therapy

GCP: good clinical practices

HR: Hazard ratio

HR+: Hormonal Receptor positive

ICO: Institut de cancérologie de l'ouest

IQR: interquartile interval

MM: millimeter

N: number

OS: overall survival

PFS: Progression free survival

PR: progesterone receptor

ROR: PAM50-based Prosigna risk of recurrence

RR: Relative risk

RS: Recurrence score

VS: versus

+: positive

-: negative

Introduction.

Breast cancer (BC) is the most common cancer in women (1). It is not a single disease; it is composed of many biologically different entities with distinct pathological features and clinical implications. About 75% of breast cancers express oestrogen receptor (ER+), while about 55% express the progesterone receptor (PR) (2)(3). They are classified as luminal A or B according to their proliferation capacity. Luminal B tumours usually present a high grade, a lower expression of hormonal receptor (HR) and sometimes an HER2 over-expression (4)(5).

In an adjuvant setting, the aim of treatment is to eradicate potential micro metastases to avoid recurrence. As a result, oncologists use different criteria to estimate the risk of relapse after surgical treatment in order to decide which patients should receive adjuvant therapy. The benefit of chemotherapy, radiotherapy and hormonotherapy is well established. (6). In 2002, The Arimidex, Tamoxifen, Alone or in Combination (ATAC) study demonstrated that 5 years of anastrozole (an aromatase inhibitor (AI)) provided a PFS benefit compared to 5 years of tamoxifen in the adjuvant setting of early breast cancer. AIs are now the mainstream adjuvant treatment in postmenopausal women with early breast cancer (7)(8).

For a long time, duration of adjuvant endocrine therapy (ET) has been recommended for a period of 5 years. However, the natural history of HR+ breast cancer show that half of recurrences occurs after the end of adjuvant ET(9). Two trials (ATLAS and aTTom) have shown that extended duration of tamoxifen improve disease-free survival and overall survival (10)(11). Recently, in post-menopausal women, the DATA, IDEAL, and NSABP B42 trials showed that extended adjuvant endocrine therapy with AIs beyond 5 years did reduce the occurrence of secondary breast tumours, but had no or only a small impact on distant metastasis free survival(12)(13)(14). Of note, these studies mixed patients treated with 5 years of Tamoxifen or AI followed par by 5 years of AI. Therefore, to decide which patients should receive 10 years of AI is a tough task, given the potential toxicity and impact on quality of life.

Various prognostic classifiers are currently used as decision-making tools for adjuvant systemic treatment such as patient age, tumour size, positive nodes, grade, hormone receptor and HER2 status (3)(15)(16). Predictors of late recurrence are not well characterized, although nodal

involvement and lobular histology are associated with greater risk of recurrence after 5 years of endocrine therapy (17)(18). Recently, the CTS5 score was published as a prognostic tool for late distant recurrence, defined as metastatic disease taking into account the tumour grade, age, tumour size in millimetres and number of lymph nodes involved (19). However, this score has been designed on a mixed population of patients treated with adjuvant tamoxifen or AI.

We aimed to develop a simple prognostic tool to estimate the risk of late recurrence of patients who had completed 5 years of AI, in order to help the decision making process of extending AI. We hypothesized that late recurrence including metastatic disease, contralateral disease, and ipsilateral recurrences after completing 5 years of AI in may be associated with initial clinical and pathological prognostic factors.

Patients and Methods.

BERENIS database.

BERENIS « Base d'Evaluation et de Recherche des Néoplasmes Infiltrants et in Situ » is a database which includes all patients treated for a breast cancer at the Institut de Cancerologie de l'Ouest (ICO). In accordance with French regulation, the French data protection authority authorized the database. ICO in compliance with the good Clinical Practices (GCP) managed it. Patients' data were retrospectively collected. Primitive tumour features as well as metastatic disease characteristics if needed were retrieved. Type of adjuvant treatment and outcome were also collected.

Study population.

All post-menopausal women treated for hormone receptor positive (Oestrogen receptor > 10% and or Progesterone receptor >10%) invasive breast cancer and who had completed at least 54 months (≈4.5 years) of adjuvant aromatase inhibitor were included. Patients relapsing during adjuvant treatment, loss of follow-up during the first five years or shortly after the end of AI were excluded. We also excluded also patients having an HR- relapse as our goal was to identify a population of patients who could benefit from extended endocrine therapy. We included patients diagnosed between 2003 and 2011 to have a minimum follow-up of 1 year after the end of their adjuvant AI in the analysis.

Objectives

The primary objective was to highlight predictive factors of late recurrence, after 5 years of AI. The secondary objective was to build a score to predict late recurrence.

Statistical analysis

The continuous variables were described by mean, standard deviation, median, minimum and as well as the interquartile interval (IQR). The qualitative variables were described by the frequency of their respective modalities.

The evolutionary variable (survival without relapse) was defined as the time between the end of ET and either the date of the first relapse or the date of last news without relapse. The relapse could be homolateral, controlateral, in situ or invasive, or metastatic.

The relapse-free survival curves were calculated by the Kaplan-Meier method and compared between interest groups through the logrank test. The median follow-up was calculated by the Kaplan-Meier inverted. The univariate search for prognostic factors for survival without relapse used the logrank test or univariate cox test.

Variables that had a p of significance <0.20 in univariate were introduced in the different semi-parametric multivariate Cox models. The validity of multivariate models for the proportional risks have been verified. A prognostic score was calculated for each model from the bootstrapped data (n=1000 repetitions) and the corresponding risk curves traced.

The models were compared by their Akaike Information Criteria (AIC). All tests were performed bilaterally and the limit of significance was set at 5%. All analyses were performed using SAS 9.4 software (SAS Institute Inc., Cary, NC, USA) and Stata Special Edition 13.1 (StataCorp, College Station, Texas, USA).

Results.

Characteristics and initial management of patients.

Between January 2003 and December 2011, 1496 women were identified in the database. Out of them, 389 were excluded including 10 recurrences occurring while on ET, nine HR- relapsing diseases and 370 patient's loss of follow up immediately after the end of ET (**Figure 1**). The main characteristics of the 1107 patients included are listed on **Table 1**. Briefly, the median age at primary diagnosis was 62.5 [32.5 –88.5] years. The pT stage was mainly pT1 (n=859; 77.6%) or pT2 (n=229; 20.7%) and 289 (26.1%) patients had a nodal involvement at the time of initial surgery. Tumour grade was I, II and III, in 29.7%, 52.8% and 12.2% of patients respectively. Regarding the histological subtype, 76.8% of tumours were ER+/PR+, while 23.2% had a dissociation of hormonal receptors (ER+/PR- 22.8%, ER-/PR+ 0.4%). HER2 status was positive in 6.6% and missing in 4.1% of cases.

At the time of the initial surgery, 792 patients (71.6 %) underwent a conservative surgery associated with an axillary node dissection or an axillary sentinel lymph node in 62% and 38% of cases respectively. Regarding adjuvant treatment, chemotherapy was administrated in 42% of patients including anthracycline, alkylant and taxane for 93.5%, 94.5% and 78.3% of patients respectively and Her2 targeted therapy for 54 patients out of the 73 Her2+ breast cancers. The chemotherapy was delivered for 10.3% of patients in the frame of a clinical trial. All the patients received adjuvant aromatase inhibitors with a median duration of 60 months [54-82]. Anastrozole was the main prescribed AI, concerning 57.4% of patients. Of note, nine patients received more than 6 years of AI without particular explanation in the patient's medical record.

Pattern, management and outcome of relapsing patients after 5 years of AI.

With a median follow-up of 32.6 [1-132] months after completion of 5 years of adjuvant AI, 89 patients relapsed corresponding to a recurrence rate after 5 years of 8% (n=89). The median time to relapse after completion of AI was 23 months [1-117]. The characteristics of these patients are listed in **Table 2**. Mean age at relapse was 63.2 years. Sixty patients (67.4%) had a metastatic relapse while the remaining patients had a local relapse including homolateral and controlateral disease in eight (9%) and 21 (23.6%) patients respectively. Local relapse was in situ disease in five

(5.6%) patients. After a median follow-up of 69.5 [43-126] months after the end of the 5 years of AI, all of the patients with homolateral relapse were alive at the end of data collection but one presented secondary metastatic evolution. For contralateral relapsing patients, after a median follow-up of 66 [21-104] months, one patient died of metastatic evolution.

Among the sixty patients with a metastatic relapse, 51.6% of patients had more than one metastatic site. Localization of metastatic sites was mainly bone (68.3 %), pleural (25%) and liver (23.3%). We also observed recurrences in lymph node, lung (16.7%), skin (13.3%), brain (8.3%), bone marrow (3.3%), peritoneum (5%) and ovary (1.7%). First line treatment of metastatic disease included ET (n=43; 71.7%), chemotherapy (n= 13; 21.6%) and best supportive care (n=4; 6.7%). The median overall survival of patients after metastatic relapse was 17 months **(supplemental-1).**

Clinical factors associated with relapse after 5 years of AI.

Univariate analysis showed that age at initial diagnosis, tumour size, node involvement, presence of emboli, lobular histology, radical surgery and delivery of neo/adjuvant chemotherapy where associated with an increased risk of relapse. Details are shown on **Table 3**. Conversely, tumour grade, HER2 positivity and HR dissociation were not associated with an increased risk of late recurrence. In multivariate analysis, tumour size, number of involved nodes and age remained independent predictive factor of recurrence. Data are shown in **Table 3**.

Integration of clinical variables for the prediction of late recurrence after 5 years of AI

We built first a pragmatic model integrating prognostic variables and secondly we built a score in points to discriminate different prognostic groups in terms of relapse free survival after 5 years of IA. For each patient the prognostic score was determined. This prognostic score corresponds to the following addition: 10 points for each millimetre of pathological tumour size, 79 points for each macro metastases and 14 points for each year of age. The mean score was 1106 points [716-2621] and the median one was 1169. The optimal cut-off to discriminate good *versus* poor prognosis was 1200 **(Figure 2)**. We applied this threshold to depict the metastasis free survival sub-group in our population **(Figure 3).** Overall, 78.8% of patients were classified as low risk and 21.2% as high risk for late recurrence. The characteristics of the population at low and high risk of relapse are reported in **(Table 4).** Low risk group had a mean 5- to 10-year recurrence risk of 9.8% (95% CI, 7.1% to

13.5%) as compared with 38.3% (95% CI, 27.6% to 50.9%) for high-risk groups. The 10% cut off was chosen in comparison to the literature (9). It corresponds to the cumulative risk of local-regional and metastatic relapse in low-risk patients 5 to 10 years after diagnosis. We represented the risk of survival without relapse after the end of the ET according to the score **(figure 4)**. The relapse rate is 16.2% when the score is 1200.

Discussion.

To estimate the risk of late recurrence is a major issue to optimize the management of post-menopausal women with HR+ breast cancer. We developed a simple tool, integrating clinic pathologic factors, able to identify women at high risk of relapse despite the completion of 5 years of aromatase inhibitors. By integrating the tumour size, the number of nodes macro-metastases and the age, our score dichotomizes patients with a low risk of local or distant recurrence between year 5 to 10 (9.8% (95% CI, 7.1% to 13.5%)) versus high risk (38.3% (95% CI, 27.6% to 50.9%)). The integration of clinical pathologic variables that are available for all patients at diagnosis means that the risk is easily calculable.

Women with HR+ early breast cancer receive generally adjuvant endocrine therapy for 5 years including tamoxifen and aromatase inhibitors for pre and post-menopausal women respectively. In 2012, a study of the group of collaboration on the preliminary clinical trials on the breast cancer (EBCTCG) gave a comprehensive view of the natural history of breast cancer and of the adjuvant treatment's effect until 15 years after diagnosis. It confirmed the long-term benefit of adjuvant chemotherapy, radiotherapy and endocrine treatment, which persisted up to 10 years after diagnosis. It also showed that despite an optimal initial management, patients kept relapsing after 5 years with more than half of recurrences occurring after the completion of adjuvant endocrine therapy. For instance, HR+ BC women who received adjuvant chemotherapy and 5 years of adjuvant ET had a risk of recurrence of 16.4% during the first 5 years and of 16.6% between years 5 and 10 years (10)(20)(21)(22). These findings have been confirmed by the long-term follow up of major adjuvant trials investigating AI with an annual recurrence risk after 5 years of 2% per year, resulting in a similar rate of recurrence in the first and second 5-years period after diagnosis (23). This temporal pattern of relapse is unique for HR+ BC, in opposition to triple negative breast cancer in whom few recurrences occur after 36 months (24).

These observations imply that patient management and decision-making process should integrate both short-term and long-term risks of recurrence. Five years of adjuvant ET reduces the risk of relapse around 50%-80% (9). Logically, several clinical trials have raised the question of the benefit of extending adjuvant ET beyond 5 years. The first two reports have demonstrated that tamoxifen prolongation during 10 years reduced breast cancer mortality and overall mortality. ATLAS study showed that 10 years of adjuvant tamoxifen *versus* 5 years reduced the risk of

recurrence during years 5-14 (RR 0.84) and overall mortality with an absolute mortality reduction 2.8% (10). This results were confirmed with aTTom study presented in 2013 but not published so far (11). Additionally, there have been studies investigating the use of AIs after 5 years of tamoxifen treatment. The ABCSG-6a, MA.17 showed a clear benefit of 5 years AI treatment after an initial 5 years of tamoxifen in terms of DFS. There was also an improvement in OS, but this was not statistically significant (17)(25) (MA.17/ ABCSG-6a/). A lack of power of these studies due to early unblinding of the study may explain these findings.

The same question subsists today for post-menopausal breast cancer women who have completed 5 years of AI. Several studies investigated the efficacy and safety of additional treatment with AIs after a sequential regimen of tamoxifen and an AI for 5 years (DATA(12), IDEAL(13), NSABP B42 (14)(12), MA 17R (26), AERAS (27), SOLE(28), LATER(29), SALSA(30)). These studies are reported in **supplemental 2.** They have not achieved their main goal. However, subgroup analyses suggest that a population at high risk of recurrence benefits from this extended strategy. Of note, none of these studies included exclusively a pure population of women having received 5 years AI and randomized to receive 5 years of additional AI.

The identification of patients who derived the most benefit of a therapeutic strategy is crucial. In a recent meta-analysis on prolonged ET, women with a lymph node involvement appeared to benefit more from prolonged ET (node positive HR 0.72 *versus* negative HR 0.83). An advantage of prolonged ET was observed in women with larger tumour sizes (> pT2, HR 0.77 compared to ≤ pT2 HR 0.88) and in those with ER+ and PR+ expression (HR 0.68 versus 1.01). A greater effect was also observed in patients who received adjuvant chemotherapy compared to those who did not (HR 0.71 versus 0.80) (31). Different scores have been developed in order to identify women at high risk of relapse after adjuvant treatment. The IHC4 score (32) is a prognostic tool that integrate four immuno-histochemical variables (ER, PR, Her2 and KI67) and clinic-pathological variable (size, nodal status and grade) to estimate the risk of late recurrence at 10 years. The CTS5 score has been recently developed from the ATAC trial by integrating data from patients who were distant recurrence free after 5 years of follow-up. It integrates clinical variables for the prediction of late distant recurrence in post-menopausal women with HR+ breast cancer treated with 5 years of endocrine therapy. This trial randomly assigned women to receive anastrozole alone or tamoxifen alone. The final CTS5 model included age (continuous), tumour size (continuous), quadratic tumour size, nodal status (five groups) and tumour grade. CTS5 (ATAC) = 0.471*nodes+0.980*(0.164*size - 0.003*size^2 + 0.312*grade + 0.03*age). CTS5 (ATAC) was significantly prognostic for late

distant recurrence in the ATAC cohort (HR, 2.47; 95% CI, 2.24 to 2.73; $P < .001$) and BIG 1-98 validation cohort (HR, 2.07; 95% CI, 1.88 to 2.28; $P < .001$). Patients categorized as low risk had a mean 5- to 10-year distant recurrence risk of 2.5% (95% CI, 1.8% to 3.4%), as compared with 7.7% (95% CI, 6.3% to 9.5%) for intermediate-risk and 20.3% (95% CI, 17.2% to 24.0%) for high-risk groups. In contrast to this score, our model is designed in a population of post-menopausal women who had received exclusively 5 years of adjuvant AI. Given the discrepant results of prolongation of AI in that population, we believe that the identification of women at high risk of late recurrence in this specific population is important. To our knowledge, our score is the only one based on a homogenous population of women who were post-menopausal at diagnosis and who completed 5 years of adjuvant AI. We believe that it adds important information in a frequent clinical setting.

Beyond these clinical tools, multigene expression profiles have significantly increased the ability to predict distant recurrence over 10 years after diagnosis in ER-positive breast cancer. The IHC4 score has been compared with two gene expression profile tests (RS and ROR). Only tumour size and nodal status provide statistically significant prognostic information in years 5 to 10 (33). Recently, in a retrospective study, six molecular signatures have been tested. Firstly, for the question of a possible extension of ET beyond 5 years in node negative patients, all signatures identified a group at low risk of late recurrences for which an extension of ET was not justified. The Breast Cancer Index assay test identified two prognostic group for late distant recurrence (34)(35). On the other hand, for the node positive patient group, only PAM50-based Prosigna risk of recurrence (ROR) and EndoPredict (Epclin) identified patients with a low risk of late relapse for whom an extension of ET was not justified (36) (37)(38)(39) (40). EndoPredict, a 12 gene expression assay, was evaluated in the ABCSG-6 (tamoxifen-only arm) and ABCSG-8 (tamoxifen-only and tamoxifen + anastrozole arms) cohort of women with ER+, HER2-, node positive and node negative BC who received 5 years of ET. Distant recurrence-free rate was assessed 10 and 15 years after diagnosis. The score distinguishes two groups of patient with low and high risk of late relapse (41). These test are approved for the decision of adjuvant chemotherapy but the cost is a real problematic contrary to our cost-less score. Further research is being done with circulating tumour cells (CTC). A single positive CTC assay in patients without clinical evidence of recurrence 5 years after diagnosis of stage II-III HR+, HER2- breast cancer has provided an independent prognostic information for late recurrence (42). Circulating biomarkers could play a major role in the future in prognostication of patients.

Our study has several limitations. We are aware of the retrospective design inducing some a selection bias. However, the ICO Berenis database included all consecutive patients of our institute. We included 9% of patients who undergone a neo-adjuvant chemotherapy which leads to a down staging of the tumour size and node involvement at the time of the pathology analysis. Given the role of the tumour size in our score, we would need to test the score with and without these patients. The follow up of patients after the first five years, was generally entrusted to their general practitioner and may have generated some monitoring bias. Finally, the choice of two risk categories of risk facilitates the decision of the best therapeutic strategy such as EndoPredict or Breast Cancer Index (BCI) tests. However, some intermediate situations inevitably exist and are not picked up by our score.

A meta-analysis in 2014 has shown that the compliance to ET was limited: 52% to 100% of patients are compliant according to studies (43)(44). Our study selected a specific population of women who apparently tolerated 5 years of therapy. We have not reported on the ET side effects and especially on bone because of the lack of data collection. A meta-analysis has shown that extended treatment with AIs is associated with an increased risk of cardiovascular events and bone fractures(45)(46). Bone-related toxic effects occurred more frequently among patients receiving AI than among those receiving placebo or Tamoxifen, including a higher incidence of bone pain and bone fractures (26). These findings require careful assessment of potential risks and benefits before recommending extended AI.

We developed a simple tool to identify women at high risk of relapse despite the completion of 5 years of aromatase inhibitors. Further investigations are needed to identify accurately women who would benefit of extending AI, including the validation of this score in an independent population.

Conclusion.

We find three independent prognostic factors of late recurrence witch are the tumour size, the number of nodes macro-metastases and the age. The integration of clinical pathologic features that are available for all patients at diagnosis means that risk is easily calculable. Any decision of extended hormonotherapy should take into consideration the age of the patient, existing comorbidities, information about bone mineral density and his opinion on toxicity as well as tumour size and nodal involvement. Futures advances are needed to identify biological markers that might predict benefit from extended AI therapy.

Annexes.

Tables et Figures:

Supplemental:

Tables.

Table 1 : Characteristics of the population.

Characteristics	n	%
Age		
Mean	63.3	
Median	62.5 [32.5-88.5]	
<50	11	1
[50-70]	899	81
>70	197	18
Tumour characteristics		
TNM classification		
T		
Tx	14	1.3
T0	498	45
T1	327	29.5
T2	226	20.4
T3	30	2.7
T4	12	1.1
N		
N0	818	73.9
N1	217	19.6
N2	59	5.3
N3	13	1.2
Micrometastasis		
Yes	97	8.8
No	1010	91.2
Hormone Receptor		
ER		
+	1102	99.5
-	5	0.5
PR		
+	855	77.2
-	252	22.8
HER2 status		
+	73	6.6
-	988	89.3
Histology		
ductal carcinoma	841	76
lobular carcinoma	197	17.8
Mix	27	2.4
Other	42	3.8
Tumour grade		
I	329	29.7
II	84	52.8
III	135	12.2
Emboly		
Yes	165	14.9
No	929	83.9
Adjuvant Treatments		
Surgery		
Radical	314	28.4
Conservative	792	71.6
Chemotherapy		
Yes	474	42.8
No	633	57.2
Adjuvant	397	35.9
Neo-Adjuvant	77	6.9
Anthracycline	443	93.5
Cyclophohphamide	448	94.5
Taxane	371	78.3
Clinical trial	49	10.3
Endocrine therapy		
Anastrozole	635	57.4
Letrozole	285	25.7
Exemestane	187	16.9

Table 2 : Characteristics of the relapsing patients

Characteristics of relapses		**n=89**	**%**
Age			
	Mean	63,2	
	Median	62 [39-83]	
	< 50	1	1,1
	[50-70]	70	78,7
	>70	18	20,2
Localization			
	Locoregional	8	9
	Contralateral	21	23,6
	metastasis	60	67,4
Histology			
	Invasive ductal carcinoma	55	61,8
	Invasive lobular carcinoma	14	15,7
	In situ	5	5,6
Time to relapse after 5 years of completed AI			
	mean	30,6	
First metastasis localization			
Single		n= 29	48.3
	Bone	12	
	Pleural	6	
	Lymph node involvement	1	
	Cutaneous	3	
	Hepatic	3	
	Brain and SNC	2	
	Osteomedullary invasion	1	
	Pulmonary	1	
Multiple, including:		n= 31	51.7
	Bone	29	
	Hepatic	11	
	Lymph node involvement	9	
	Pleural	9	
	Pulmonary	7	
	Cutaneous	5	
	Brain and SNC	3	
	Peritoneal	3	
	Ovarian	1	
	Osteomedullary invasion	1	
Management for metastatic relapse			
	Chemotherapy	13	21,7
	Hormonotherapy	43	71,7
	Best supportive care only	4	6,6

table 3 : Tumour characteristics and management of localized disease

Characterictics		**n=89**	**%**
Classification TNM :			
T			
	T0	20	22,5
	T1	29	32,6
	T2	25	28,1
	T3	9	10,1
	T4	6	6,7
N			
	N0	77	86,5
	N1	7	7,9
	N2	4	4,5
	Nx	1	1,1
Micrometastasis			
	Yes	7	7,9
	No	82	92,1
Hormone receptor			
	ER		
	+	81	91
	-	8	9
	PR		
	+	62	69,7
	-	27	30,3
	Her2 status		
	+	4	4,5
	-	85	91
Histology			
	Invasive ductal carcinoma	66	74,2
	Invasive lobular carcinoma	22	24 ,7
	Mix	1	1,1
Tumour grade			
	I	19	
	II	43	
	III	15	
Emboly			
	Yes	23	25,8
	No	62	69,7
Primitive treatment			
Surgery			
	Radical	40	44,9
	Conservative	49	55,1
Chemotherapy			
	Adjuvant	41	46,1
	Neoadjuvant	15	16,9
	No	33	37
Radiotherapy			
	Yes	87	97,8
	No	2	2,2

Table 4 : Univariate and multivariate analysis

characteristics	**Univariate analysis**						**Multivariate analysis**					
	Hazard Ratio	Standard error	z	P>|z|	95% CI		Hazard Ratio	Standard error	z	P>|z|	95% CI	
Age >= 65 vs. <65	**1.59**	**0.35**	**2.15**	**0.032**	**1.04**	**2.43**						
Age (continuous)	**1.03**	**0.02**	**1.83**	**0.067**	**0.99**	**1.06**	**1.04**	**0.02**	**2.52**	**0.012**	**1.01**	**1.07**
Number of macro metastase (continuous)	**1.20**	**0.03**	**6.77**	**0.000**	**1.14**	**1.27**	**1.16**	**0.04**	**4.24**	**0.000**	**1.09**	**1.25**
pN 2-3 vs 0-1	**4.30**	**1.08**	**5.82**	**0.000**	**2.63**	**7.02**						
pN>=1 vs 0	**2.56**	**0.55**	**4.40**	**0.000**	**1.68**	**3.89**						
Tumour size (continuous)	**1.03**	**0.004**	**5.58**	**0.000**	**1.02**	**1.03**	**1.02**	**0.01**	**2.11**	**0.035**	**1.00**	**1.03**
pT 2-3 vs 0-1	**2.75**	**0.59**	**4.81**	**0.000**	**1.81**	**4.18**	**1.77**	**0.50**	**2.03**	**0.043**	**1.02**	**3.08**
pT>=1 vs 0	**2.39**	**0.61**	**3.42**	**0.001**	**1.45**	**3.93**						
Tumour grade II vs I	1.28	0.35	0.89	0.374	0.74	2.19						
Tumour grade III vs I	1.85	0.64	1.77	0.076	0.94	3.66						
Tumour grade III vs I-II	1.57	0.46	1.56	0.119	0.89	2.77						
Number of micrometastase	1.22	0.30	0.82	0.41	0.76	1.98	1.42	0.46	1.09	0.274	0.76	2.66
Number of micrometastase 0 vs +	1.32	0.41	0.88	0.38	0.72	2.42						
ER and PR dissociation vs no	0.94	0.23	- 0.23	0.82	0.58	1.53	0.96	0.25	-0.14	0.89	0.59	1.59
Her 2 overexpressed vs no	0.58	0.29	- 1.05	0.29	0.21	1.59	1.28	0.46	0.70	0.48	0.64	2.60
Emboli 0 vs. positive	**1.65**	**0.41**	**2.05**	**0.04**	**1.02**	**2.68**	1.13	0.32	0.44	0.663	0.65	1.98
Lobular histology vs. other	**1.63**	**0.40**	**1.98**	**0.047**	**1.01**	**2.64**	1.03	0.30	0.12	0.907	0.59	1.82
Lobular or ductal histology vs other	1.38	0.34	1.34	0.181	0.86	2.23						
Radical Surgery vs conservative	**1.90**	**0.41**	**3.00**	**0.003**	**1.25**	**2.89**	1.20	0.30	0.72	0.47	0.73	1.95
Revision surgery vs no	0.73	0.20	-1.14	0.25	0.43	1.25						
Chemotherapy vs. no	**2.07**	**0.46**	**3.32**	**0.001**	**1.35**	**3.18**	1.08	0.32	0.27	0.79	0.61	1.93
Neoadjuvant treatment vs. no	**2.24**	**0.61**	**2.98**	**0.003**	**1.32**	**3.80**						
Radiotherapy vs no	2.22	1.59	1.11	0.27	0.55	9.03						

Characteristics that are clinically significant are highlighted. Only some variables from the same category were tested in multivariate analysis.

Variables that had a p of significance <0.20 in univariate were introduced in the different semi-parametric multivariate Cox models.

Table 5 : Characteristics of low and high risk population definied by our prognostic score

	Low risk group < 1200		High risk group >1200		
Characteristics	n=872	%	n=235	%	p
Age					
mean	61,9		68,6		
median	61,4[32,5-80,4]		69,6[38,6-88,5]		
TNM classification					
T					
T0	452	51.8	46	19.6	
T1	285	32.7	42	17.9	
T2	115	13.2	111	47.2	
T3	9	1	21	8.9	
T4	1	0.1	11	4.7	
TX	10	1.2	4	1.7	**<0.001**
N					
N0	838	96.1	196	83.4	
N1	31	3.6	26	11.1	
N2	2	0.2	11	4.7	
NX	1	0.1	2	0.8	**<0.001**
Micrometastasis					
Yes	55	6.3	5	2.1	
no	817	93.7	230	97.9	**0.009**
Hormone receptor					
ER					
+	868	99.5	234	99.6	
-	4	0.5	1	0.4	0.99
PR					
+	674	77.3	181	77	
-	198	22.7	54	23	0.93
Her2 status					
+	58	6.7	15	6.4	
-	775	88.9	213	90.6	0.99
Histology					
Invasive Lobular carcinoma	132	15.1	65	27.7	
Invasive Ductal carcinoma	685	78.6	156	66.4	
Mix	18	2.1	9	3.8	
Other	37	4.2	5	2.1	**<0.001**
Tumour grade					
I	301	34.5	28	11.9	
II	450	51.6	134	57	
III	87	10	48	20.4	**<0.001**
Emboly					
yes	97	11.1	68	28.9	
no	766	87.8	163	69.4	**<0.001**
Treatment					
Surgery					
Radical	182	20.9	132	56.2	
Conservative	689	79	103	43.8	**<0.001**
Chemotherapy					
Yes	295	33.8	179	76.2	
No	577	66.2	56	23.8	
Adjuvant	249	28.6	148	63	
Neoadjuvant	46	5.3	31	13.2	**<0.001**

Figures.

Figure 1 : Flow chart

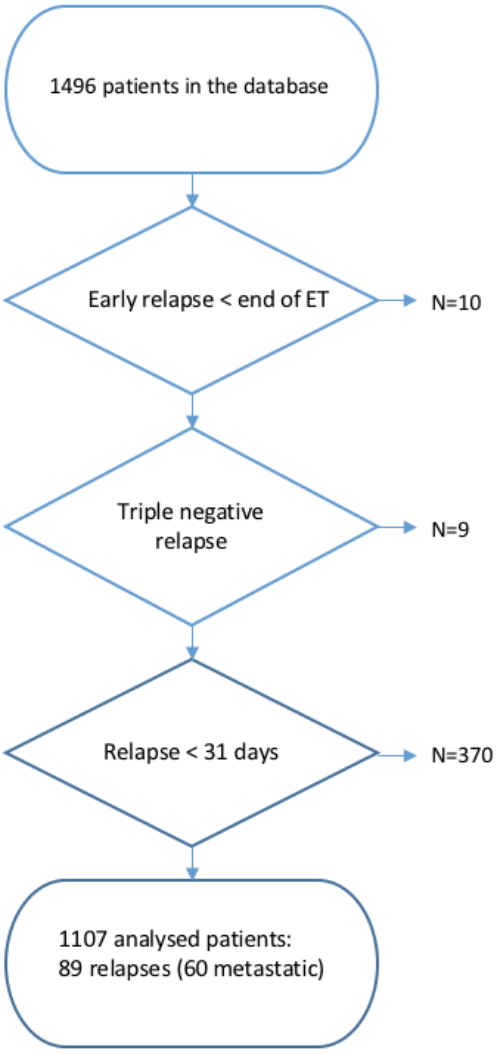


Figure 2 : Probability of relapse free survival according to low and high risk score determined by our score.

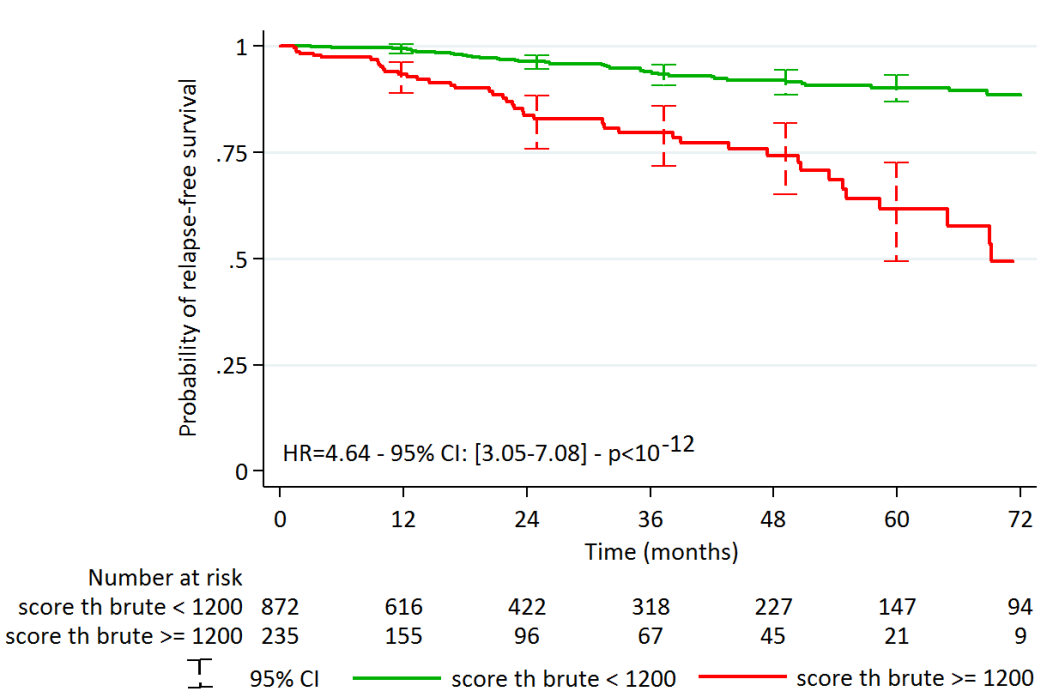


figure 3 : Probability of metastasis free survival according to low and high risk score determined by our score

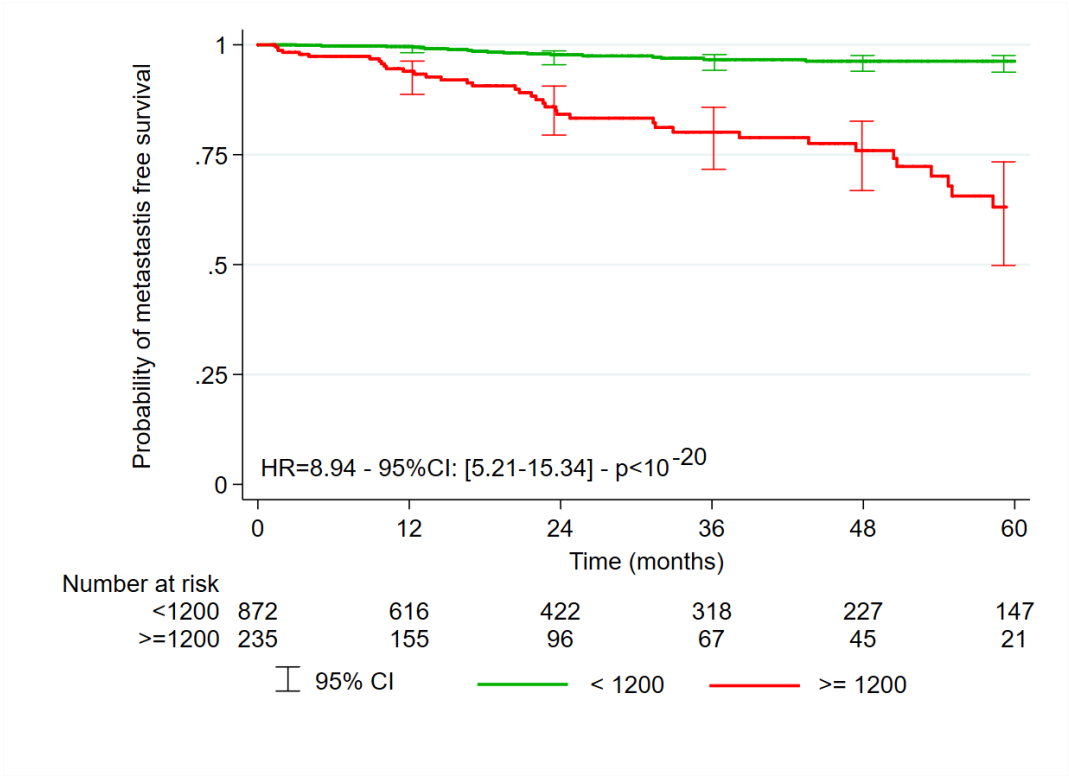
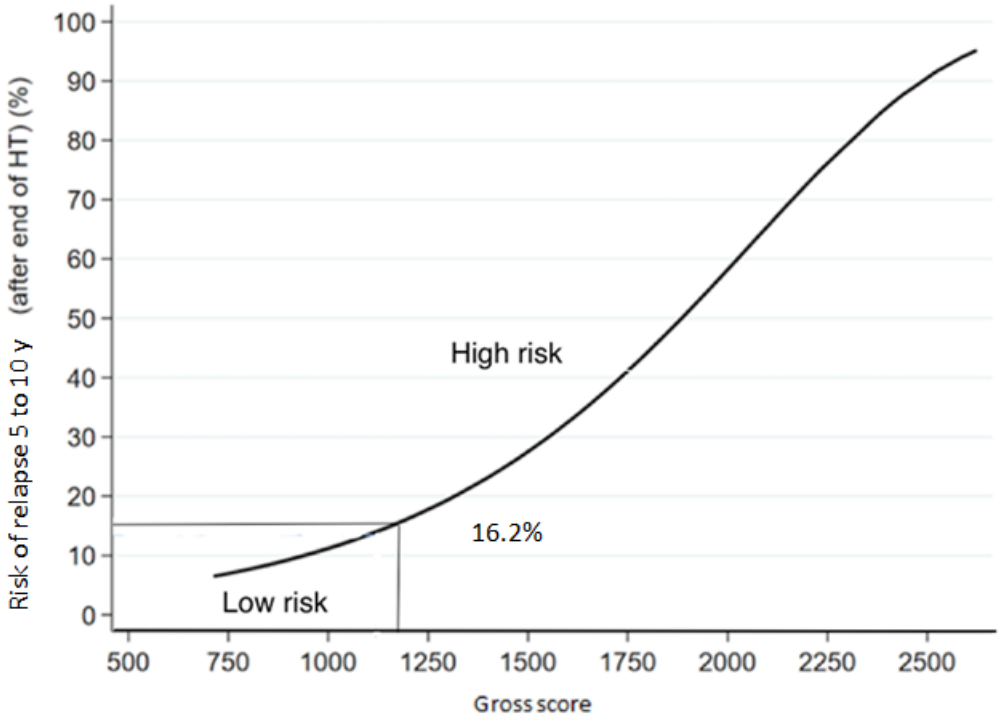


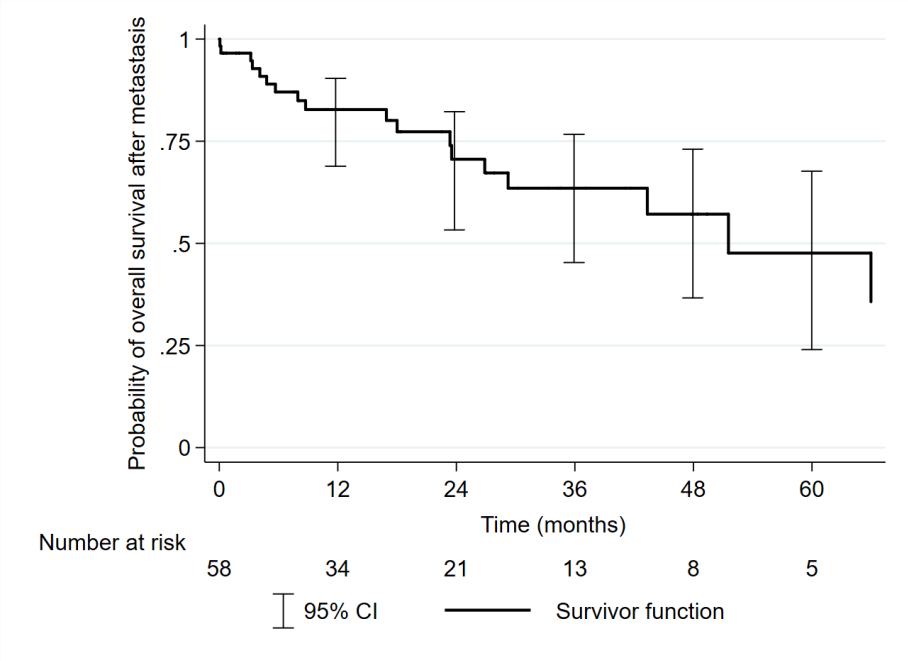
Figure 4 : Risk of relapse between 5 and 10 years depending on the score.



Predicting 5 to 10 years recurrence risk. Solid vertical line indicates cut-off points for risk groups.

Supplemental.

supplemental 1: Overall survival of patients who had a metastatic relapse



supplemental 2: studies concerning the prolongation of endocrine therapy

Studies	Author	recruitment period	Publi-cation	number of patients	Meno-paused	median follow up	study design	OS (HR-CI)	DFS (HR-CI)
TAM after TAM									
ATLAS	Davies	1996-2005	2013	6846	90%		TAM 5y or placebo		
ATTom	Gray	1991-2005	2013	6953	90%		TAM 5y or placebo		
AI after TAM									
MA 17	Goss	1998-2002	2003	5187	yes	5.3	5y AI or placebo	0.82 (0.57-1.19)	0.58 (0.45-0.76)
ABCSG6a	Jakesz	1990-1995	2007	856	yes	5.2	3y AI or placebo	0.89 (0.59-1.34)	
NSABP B33	Mamounas	2001-2003	2008	1598	yes	2.5	5y AI or placebo		RR 0.68
AI after TAM/AI									
DATA	Tjan-Heijnen	2006-2009	2016	1660	yes	4.1	3y or 6y AI	0.91 (0.65-1.29)	0.79 (0.62-1.02)
IDEAL	Blok	2007-2011	2016	1824	yes	6.6	2.5y or 5y AI	1.08 (0.81-1.45)	0.96 (0.76-1.20)
NSABP-B42	Mamounas	2006-2010	2016	3923	yes	6.9	5y AI or placebo	1.15 (0.99-1.44)	0.85 (0.73-0.99)
MA17-R	Goss		2016	1918	yes	6.3	5y AI or placebo	0.97 (0.73-1.28)	0.66 (0.48-0.91)
AERAS	Ohtani	ASCO	NP	1697	yes	4.9	5y AI or placebo		
SOLE	Colleoni	ASCO	NP	4884	yes	5	5y AI continous or intermittent	0.85(0.68-1.06)	1.08 (0.93-1.26)
SALSA/ ABCSG16	Gnant	2004-2010	NP	3484	yes		2y or 5y AI		
LATER	Zdenkowski	2007-2012	2016	360	yes	3.9	5y AI or placebo		

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NOM : MOREAU--BACHELARD PRENOM : Camille

Titre de Thèse : Identification des facteurs prédictifs de récidive d'un cancer du sein à récepteurs hormonaux positifs après 5 ans de traitement par inhibiteur de l'aromatase et développement d'un outil pronostique. Une analyse de 1496 femmes de la base de données de l'ICO.

RESUME

INTRODUCTION : Les femmes atteintes d'un cancer du sein localisé à récepteurs hormonaux positifs reçoivent généralement une hormonothérapie (HT) adjuvante pendant 5 ans, par tamoxifène ou inhibiteurs de l'aromatase (IA) pour les femmes pré et post-ménopausées respectivement. Toutefois, plus de la moitié des récidives surviennent après cette période et la prolongation de l'HT est une option. L'identification des patientes qui pourraient bénéficier le plus de l'extension de l'HT est un enjeu majeur. Nous voulions développer un outil pronostique simple pour estimer le risque de récidive tardive chez les patientes ayant terminé 5 ans d'IA, afin d'aider à la prise de décision concernant l'extension de l'IA. Nous avons émis l'hypothèse qu'une récidive tardive, qu'elle soit métastatique, controlatérale ou homolatérales après 5 ans d'IA, pouvait être associée à des facteurs pronostiques cliniques et pathologiques initiaux.

MÉTHODES : Dans cette analyse monocentrique, rétrospective et descriptive de la base de données BERENIS, nous avons inclus toutes les femmes ménopausées, atteintes d'un cancer du sein localisé et ayant suivi 54 mois d'HT.

RÉSULTATS : Entre janvier 2003 et décembre 2011, 1 107 femmes ménopausées ont été incluses. Après une durée médiane de suivi de 32,6 mois [1-132], le taux de récidive était de 8 %, incluant 60 rechutes métastatiques, 8 et 21 rechutes homolatérales et controlatérales respectivement. L'analyse multivariée a montré que la taille histologique de la tumeur (HR = 1,02 ; p = 0,035), le nombre de macro-métastases (HR = 1,17 ; p = 0,001) et l'âge (HR = 1,04 ; p = 0,012) étaient des facteurs pronostiques indépendants de la survie sans récidive. Nous avons conçu un score pronostique de rechute tardive correspondant à : 10*(taille de la tumeur (mm)) +79*(nombre de macrométastases) +14*(années) avec un seuil à 1200 points. Dans notre population, 78,8 % ont été classés comme présentant un risque faible et 21,2 % comme présentant un risque élevé de récidive tardive. Le risque moyen de récidive locale ou à distance de 5 à 10 ans était de 9,8% (IC 95 %, 7,1% à 13,5%) pour le groupe à faible risque, comparativement à 38,3% (IC 95 %, 27,6% à 50,9%) pour celui à risque élevé.

CONCLUSION : Ce score prédit le risque de récidive après 5 ans d'utilisation de l'IA et peut être un outil simple pour aider les cliniciens à sélectionner les patientes qui pourraient tirer le plus d'avantages d'une prolongation de l'HT par IA après 5 ans.

MOTS-CLES

CANCER DU SEIN LOCALISE – RECEPTEURS HORMONAUX POSITIFS – RECIDIVE TARDIVE – PROLONGATION DE L'HORMONOTHERAPIE- SCORE PRONOSTIQUE