Liste des abréviations

DCIS :	Ductal Carcinoma In Situ
LIR :	Local Invasive Recurrence
BCS :	Breast Conserving Surgery
BCT :	Breast Conserving Treatment

Plan

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Evaluation of predictor risk factors and calculation of a margin index for ipsilateral invasive recurrence following treatment of DCIS: a Fifteen year observational study.

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ABSTRACT:

Background: The goal of ductal carcinoma in situ (DCIS) treatment is the local control of the disease, preventing or reducing potential occurrence of invasive breast cancer. The understanding of predictor risk factors for local invasive recurrence is a priority. The main objective was to evaluate patient and tumor characteristics as a risk for ipsilateral invasive recurrence. The second objective was calculation of a margin index to predict residual tumor on re-excision.

Patients and Method: Retrospectively, all female patients diagnosed and treated for DCIS from 2000 to 2015, from both Institut de Cancerologie of Angers and Nantes, were included. Risk for ipsilateral invasive recurrence following DCIS was evaluated according to patients and tumor characteristics. Margin index was calculated based on the original tumor size and the closest margin: *(closest margin / tumor size) in mm x 100*.

Results: The study retrospectively included 1388 patients with histologically confirmed DCIS. After five years of follow up, chance to survive without an ipsilateral invasive recurrence was 96.91%, IC 95% [95.64-97.81] A High nuclear grade, previous history of contralateral ductal carcinoma and breast conserving treatment were found to be predictor risk factors for local invasive recurrence in multivariate analysis HR1.96; IC 95% [1.06-3.62] p=0.031; HR2.83; IC 95% [1.09-7.37] p=0.032; HR2.22 IC 95% [1.02-4.83] p=0.043, respectively. Within the sub group population undergoing conserving treatment, only tendency was found for some factors to increase risk for LIR. A margin index of 5.6 was found to be the most suitable index to predict a risk for residual tumor on re-excision after the first surgery.

Key Words: DCIS; predictor risk factors, invasive recurrence, margin index

INTRODUCTION:

Ductal carcinoma in situ (DCIS) is a nonlethal pre malignant disease of the breast composed by a heterogeneous group of lesions. Since the introduction of screening mammography in the 1980s, detection of DCIS drastically increased and now represents nearly 20% of all newly diagnosed breast malignancies detected by mammography [1, 2, 3].

The purpose of treating DCIS is the local control of the disease, to prevent potential occurrence of an invasive breast cancer, as well as to maximize breast conservation and to maintain an acceptable cosmetic result. The natural history of DCIS remains unknown and some DCIS may turn into an invasive breast cancer.

There is currently no information to accurately identify women with a greater risk for subsequent disease recurrence which should be treated or followed more aggressively. Some factors, such as the tumor and patient's characteristics, biomarkers, and surgical margin status after breast conserving surgery (BCS) were found to be associated with a higher and or a lower risk of local invasive recurrence (LIR) [1, 4, 5]. Within the past 20 years, randomized clinical trials have established that breast conserving surgery in addition to radiotherapy (BCT) may decrease the risk for a local recurrence [6, 7]. It is therefore the gold standard for DCIS treatment. Yet, this treatment appears not suitable for all patients and offers no benefit to some. Discovering which specific features (from patient or from the original tumor) are predictors and increase the risk for LIR is a priority for DCIS treatment. The understanding of such factors, proven to be predictors and leading to a higher risk for LIR, could help health care providers to choose a more appropriate and tailored treatment for patients undergoing DCIS.

There is general agreement that clear margins decrease the risk of local recurrence for DCIS. However, there is no consensus on what is considered a clear margin following BCS [5, 8, 9]. A previous study [10] created a margin index among a population presenting an invasive breast

cancer, who benefitted from BCS. If this margin index is determined to be a better predictor of residual disease after BCS it will help in deciding whether or not to perform a re-excision.

In light of the Zhang et al [11] meta-analysis outcomes, the primary endpoint of the study was to evaluate if within the population diagnosed and treated for DCIS of the breast, some patient characteristics or tumor characteristics could be predictive risk factors for LIR. The second objective was to evaluate, among this same population, if the calculation of the margin index could accurately predict risk for residual tumors after surgery.

PATIENTS and METHOD:

Study design:

This retrospective observational study occurred on both campuses of the Institut de Cancerologie de l'Ouest (ICO) in Angers and Nantes. The study evaluated predictor risk factors for an invasive ipsilateral recurrence of DCIS between the first of January 2000 and the first of January 2015.

Population inclusion and exclusion:

Retrospectively, all female patients diagnosed and treated for DCIS were included. Every patient included in the study presented a histologically proved diagnosis of DCIS. Each case of DCIS was followed for diagnosis of a local invasive recurrence (LIR). Cases of (LIR) were defined as those diagnosed six months or more after DCIS diagnosis. Female patients younger than 18 years old or patients who underwent Lobular Carcinoma in situ were excluded from the study population.

In both institutes, patients received the surgical treatment (either BCS, BCS in addition to radiation therapy or radical mastectomy) or received only radiation therapy when surgery had been previously completed in another medical center. Patient medical records were the principal source of data. Data was collected through both Angers and Nantes ICO databases by researching for key words such as DCIS and invasive recurrence.

Follow up:

Follow up was through annual consultation, whether by the surgeon who performed the original surgery or the radiotherapist giving the radiotherapy. Annual follow up was

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considered until July 2016. Each patient follow up duration was calculated in years from the date of diagnosis to the year last known alive. Each of the following events that occurred after the date of DCIS diagnosis was considered the first event: DCIS ipsilateral recurrence, LIR, occurrence of a second breast cancer, distant recurrence of the breast malignancy, and death of the patient. LIR or DCIS recurrence were always confirmed by a histological examination of the recurrence biopsy.

Description of tumor and patient's features analyzed:

During the primary part of the study, evaluation of each patient and tumor characteristics were made to estimate the risk for LIR following DCIS. Sub group analysis was done only on patients undergoing BCT or BCS treatment to evaluate survival without LIR and the predictive risk factors for LIR.

The patient characteristics analyzed were age, menopausal status and biomarkers. Patient age was defined as above or below 40 years old, menopausal status was whether patient was in menopause at the date of CCIS diagnosis or not. The biomarkers evaluated were the expression of estrogen receptors (positive versus negative), progesterone receptors (positive versus negative) and epidermal growth factor 2 (HER2) (positive versus negative). For each tumor characteristic, discrimination was made on nuclear grade (high versus intermediate and low), tumor size (≤20 millimeters (mm) or > 20 mm), comedonecrosis (positive or negative), focality (multifocal / multicentric versus unifocal), mode of detection (screening mammography or none), treatment received (lumpectomy alone, BCS with radiotherapy, mastectomy) and margin status. Even though there were no standardized definitions of a free margin, it was considered positive if ≤ 1 mm or involved and negative if > 1 mm or free of tumor. Regarding the lack of definition for tumor size, agreement was made that tumors measuring ≤ 20 mm were considered small.

Margin index calculation:

During the second part of the study, calculation of a margin index was done based on an equation including the original tumor size and the closest margin from each patient's first surgery: ***(closest margin / tumor size) in mm x 100*.** This calculation was made for every patient included in the study and within the sub group analysis for patients whom only benefitted from BCT or BCS treatment. For every patient, occurrence of a second surgery, and whether or not a residual tumor was found, was evaluated. Finally, a comparison was made between margin index and characteristics of potential second surgery to determine the best margin index value which could accurately predict if a residual tumor would be found during a second surgery. The feasibility of this index calculation as well as its reproducibility could avoid an unnecessary second surgical procedure.

Statistical analysis:

Quantitative parameters were described using their mean ± standard deviation. Qualitative parameters were described using frequencies of their modalities. Time to invasive or DCIS relapse was defined as the time between date of diagnosis and date of the relapse event (or date of last visit if no recurrence occurred during the mean time). Survival curves were calculated using the Kaplan-Meier method. Groups of interest were compared using Student's t test for quantitative parameters, using the Pearson Chi-square test for qualitative parameters and a log-rank test for survival. Multivariate analysis was conducted if necessary using logistic regression (for the binary dependent variable) or Cox regression (time dependent variable). Every patient's characteristics or tumor's characteristics with a p value ≤0.15 in the univariate analysis were included in the multivariate analysis allowing for interaction. All tests were two-sided with p considered significant when p < 5%. All

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calculations were done using Stata SE 13.1 (StataCorp, College Station, Texas, USA) and SAS 9.4 (SAS Institute, Cary, NC, USA).

Both patients and the ethics committee (CNIL) received an informational letter to inform them about the ongoing study and for them to give their approval.

RESULTS :

1. Population and tumor characteristics description:

The study retrospectively included 1,388 patients, 784 patients from Angers and 604 patients from Nantes, with histologically proved DCIS. Populations were similar in both institutes. Characteristics of the population are described (Table 1). Out of the 1,388 patients included, 4.0% of the population presented a LIR, during follow up. An ipsilateral DCIS recurrence was found for 2.5% of the patients included (34 patients total). For 1,140 patients (82.1%), no event was reported through the end of their follow up.

Table I : Population characteristics

Population characteristics	Population (n= 1388)	Percentage (%)
RE status:		
Positive	344	24.8%
Negative	104	7.5%
Unknown	746	67.7%
RP status:		
Positive	269	19.4%
Negative	179	12.9%
Unknown	940	67.7%
HER 2 status:		
Positive	12	0.9%
Negative	43	3.1%
Unknown	1333	96.0%
Nuclear grade status:		
high	579	41.7%
moderate/low	765	55.1%
unknown	44	3.2%

Comedonecrosis status:		
Positive	968	69.7%
Negative	277	20.0%
unknown	143	10.3%
Tumor size:		
≤20mm	753	54.3%
>20mm	489	35.2%
Unknown	146	10.5%
Margin status:		
Margin ≤ 1mm	556	40.0%
Margin > 1mm	799	57.6%
Unknown	33	2.4%
Treatment received:		
Surgery alone	20	0.7%
BCS+ RT	921	66.4%
Mastectomy	447	32.2%
unknown	2	0.7%
Previous contralateral breast cancer:		
Positive	88	6.3%

RE: Receptor Estrogen; RP: Receptor Progesterone

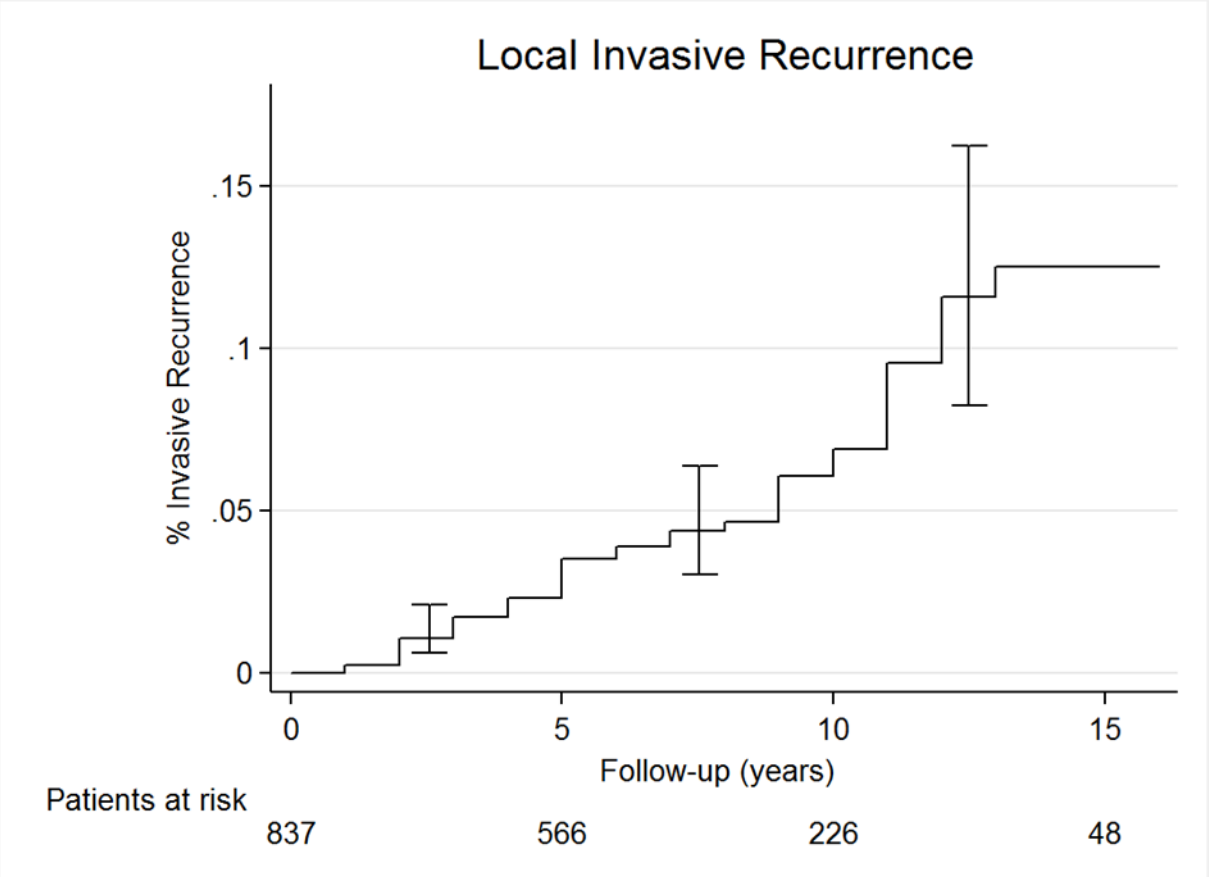
RT: radiotherapy; BCS: Breast Conserving Surgery

CCI: Invasive Ductal of the breast; CLI: Lobular Carcinoma of the Breast

2. Median of follow up, overall survival:

The median of follow up was five years for every patient included in the study. After five years of follow up, the chance to survive without a LIR was 96.91%, CI 95% [95.64-97.81]. The median for LIR was five years (4.99 years). Within the sub group analysis for patients undergoing BCT or BCS treatment, median of follow up was five years. Within this population, the calculated survival rate without LIR after five years was 96.5% and after fifteen years of follow up was 87.5% (Figure 1).

Figure 1: Local invasive recurrence in BCS and BCT population (n= 941)



Interval calculated at 2.5 years, 7.5 years and 12 years.

3. Predictor risk factors for ipsilateral invasive recurrence within the whole population:

The univariate analysis for the whole population revealed three significant predictor risk factors for a LIR: a high nuclear grade of the tumor, previous treatment for a contralateral ductal carcinoma and treatment by BCT for this current episode of DCIS (Table 2). Predictor risk factors such as tumor size >20mm and /or patients who presented a micro invasive carcinoma (CCI) associated to the actual DCIS showed a tendency toward a risk for a LIR. However, they were not statistically significant: HR= 0.58; CI 95% [0.31- 1.09] p= 0.094 for large tumor size (> 20mm) and HR=2.07; CI 95% [0.93-4.61] p=0.072 for CCI associated to DCIS. (Table 2). After adjusting for the characteristics with a p value ≤0.15 (necrosis, tumor size, type of treatment, margin status, margin index and association with a micro invasive carcinoma), the multivariate analysis highlighted the same predictor risk factors to be significantly at risk for a LIR than those found from the univariate analysis. For high nuclear grade, patients with previous history of contralateral ductal carcinoma and patients treated by BCT, results were HR 1.96; CI 95% [1.06-3.62] p=0.031; HR 2.83; CI 95% [1.09-7.37] p=0.032; HR 2.22 CI 95% [1.02-4.83] p=0.043, respectively (Table 3).

Table II: Univariate analysis for Predictor Risk factors for an Ipsilateral Invasive Recurrence in population treated by mastectomy and BCT (n=1388)

Features evaluated	Hazard Ratio	Standard Error.	z	P>|z|	[95Conf.Interval]	
Estrogen No Vs Yes	1.420699	0.8548992	0.58	0.560	0.4368129	4.620711
Progesterone No Vs Yes	2.391237	1.363917	1.53	0.126	0.7818319	7.313614
Nuclear Gr Low Vs High	0.5163464	0.1450223	-2.35	0.019	0.297763	0.895388
Necrosis No Vs Yes	0.775568	0.2913936	-0.68	0.499	0.3713723	1.619684
Tumor size > 20mm	0.5885844	0.1861794	-1.68	0.094	0.3166351	1.094104
Margin>1mm vs ≤1mm	0.8536121	0.242443	-0.56	0.577	0.4892177	1.489426
Mastectomy Vs BCT	0.4694626	0.1491378	-2.38	0.017	0.2518798	0.875001
Previous CCI No Vs Yes	0.4089302	0.1778129	-2.06	0.040	0.1743917	0.958898
Closest margin	1.022235	0.0462337	0.49	0.627	0.9355184	1.116989
Margin Index	0.9994585	0.0021481	-0.25	0.801	0.995257	1.003678

p ≤0.05 significant
Nuclear Gr= Nuclear grade
BCT =Breast Conserving Treatment

Table III: Multivariate analysis for predictor risk factors for ipsilateral invasive recurrence in population treated by mastectomy and BCT (n= 1388):

Predictor risk factors	Hazard Ratio	Standard Error	z	P>|z|	[95% Conf. Interval]	
Year of diagnosis	0.9079171	0.0442558	-1.98	0.047	0.825191	0.998935
Nuclear Grade H Vs L	1.965106	0.6137648	2.16	0.031	1.06544	3.624459
Previous CCI	l2.837402	1.382744	2.14	0.032	1.09171	7.374537
BCS Vs Mastectomy	2.226733	0.8802098	2.03	0.043	1.02611	4.83216

Nuclear Grade H Vs L= Nuclear Grade High versus Low
Previous CCI= Previous contralateral Ductal carcinoma
BCS = Brest Conserving Surgery

p ≤0.05 significant

4. Predictor risk factors for ipsilateral invasive recurrence within sub group population with BCT and BCS treatment:

Outcomes from the univariate analysis within this sub group of the population did not find any predictor factors to be significantly at risk for LIR (Table 4). Only an increased tendency was found for negative progesterone receptor status, high nuclear grade, margin ≤1mm and previous history of carcinoma to be more at risk for LIR: HR 3.3 CI 95 [0.8-13.3] p=0.09; HR 0.5 CI 95 [0.3-0.04] p=0.07; HR 0.5 CI 95 [0.3-1.04] p=0.07; HR0.4 ci 95 [0.17-1.1] p= 0.09, respectively.

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Table IV: Univariate Analysis on predictor risk factors for population with BCT and BCS treatment (n= 941):

Features evaluated	Hazard Ratio	Standard Error	z	P>|z|	[95% Conf. Interval]	
ER No Vs Yes	2.07519	1.478873	1.02	0.306	0.5133971	8.388072
PR No Vs Yes	3.331369	2.365134	1.70	0.090	0.8285235	13.39494
HER2 No Vs Yes	0.3481187	0.4264164	-0.86	0.389	0.0315556	3.840416
Nuclear Gr Low Vs High	0.5718561	0.176871	-1.81	0.071	0.3119007	0.048473
Necrosis No Vs Yes	0.6630466	0.2695903	-1.01	0.312	0.2988486	1.471082
Tumor size>20mm	0.7220691	0.3004924	-0.78	0.434	0.3194091	1.632339
Margin>1mm Vs≤1mm	0.5687377	0.177907	-1.80	0.071	0.3080686	1.049969
Previous CCI No Vs Yes	0.4478405	0.2132772	-1.69	0.092	0.1760969	1.138925
Closest margin	0.9872365	0.0490232	-0.26	0.796	0.8956804	1.088151
Margin Index	0.9983448	0.0025296	-0.65	0.513	0.9933992	1.003315

ER= Estrogen Receptor
PR= Progesterone Receptor
Nuclear Gr= Nuclear Grade

p ≤0.05 significant p<0.10 tendency

5. Margin index:

Evaluation on the risk to find a residual tumor after surgery and calculation of the margin index showed a mean tumor size for the entire population of 22mm with a mean closest margin of 3.22 mm. This resulted in a calculation of a mean margin index value of 43.37. Univariate analysis indicated that presence of comedonecrosis, large tumor size (>20mm),

presence of micro invasive ductal carcinoma and treatment by radical mastectomy (performed during second surgical procedure) were predictor risk factors for residual tumor on re-excision. Meanwhile, the multivariate analysis highlighted only the large tumor size (>20mm), the presence of comedonecrosis and the mastectomy to be predictor risk factors for finding residual tumors after the first surgical procedure. For comedonecrosis, large tumor size and mastectomy results were OR= 1.99; CI 95% [1.08-3.63] p=0.026; OR= 2.37; CI 95% [1.42-3.93] p= 0.001; 0R= 4.88; CI 95% [2.89-8.24] p<0.00001, respectively. Within the sub group population undergoing BCT or BCS treatment, the mean closest margin was 3.82mm, mean tumor size was 15.6 mm which resulted in a calculation of a mean margin index value of 52.5. Within this same sub group population, a multivariate analysis found the presence of comedonecrosis and a larger tumor size > 20mm to be significant risk factors for finding residual tumors. Presence of comedonecrosis multiplies the risk of residual tumors by 2.06, and large tumor size (>20mm) multiplies the risk of residual tumors by 2.66. For comedonecrosis and large tumor size outcomes were OR 2.06 CI95[0.9-4.2] p=0.055; OR 2.66 CI 95 [1.4- 5.04] p= 0.003 respectively.

A margin index of 5.6 was found to be the most suitable index to predict a risk for residual tumor after the first surgery. According to this index value, the rate for false negatives was at its lowest (20%) which correlated to the lowest risk for false positive (55.2%). The rate of true positive and true negative for this value of margin index was 65.83%. Sensitivity and specificity for a 5.6 margin index were 80% and 44.72% respectively with a positive predictor value of 63.3% and a negative predictor value of 60% (Figure 2). Patients with a margin index higher than 5.6 were less likely to have residual tumor if re-excision was performed. Conversely, the presence of a residual tumor after the first surgical procedure was more likely if the patient presented a margin index lower than 5.6.

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Figure 2: Determination of the Margin Index in global populations (mastectomy and BCT)

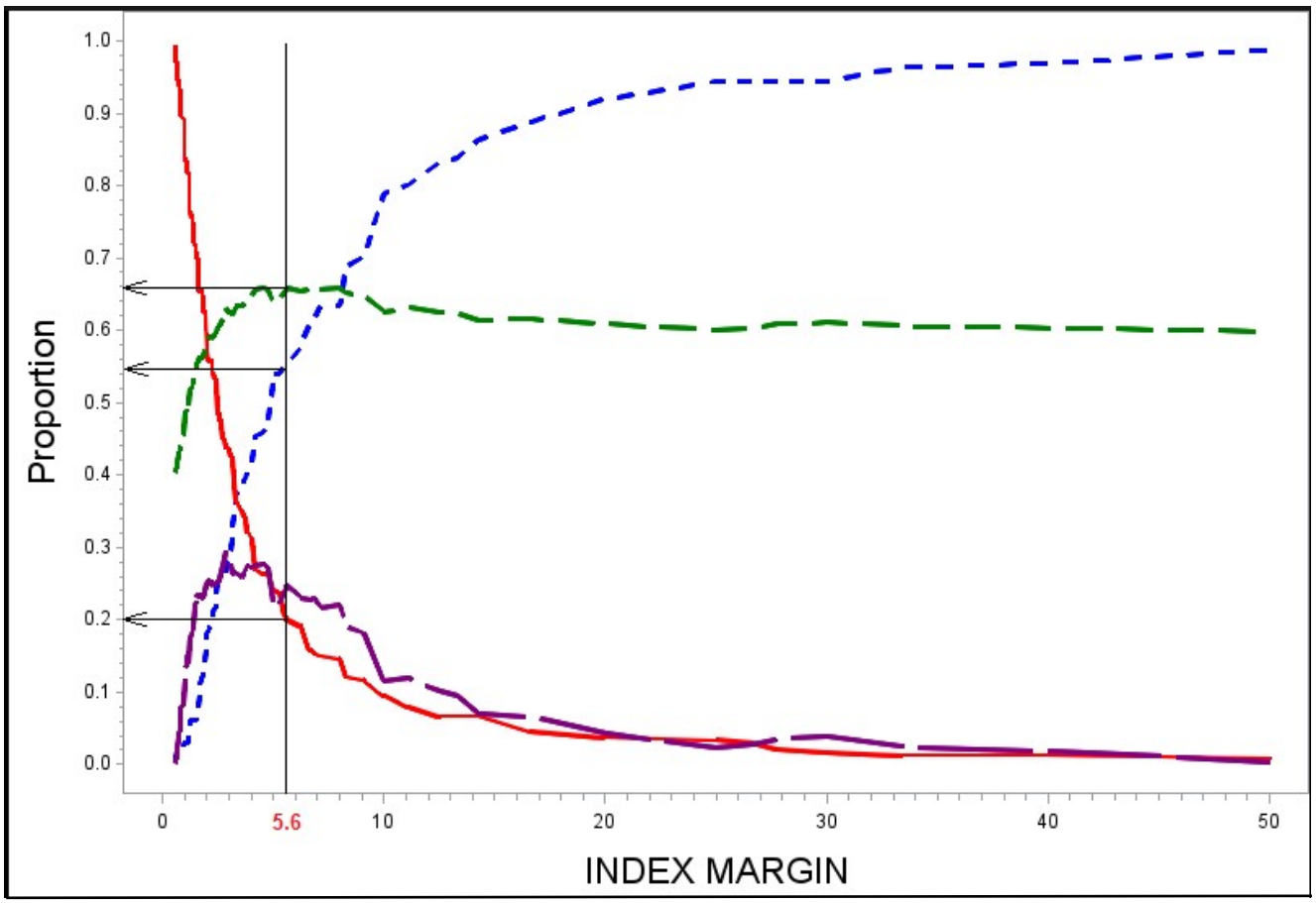

Figure legend: Operating characteristics:

- False Positive Rate
- Accuracy: True Negative and True Positive Rate
- False Negative Rate
- Younden Index

Determination of the margin index in comprehensive method included the lowest false positive rate with the most acceptable false negative rate.

DISCUSSION AND CONCLUSION

To our knowledge, this evaluation of predictors factors associated to a calculation of a margin index represent a unique way to determine predictor risk factors for LIR of DCIS and risk for residual tumor after the first surgical procedure.

Regarding the survival rate without LIR, our results showed only 3.5 % LIR after five years of follow up within the population whom benefitted from BCT or BCS treatment. After 15 years of follow up only 12.5 % of this precise population relapsed with a LIR. Our invasive recurrence rate concurred with those from the literature as Donker et al [12] showed that populations whom benefitted from the same treatment (BCT) had a 15 years' invasive free local recurrence rate of 90%. In its own study, Falk et al [13] found that female patients with a primary diagnosis of DCIS had 11.2% risk to develop a subsequent breast malignancy within 10 years when treated by BCT. Our median of follow up of five years also concurred with these from Collins et al study [14].

According to our multivariate analysis within the whole population (patients treated by BCT and those treated by radical mastectomy), previous history of ductal carcinoma, high nuclear grade of the tumor and BCT treatment appear to be predictive risk factors for LIR. The high nuclear grade, being a predictor factor for local recurrence, has been previously evaluated in Collins et al study [14]. However, in this study [14], even though there was a tendency for patients with a high nuclear grade of the tumor to present a local relapse, it was not statistically significant. Regarding the size of the tumor, our study highlighted that a larger size (>20mm) was associated with a tendency toward the risk for LIR, without being statistically significant unlike in the Collins et al study[14].

Within our sub group population who benefitted from BCT analyzed for LIR, no predictor factors were found to be significantly at risk for LIR. Only high nuclear grade, negative progesterone receptor, or a previous history of breast carcinoma demonstrated a tendency

toward risk for LIR. Zhang's meta- analysis[11] highlighted this same tendency for LIR regarding the progesterone status, and the high nuclear grade. Others studies [15, 16] presented biomarkers to be predictor factors for LIR such as HER2 overexpression and negative progesterone status. Except for a tendency toward risk to LIR for negative progesterone receptor in our sub group population analysis, our outcomes did not indicate biomarkers to be predictive risk factors for LIR. Yet, the lack of information for biomarkers status may constitute a bias regarding their involvement in this type of recurrence.

Evaluation of Zhang's study [11] and several other studies [14, 17, 18] pointed out involved margin as a predictor risk factors for LIR. However, unlike in those studies [11, 14, 17, 18], neither in our whole population nor in our sub group of patients treated by BCT did the margin status represent a predictive risk factor for LIR. This can be explained by our mean closest margin of 3.82mm for patients treated by BCT or BCS which was considered as a clear margin in Zhang's meta-analysis [11]. In this same meta-analysis [11], the other predictor risk factor found to be associated to an increased risk for LIR was the clinical detection of DCIS. In our study, this factor was not found to be predictor since more than 98% of the whole population presented a screening detection by mammography.

In a second part of our study, evaluation of a margin index was made, according to the same equation J.A. Margenthaler et al calculated in their own study [10]. Since no definition of a clear margin existed, they hypothesized that the optimum margin after BCS should depend on the original size of the tumor more so than on a standardized margin width. Therefore, they presented a new calculation of a margin index tailored to the relationship between the closest margin and the original size of the tumor. This margin index, being a better predictor of residual disease on re-excision than margin alone, will help to decide whether or not to perform a re-excision before adjuvant radiotherapy. Indeed, some studies such as the one from Jaffre et al [19], evaluated the usefulness of a surgical re-excision after BCS in the case of

close or involved margin. Their outcomes demonstrated that there was no need to perform a systematic surgical re-excision for patients with close or involved margins. In Margenthaler's study, calculation of this margin index was done on a population undergoing invasive carcinoma of the breast stage I or II. As the index does not depend on histological features of the tumor but only on the closest margin and the original tumor size, extrapolation of the margin index was possible on our DCIS population. Our study showed that the most suitable margin index to predict risk for residual tumor was 5.6 with a false negative rate of 20%. This result corresponds to J.A Margenthaler study's outcomes which found an index value of five. According to both the J.A Margenthaler study and ours, the margin index appears to be a sensitive factor to help health care providers in their decision on whether or not to perform re-excision after the removal of the original tumor. Margin index's sensitivity for both studies, Margenthaler's and ours, was a similar 85% and 80% respectively. In the future, prospective controlled randomized trials should be done to more thoroughly evaluate its application in daily practice.

Our study presents some limitations. Firstly, the lack of data regarding the use of hormonal therapy that could influence the future development of invasive carcinoma. Indeed, the evaluation of biomarkers were not researched before 2010, consequently, patients treated before this year did not benefit from this medical treatment. Secondly, even though each patient included in the study presented a histological proved diagnosis of DCIS, this diagnosis was performed by pathologists from multiple institutions and hospitals which can lead to a certain degree of misclassification error, due to varying criteria among pathologists. Thirdly, our median follow-up of five years is relatively short and does not allow us to identify risk factors for LIR which could occur in a longer term interval. Last but not least, authors are aware that this study remains retrospective and observational, consequently, its results cannot influence clinical guidelines for DCIS treatment without supportive data from

controlled randomized trials. Despite those limitations, the study's strength lies in its large sample size population (1388 patients included). Moreover, the population included came from several hospitals and institutions from all France's north western region.

To conclude, our study suggested high nuclear grade, previous history of ductal carcinoma on the contralateral breast and patients treated with BCT to be predictor risk factors for LIR following DCIS. A 5.6 value for the margin index was the best value to identify risk for residual tumor after surgery. The understanding of those factors leading to a LIR is a priority for clinicians and surgeons. It will help them to provide the best tailored treatment for their patient, minimizing unnecessary procedures without reducing the local control of the tumor. Further studies should be done with larger sample size and longer follow up to support those outcomes.

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2. Median of follow up, overall survival

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ANNEXES

Annexe 1: Ipsilateral Invasive Recurrence Free Survey in whole population (mastectomy + BCT and BCS population)

Time (years)	Beg. Total	Fail	Survivor Function	Standard Error	[95% Conf. Int.]	
1	1193	3	0.9975	0.0014	0.9922	0.9992
2	1186	8	0.9908	0.0028	0.9834	0.9949
3	1112	5	0.9863	0.0034	0.9778	0.9916
4	972	7	0.9793	0.0043	0.9689	0.9862
5	857	9	0.9691	0.0054	0.9564	0.9781
6	738	3	0.9651	0.0059	0.9516	0.9750
7	628	2	0.9621	0.0062	0.9477	0.9725
8	508	2	0.9583	0.0068	0.9428	0.9697
9	431	4	0.9495	0.0080	0.9312	0.9630
10	370	3	0.9418	0.0091	0.9211	0.9572
11	290	5	0.9256	0.0115	0.8996	0.9451
12	217	3	0.9130	0.0134	0.8826	0.9358
13	165	1	0.9075	0.0144	0.8747	0.9320
15	126	0	0.9075	0.0144	0.8747	0.9320

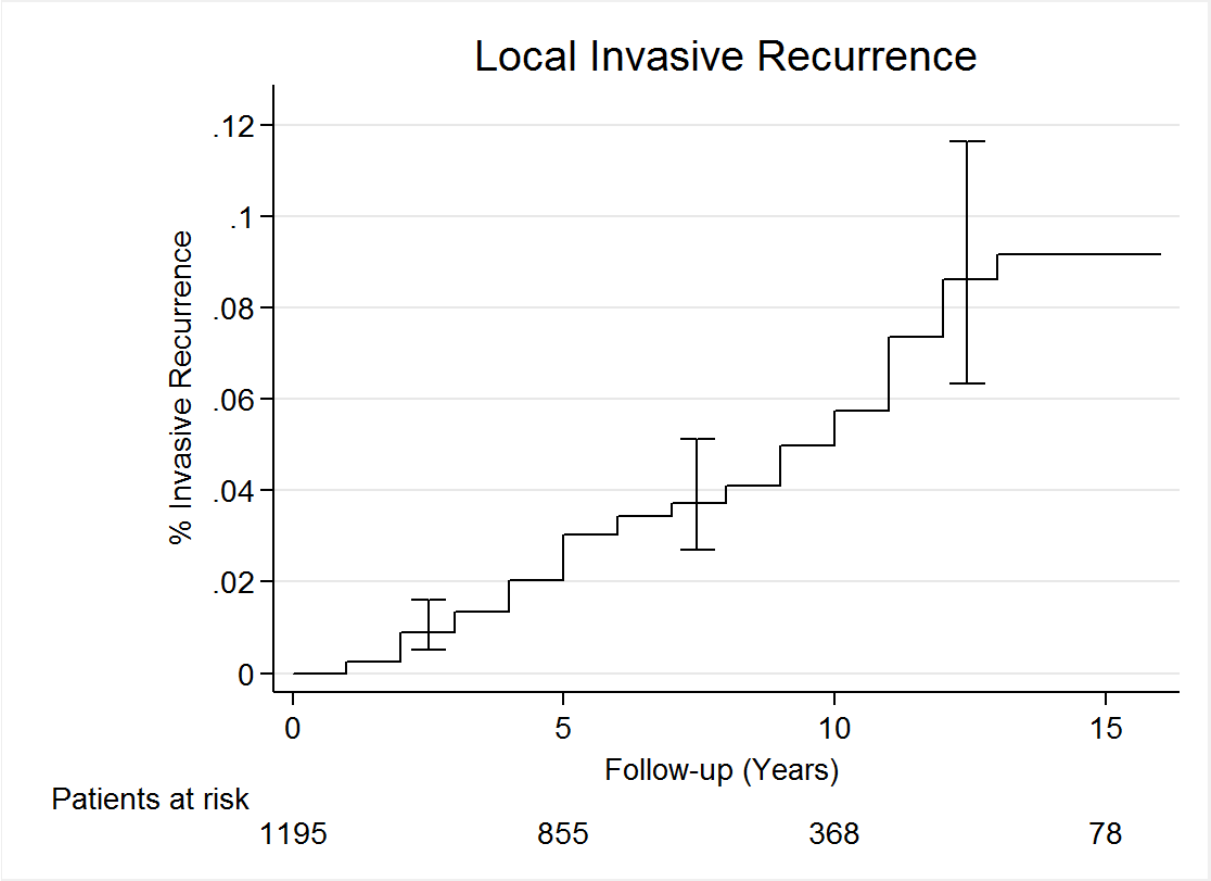
Annexe 2: survival rate without invasive recurrence for population with BCT and BCS treatment (n=941):

Time (years)	Beginner Total	Fail	Survivor Function	Standard Error	[95% Conf. Int.]	
1	834	2	0.9976	0.0017	0.9905	0.9994
2	821	7	0.9892	0.0036	0.9793	0.9944
3	762	5	0.9827	0.0046	0.9709	0.9897
4	659	4	0.9768	0.0054	0.9634	0.9853
5	571	7	0.9650	0.0070	0.9483	0.9763
6	481	2	0.9610	0.0075	0.9432	0.9732
7	408	2	0.9563	0.0082	0.9371	0.9697
8	323	1	0.9533	0.0086	0.9330	0.9676
9	269	4	0.9393	0.0110	0.9136	0.9575
10	227	2	0.9311	0.0123	0.9024	0.9516
11	174	5	0.9045	0.0168	0.8657	0.9325
12	130	3	0.8842	0.0201	0.8381	0.9179
13	96	1	0.8750	0.0219	0.8248	0.9116
14	95	0	0.8750	0.0219	0.8248	0.9116
15	71	0	0.8750	0.0219	0.8248	0.9116

Annexe 3: Specificity and Sensibility for Margin Index value of 5.6 for patients with known results for residual tumor during second surgery (n=401)

True D defined as residual Tumor = YES		[95% Conf. Inter.]
Sensitivity	Pr (+| D) 80.00%	[76.08% - 83.92%]
Specificity	Pr(-|~D) 44.72%	[39.85% - 49.59%]
Positive predictive value	Pr (D| +) 68.33%	[63.77% - 72.88%]
Negative predictive value	Pr(~D| -) 60.00%	[55.21% - 64.79%]
Prevalence	Pr(D) 59.85%	[55.05% - 64.65%]

Annexe 4: Risk for an Invasive Ipsilateral Recurrence in Years for whole population (Mastectomy + BCT and BCS population)



Interval calculated at 2.5 years, 7.5 years and 12 years

Annexe 5: Mutlivariate analysis for BCT and BCS treatment population to find residual tumor after first surgical procedure.

Residual tumor	Odds Ratio	Standard Error	z	P>|z|	[95% Conf. Interval]	
Necrosis presence	2.058516	0.7733823	1.92	0.055	0.9857316	4.298825
Tumor size >20mm	2.659539	0.8676407	3.00	0.003	1.403177	5.040806

p ≤0.05 significant

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Evaluation des facteurs de risque péjoratifs et calcul d'un index de marge dans le risque de récidive infiltrante homolatérale après traitement d'un Carcinome in Situ du sein : une étude observationnelle de 15 ans.

RÉSUMÉ

Introduction : Le but du traitement des carcinomes canalaires in situ (CCIS) est le contrôle local de la maladie, afin de prévenir le risque de survenue d'une récidive infiltrante. La connaissance des facteurs de risque de récidive locale invasive apparait de fait comme une priorité. L'objectif principal de l'étude était l'évaluation de ces facteurs de risque de récidive infiltrante au sein des caractéristiques propre au patient et à sa tumeur initiale. L'objectif secondaire était l'élaboration d'un index de marge prédisant le risque de reliquat tumoral avant une éventuelle décision de reprise chirurgicale.
Sujets et Méthodes : Rétrospectivement, toutes les patientes diagnostiquées et traitées pour un CCIS entre 2000 et 2015 entre les centres anti cancer de Angers et de Nantes étaient incluses dans l'étude. Le risque de récidive infiltrante homolatérale était évalué selon l'étude des caractéristiques du patient et de la tumeur. L'index de marge était calculé selon le rapport entre la taille de la tumeur initiale et la taille de la marge la plus proche de la tumeur selon l'équation : (marge la plus proche/taille de la tumeur) en mm x100.
Résultats : L'étude a permis l'inclusion de 1388 patientes toutes présentant un diagnostic histologique de CCIS. Après un suivi de 5 ans, la chance de survie sans récidive infiltrante était de 96.91%, IC 95% [95.64-97.81]. Le grade nucléaire élevé, l'antécédent de cancer du sein controlatéral et le traitement conservateur étaient retrouvés comme étant significativement prédictifs d'un risque de récidive infiltrante homolatérale en analyse multivariée, respectivement : HR1.96 ; IC 95% [1.06-3.62] p=0.031 ; HR2.83 ; IC 95% [1.09-7.37] p=0.032; HR2.22 IC 95% [1.02-4.83] p=0.043. Au sein de l'analyse en sous-groupe pour la population ayant bénéficié d'un traitement conservateur, seule une tendance était retrouvée comme a risque de récidive locale infiltrante sur certains facteurs. La valeur de 5.6 pour l'index de marge était la plus performante pour prédire le risque de reliquat tumoral sur une ré excision chirurgicale pratiquée après chirurgie conservatrice première.

Mots-clés : CCIS, facteurs de risque péjoratifs, récidive infiltrante, index de marge

Evaluation of predictor risk factors and calculation of a margin index for ipsilateral invasive recurrence following treatment of DCIS: a Fifteen year observational study.

ABSTRACT

Background: The goal of ductal carcinoma in situ (DCIS) treatment is the local control of the disease, preventing or reducing potential occurrence of invasive breast cancer. The understanding of predictor risk factors for local invasive recurrence is a priority. The main objective was to evaluate patient and tumor characteristics as a risk for ipsilateral invasive recurrence. The second objective was calculation of a margin index to predict residual tumor on re-excision.
Patients and Method: Retrospectively, all female patients diagnosed and treated for DCIS from 2000 to 2015, from both Institut de Cancerologie of Angers and Nantes, were included. Risk for ipsilateral invasive recurrence following DCIS was evaluated according to patients and tumor characteristics. Margin index was calculated based on the original tumor size and the closest margin: (closest margin / tumor size) in mm x 100.
Results: The study retrospectively included 1388 patients with histologically confirmed DCIS. After five years of follow up, chance to survive without an ipsilateral invasive recurrence was 96.91%, IC 95% [95.64-97.81] A High nuclear grade, previous history of contralateral ductal carcinoma and breast conserving treatment were found to be predictive risk factors for local invasive recurrence in multivariate analysis HR1.96; IC 95% [1.06-3.62] p=0.031; HR2.83; IC 95% [1.09-7.37] p=0.032; HR2.22 IC 95% [1.02-4.83] p=0.043, respectively. Within the sub group population undergoing conserving treatment, only tendency was found for some factors to increase risk for LIR. A margin index of 5.6 was found to be the most suitable index to predict a risk for residual tumor on re-excision after the first surgery.

Keywords: DCIS; predictor risk factors, invasive recurrence, margin index

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