



Original Research

Factors Associated with Borderline or Invaded Margins in Breast Cancer Surgery at the Val d'Aurelle Center for Cancer Research and Control

Facteurs associés aux marges limites ou aux berges envahies en chirurgie conservatrice du cancer du sein au CRLC de Val d'Aurelle Montpellier

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HIGHLIGHTS OF THE STUDY

What is already known on this topic

Breast-conserving surgery is widely accepted as standard therapy of breast cancer in an early stage. Nevertheless, after this conserving procedure, positive resection margins is the most important risk factors for local recurrence.

What question this study addressed

Factors associated with positive or invaded surgical resection margins after breast-conserving surgery in Val d'Aurelle Regional Cancer Center

What this study adds to our knowledge

Young patients and non-menopausal patients, T1N0 tumours, invasive cancers with intraductal component are associated with a significant high risk of positive margins.

How this is relevant to practice, policy or further research.

The knowledge of these factors could facilitate an individualized and optimal surgical technique.

ABSTRACT

Introduction. The inadequate status of the resection margins after breast cancer surgery is an important predictor of local tumor recurrence. The objective of our study was to determine the factors associated with positive or invaded resection margins. **Methodology.** Our retrospective study included a cohort of 652 patients with early invasive breast cancer who underwent breast cancer conserving surgery at the Val d'Aurelle Regional Cancer Center. We defined positive margins as those with a distance of less than or equal to 2 mm from the tumour. **Results.** In our study, The median distance from the tumour to the surgical resection site was 5mm [0.0 - 35.0 mm]. Resection margins were positive in 208 patients (31.9%). The rate of positive resection margins was significantly higher in non-menopausal patients (P = 0,0050), , in those with tumours less than 2 cm in size (P = 0,0004), with ductal carcinoma in situ (DCIS) component and without lymph node involvement (P = 0,0082) . Re-excision surgery was performed in 229 patients (35.1%). **Conclusion.** Consideration of each of these factors associated with positive resection margins should help the surgeons to perform a wider excision, in other to obtain clear resection margin during the initial breast cancer surgery.

RÉSUMÉ

Introduction. Le statut inadéquat des berges d'exérèse après chirurgie conservatrice du cancer du sein, représente le facteur prédictif prépondérant de récurrences locales. L'objectif de notre étude était de déterminer les facteurs associés à des berges chirurgicales positives ou envahies. **Méthodologie.** Notre étude rétrospective a porté sur une cohorte de 652 patientes avec cancer invasif du sein au stade précoce, opérées au Centre régional de lutte contre le cancer Val d'Aurelle. Nous avons défini comme berges positives celles dont la distance les séparant de la tumeur était inférieure ou égale à 2 mm. Les données ont été analysées à l'aide du logiciel STATA® 10.0. **Résultats.** L'âge médian des patientes était de 54 ans [26-85 ans]. 53,7% (350) était ménopausées. La taille tumorale moyenne était de 1,99 cm (+/- 0,95). 66,3% (432) des tumeurs était < 2cm (T1). La distance médiane de la tumeur, à la berge d'exérèse chirurgicale était de 5mm [0,0 – 35,0mm]. 31,9% (208) des berges étaient positives, et 68,1% (444) étaient saines. La proportion de berges positives, était significativement plus élevée chez les patientes non ménopausées, chez celles avec tumeurs de moins de 2 cm, avec composante intracanalair et sans envahissement ganglionnaire. **Conclusion.** la considération de chacun des facteurs associés à des berges positives, faciliterait le choix de l'étendue de la résection chirurgicale, limitant ainsi les risques de reprises chirurgicale.

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Key words: breast cancer, conservative surgery, resection margins, risk factors for positive margins

Mots clés : cancer du sein, traitement conservateur, berges chirurgicales, facteurs de risque des berges positives

INTRODUCTION

In France, women, breast cancer is the leading cause of cancer deaths (58,500 cases in 2018) (1). Breast-conserving surgery (BCS) is widely accepted as standard therapy as most of the breast cancer are diagnosed in an early stage. Nevertheless, after this conserving procedure, recurrence is a dreaded event and positive resection margins is the most important risk factors for local recurrence (2). In a study of 212 patients, by Randy and al, 6.8% developed local recurrence at a mean of 4.5 years after breast-conserving surgery (3). This recurrence rate was influenced by the status of the margins. Kouzminova estimated the rate of local recurrence to be 15.5% in case of positive resection margins, compared with 4.9% for clear margins (hazard ratio, 3.6; 95% CI [5- 8.7]; P=0.003)(4). The goal of a surgical therapy in breast cancer is to entirely remove the tumour and obtain a clear margin. Several study has been done in order to determine the predictive factors of the margins' status. A particular emphasis has been placed on preoperative imaging of the tumour and intraoperative assessments of the excised specimens 'margins. However, the rate of breast-conserving surgery with positive resection margins, or further re-excision has not been reduced (5). The aim of this study was to identify the factors associated with positive or invaded surgical resection margins after breast-conserving surgery in Val d'Aurelle Regional Cancer Centre.

PATIENTS AND METHODS

Patients

Our study included 652 patients with early stage invasive breast cancer, operated and followed at the Val d'Aurelle Regional Cancer Center between January 2006 and December 2011. We recorded all available anatomical and clinical data as well as the therapy performed (surgery, adjuvant therapy). In accordance with the recommendations of the French National Cancer Institute (INCa), we considered as clear margins, all the edge of surgical excision previously marked with Indian ink and free of carcinomatous cells, either ductal carcinoma in situ (DCIS) or invasive cancer (2). We also defined a distance of 2mm between the tumour cells and the surgical resection margin as a clear margin, according to the work of Pilewskie et al (6).

All the data were collected and analysed in order to define a correlation between the different parameters and the status of the margins

Study design

This was a retrospective, monocentric study evaluating the relationship between the resection margins 'status, socio-demographic data and other clinical and pathologic data in patients who underwent breast surgery for early stage invasive breast cancer at the Val d'Aurelle Centre, between January 2006 and December 2011.

The Val d'Aurelle Centre is currently renamed the Montpellier Regional Cancer Institute (ICM). It is a reference center in Occitania, and one of the best centre in France, for breast cancer management. About 1100 new cases of breast cancer are managed there each year.

The sampling was consecutive and exhaustive. We retrospectively included patients from a prospectively maintained database at the Val D'Aurelle Centre.

We excluded patients who had one of the following non-inclusion criteria: Previously treated breast cancer, Local recurrence of breast cancer, Neoadjuvant chemotherapy, Bilateral breast cancer, Other neoplastic pathology, Pre-cancerous or benign pathology (fibrocystic mastopathy.) or phyllodes tumours.

Data collection

For each patient, retrospective information relating to her identification, diagnosis, preoperative evaluations, adjuvant therapy and follow-up were collected from the medical records and entered into a database using a form developed with the biostatistics department of the Val d'Aurelle CRLC.

Variables

The study variables were: sex, age at diagnosis, menopausal status, type of surgery, histology: lobular, ductal, or other, whether the breast cancer is inflammatory or not, SBR grade (1, 2, 3), Peri-tumour emboli, Extensive intraductal component (EIC) and necrosis, The status of the surgical resection margins, Distance of the resection margins from the tumour, and the type of cells present on the excision edge, Whether a re-excision or mastectomy was performed, Tumour size and nodal status (metastatic, micrometastases or isolated tumour cells), Hormone receptors (HR) : The expression of oestrogen receptor (ER), progesterone receptor (PR), , and Ki-67 expression were evaluated and reported in fmol (radioligand assay) and/or %, using immunohistochemistry (IHC). Hormonal receptor(HR) was negative when Progesteron receptor(PR) and Estrogen receptor (ER) were negative, Human epidermal growth factor receptor 2 (HER2) status, KI67 level, Adjuvant therapy, Last available clinical follow-up.

Statistical analysis

Data were analysed in STATA® 10.0. Descriptive statistics were used. Quantitative variables were presented as mean, variance, standard deviation, minimum, maximum, median. In case of comparison on quantitative criteria, the Kruskal-Wallis test is used.

Categorical variables were presented using numbers and percentages. In case of comparisons involving qualitative criteria, the Chi2 test or Fisher's exact test was used if the conditions for applying the Chi2 test was not valid. Multivariate logistic regression analysis was used to analyse each variable with a P value <0.05.

RESULTS

Characteristics of the population

Among the breast cancer patients managed in Val D'Aurelle cancer centre from January 2006 to December 2011, 652 patients were included in our study. The mean age at diagnosis was 53.3 years (+/- 9.33). More than half of the patients were postmenopausal 53.7% (350).

Table 1: Patient characteristics at inclusion.

Characteristics of the patients	N	Percent
Men age at diagnosis (years)	652	53,3 (+/- 9,33)
Menopause		
No	302	46,3%
Yes	350	53,7%

Anatomoclinical and biological characteristics of the operated breast cancers

The tumour was mainly on the left breast 334 (51.2%), right 318 (48.8%). The mean tumour size was 1.99 cm (+/- 0.95). Between the included patients, 66.3% (432) had tumours smaller than 2cm (T1). 75.9% of patients were node negative (N0).

91.1% (594) of patients had extensive intraductal component. 85.9% of the tumours were SBR 2 or 3. HER2 status was analysed in all patients, only 74 (11.3%) had an overexpressed HER2 status. Triple negative tumours (RE-, RP-, HER2-) were present in 11% of patients (72 patients). The mean Ki67 value, assessed in 151 patients, was 20% (0.0 - 75.0). UPA and PAI-1 levels were measured in all patients and were elevated in 45.6% of patients for uPA and 56.1% for PAI-1. Vascular emboli were present in 182 patients (29.1%) and absent in the majority, 443 (70.9%). In 27 patients we had no information on the existence or absence of emboli.

453 (69.5%) of the invasive tumours had an associated Ductal carcinoma insitu component. 2.1% (13) of patients had skin invasion at diagnosis.

Surgery

Breast-conserving surgery was performed in 536 patients (82.2%) and 116 patients (17.8%) had mastectomy. Mastectomies were mainly performed for tumours graded at least T2 (34.5% vs 9.3%, $P < 0.01$).

Re-excision was performed in 229 patients (35.1%). The re-excision rate was significantly lower for patients without tumor cells found 1 mm from the resection margin (32.8% vs 54.3%, $p < 0.001$).

Of the 536 patients with conservative surgery, 385 (71.83%) had a sentinel node research and 151 (28.17%) an axillary lymph node removal.

Tableau 2 : Types of surgery

Types of surgery	number	%
Conservative surgery	536	82,2
Mastectomy	116	17,8
Surgery (lymph node)		
Sentinel node	412	63,2
Lymph node dissection	240	36,8
Surgical re-excision	229	35,1

Margin status

The mean distance from the tumour to the surgical resection margin was 5 mm (0.0 - 35.0).

10.7% (70) of the resection margins were at 0mm from the tumour, and 89.3% (582) were at least 1mm far from the tumour.

In the other hand, 31.9% of the patients (208) had borderline margins, with resection margins at less or

equal to 2mm far from the tumor, and 68.1% (444) had adequate clear margins (> 2 mm) with margins at least 3mm from the tumor.

39 patients had diffuse, non-focal invasion of the margins, with a median extension of involvement of 4 mm (1.0 - 20.0)

Additional lumpectomies were performed in 229 patients (35.1%), almost all 208 with margins < 2 mm.

Table 3: Analysis of surgical excision margins

Distance to surgical edge (mm)	N	%
0	70	10,7
1+	582	89,3
Distance to surgical edge (mm)		
< 3 mm	208	31,90
3 and more	444	68,10
Type of surgical edge involvement (n=70)		
Ductal carcinoma in situ	19	27,9
Invasive carcinoma	47	69,1
Not available	1	1,5

Patient outcome

The median follow-up of 38.7 months (0.2-76.3) allowed us to observe a recurrence-free survival rate of 93% at 5 years in this population of early stage breast cancers. For the 652 patients in our study, the local recurrence rate was 0.6%. Progression to metastasis was estimated at 3.5%. Complications such as local recurrence and associated metastasis were observed in 4.1% of cases. At the end of our study, we noted 6 deaths and 3 patients lost to follow-up. The median time to last news was 38.7 months (0.2- 76.3). Patient follow-up was assessed at 12 months, 36 months and 60 months.

The analysis focused on the associations between the status of the margins and the other decision variables.

Table 4 : Patient outcome

Becoming of patient	number	Percent
Alive	643	98,6
Deceased	6	0,9
Lost to follow-up	3	0,5
Cause of death (n= 6)		
Cancer (Progression)	3	0,5
Intercurrent disease	1	0,2
2nd cancer	1	0,2
Patient's clinical status		
No disease	597	91,6
Local recurrence	4	0,6
Metastatic recurrence	22	3,4
2nd Cancer	12	1,8
Not known (NK)	8	1,2
Not specified	4	0,6

Associations between margin status and other anatomoclinical variables

More than half of the patients, 69.5% (453), had invasive cancer with an associated intraductal component. Therefore, we defined as positive edges or margins, those whose distance from the tumour was less than or

equal to 2 mm (i.e. from 0 mm to 2 mm). We retained as clear edges those located at least 3 mm from the tumour.

Statistical relationships were found with certain anatomical variables.

The proportion of positive margins was higher in the non-menopausal patients, i.e. 54.3% compared with 45.7% (P= 0.005). The rate of positive margins was higher for tumours less than 2 cm (P= 0.0004). Of the 208 patients with positive margins, 56.7% (118) were treated for tumours classified as T1 and 43.3% (90) for tumours classified as T2 or higher.

N0 tumours were associated with a higher rate of positive margins than those classified as N+; respectively, 68.3% (142) and 31.7% (66), (P= 0.0018).

The presence of peri-tumour emboli was not significantly associated with the status of the margins when they were classified as either ≤ 2 mm or ≥ 3 mm.

However, for tumours with excision margins ≥ 1 mm, we noted the presence of vascular emboli in 27.7% (155), and in 72.3% of cases, these emboli were absent. While for 0 mm margins, 40% (27) of the tumours had emboli, compared to 59.1% (39) that were devoid of them. The more peri-tumour emboli were present, the further apart the margins were ≥ 1 mm (P = 0.0258).

The presence of intracanal carcinoma was associated with the status of the margins. 76.4% (159) of the resections with positive margins were of tumour with ductal carcinoma in situ (DCIS) component, while 23.6% (49) of the positive margins were of tumour without an associated intracanal component (P = 0.0082).

The status of the margins was significantly associated with the performance of adjuvant chemotherapy. 72.6% (151) of patients with positive margins had chemotherapy, compared with 64.4% (286) of those with negative margins (P= 0.0383).

No significant correlation was demonstrated between the status of the margins and the SBR score, the presence of hormone receptors, the molecular profile and the Ki67 level.

Patient Characteristics	Surgical edges (mm)			p
	3+	0/1/2	Total	
Menopause				0,0050
No	189 (42,6)	113(54,3)	302	
Yes	255 (57,4)	95 (45,7)	350	
T (TNM)				0,0004
T1	314 (70,7)	118 (56,7)	432	
T2+	130 (29,3)	90 (43,3)	220	
N (TNM)				0,0018
N-	353 (79,5)	142 (68,3)	495	
N+	91 (20,5)	66 (31,7)	157	
Type Carcinoma				0,8820
Ductal	404 (91,0)	190 (91,3)	594	
Lobular	40 (9,0)	18 (8,7)	58	
Grade SBR				0,2031
1	70 (15,8)	22 (10,6)	92	
2	232 (52,3)	117 (56,3)	349	
3	142(32,0)	69 (33,2)	211	
Differentiation				0,0263
1/2	140(31,5)	48 (23,1)	188	
3	304(68,5)	160 (76,9)	464	

Patient Characteristics	Surgical edges (mm)			p
	3+	0/1/2	Total	
Emboli				0,3500
Not seen	309(72,0)	134 (68,4)	443	
Present	120(28,0)	62 (31,6)	182	
No information	15	12	27	
ER				0,8444
Negative	72 (16,2)	35 (16,8)	107	
Positive	372(83,8)	173(83,2)	545	
PR				0,7045
Negative	154(34,7)	69 (33,2)	223	
Positive	290(65,3)	139(66,8)	429	
HER2				0,5262
Negative	396(89,2)	182(87,5)	578	
Positive	48 (10,8)	26 (12,5)	74	
Molecular profile.				0,7387
HER2 positive	48 (10,8)	26 (12,5)	74	
HR+HER2-	345(77,7)	161(77,4)	506	
TN	51 (11,5)	21 (10,1)	72	
Ki67(%)				0,3097
≤15	50 (46,3)	16 (37,2)	66	
>15	58 (53,7)	27 (62,8)	85	
Missing	336	165	501	
Intra ductal carcinoma				0,0082
No	150 (33,8)	49 (23,6)	199	
Yes	294 (66,2)	159 (76,4)	453	

DISCUSSION

Much work is being done to improve the decision-making algorithm for surgical therapy of early invasive breast cancer. The selection criteria for breast-conserving surgery (BCS), developed in the 1980s and in use today, are related to the measurement of tumour size and the ability to safely deliver radiotherapy (7). The most important determinant of the quality of surgical tumour reduction in uni-focal breast cancer is the status of the margins. Although it is clear that patients with cancer cells in contact with the margins have a high risk of local recurrence compared to those with clear margins (8), to date there is no consensus on the optimal distance from the margins to the tumour. A meta-analysis by Houssami et al showed that clear margins, regardless of their thickness, significantly reduce the incidence of local recurrence(8). What would be the factors associated with margin invasion or borderline margins?

Our retrospective study was carried out on a cohort of 652 patients treated from January 2006 to December 2011, for early stage breast cancer, at the Center de recherche et de lutte contre le cancer, Val d'Aurelle.

The mean age of the patients at diagnosis of breast cancer was 53.3 years (+/- 9.33), which is younger than the average age generally noted at diagnosis of breast cancer (9). More than half of the patients, 53.7% (350) were postmenopausal.

66.3% (432) of the patients had tumours smaller than 2 cm (T1). 75.9% of patients were node negative (N0). This is in line with the majority of studies in which the majority of breast cancers are diagnosed at an early stage, thanks to the progress made in screening (1)

Conservative surgery was performed in 536 patients (82.2%) and 116 patients (17.8%) had a mastectomy. Re-excision surgery (lumpectomy complement or mastectomy) was performed in 229 patients (35.1%). This rate represents 1 in 3 patients and is higher than the result of a study reported in 2008, which found a

recurrence rate of 17.1% in 1648 patients operated on by breast-conserving surgery after cancer (10).

This is lower than the 75.6% described by Kouzminova in a study of 437 patients, with 13% (57) of insufficient margins (>0 and < 2 mm); 59% (258) of positive margins ($=0$) and 27.9% (122) of negative margins (≥ 2 mm) (11). This difference could be explained by the lower rate of resection with a margin of less than 2 mm observed in our study, 31.9% (208).

More than half of the patients, 69.5% (453), had invasive cancer with an associated intracanal component.

We defined positive margins as those with a distance of less than or equal to 2 mm from the tumour (i.e. from 0 mm to 2 mm). We considered as clear edges those located at least 3 mm from the tumour. According to the literature, surgical margins 0mm away from the tumour are associated with a 6% risk of local recurrence at 5 years. For margins at least 2 mm away, the risk of recurrence is 1.6%, without any adjuvant therapy (12).

The work of the National Comprehensive Cancer Network (NCCN) in 2011 defined a clear margin as the histological absence of tumour cells on the excisional margin (0 mm) in the case of invasive cancer, whereas for intracanal cancers, any margin less than 1 mm, although histologically free of tumour, is considered insufficient and those > 2 mm are considered clear (13).

In our study, the median distance from the tumour to the surgical excision site was 5 mm (0.0 - 35.0).

10.7% (70) of the edges were located 0 mm from the tumour and 89.3% (582) were located at least 1 mm from the tumour. In addition, 31.9% (208) of the edges were less than or equal to 2 mm away and 68.1% (444) were at least 3 mm away from the tumour.

The tumour resections were therefore extensive, although the therapy was mainly conservative. This could be explained by the use of oncoplastic techniques by the center's surgeons.

With 31.9% (208) positive margins, our results differed from those of Hee-Chul Shin and colleagues who, in May 2012, found positive margins in 151 patients (14.6%) after conservative surgery in 1034 patients (14). The criteria for selecting patients for conservative surgery, the surgical techniques used, and the sample size could explain this difference.

39 of our patients had diffuse, non-focal invasion of the margins, with a median extension of 4 mm (1.0 -20.0).

The proportion of positive margins was higher in non-menopausal patients, 54.3% versus 45.7% ($P= 0.005$). This could be explained by the young age of these patients, which would lead the surgeon to limit the extent of resection.

The rate of positive margins was higher for tumours smaller than 2 cm ($P= 0.0004$), and of the 208 patients with positive margins, 56.7% (118) were treated for tumours classified as T1 and 43.3% (90) for tumours classified as T2 or higher. This could have been related to the fact that the boundaries of large tumours may appear more obvious. However, in contrast to our results, Reedijk showed that tumours larger than 2 cm were associated with more positive margins than subcentimetric tumours ($P=0.0001$) (15). This difference

could be explained by different criteria for conservative therapy choices and by the surgical techniques used.

The presence of peri-tumour emboli was not significantly associated with the status of the margins when they were classified as either ≤ 2 mm or ≥ 3 mm.

However, fewer peri-tumour emboli were present when the edges were ≥ 1 mm apart ($P = 0.0258$). A similar result was found by Lovrics et al. in 489 patients, after multiparametric analysis(16).

The presence of ductal carcinoma in situ (DCIS) component was significantly associated with positive margins ($P=0.0082$). This is consistent with the findings of Shin et al, who found that clear excisional margins were more readily obtained in the absence of an associated ICC (14).

On the other hand, there was no significant relationship between rim status and SBR score, presence of hormone receptors, molecular profile and Ki67 level.

Our sample size allowed for multiparametric analyses. The median follow-up of 38.7 months (0.2- 76.3) allowed us to observe an overall recurrence-free survival rate of 93% at 5 years. In a study of 452 patients, with a median follow-up of 80 months, a 96% recurrence-free survival rate at 5 years was found in women with negative margins, compared with 88% for those with positive margins (17).

For the 652 patients in our study, the local recurrence rate was 0.6%. Progression to metastasis was estimated at 3.5%. Complications, combining local recurrence and metastasis, were observed in 4.1% of cases. At the end of our study, we noted 6 deaths and 3 patients lost to follow-up. In a 2009 study, the rate of local recurrence observed was 5.3%. The rate of local recurrence was 4.9% in the case of negative margins and 5.4% in the case of positive margins (HR: 1.24; CI95%: 0.47-3.24; $P=0.6$) (11). Recent studies have shown that in the case of adjuvant therapy, and whatever the bank, the risk of locoregional recurrence, including lateral cancers, varies from 1.4% to 8.7% over 15 to 16 years (18).

However, our study has several limitations. Firstly, it is a retrospective study of prospectively determined prognostic factors, with a follow-up time that is still not very long given the prognosis of this population. Biases could exist in the collection and consequently the analysis of the data. Secondly, this was a monocentric, non-randomised study which could be associated with variations in the interpretation of clinical and paraclinical elements in the preoperative phase and in surgical techniques.

A prospective randomised study is needed to assess the factors influencing the status of the edges, while ensuring external validity of this work.

Consideration of the factors predictive of breast margin status in the preoperative setting and their application to patients with invasive breast cancer may allow the surgeon to better tailor an individualised and optimal surgical protocol for each patient, with the goal of obtaining a clear breast margin. In addition, identification of these risk factors would help patients to understand the need for extensive resection surgery and to participate in the choice of surgery.

CONCLUSION

In breast cancer surgery, young age, absence of menopause, T1N0 tumours, invasive cancers with intraductal component, are associated with positive margins. Taking into consideration these predictive factors of the margin's status, preoperatively, could allow the surgeon to propose an individualized and optimal surgical technique, with the aim of obtaining clear margins. Furthermore, presenting these risk factors to patients could help them understand the need for extensive resection surgery and help them choose the type of surgery.

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