Artigo de investigação original

Existe necessidade de realizar estadiamento axilar na totalização de mastectomia por carcinoma ductal *in situ*?

Do we still need axillary staging in the context of mastectomy after at least one breast conservative surgery for ductal carcinoma in situ?

Autores:
Cátia Ribeiro[1]
Pedro Antunes[1]
Ana Mesquita[1]
Pedro C. Martins[1]
Mariana Peyroteo[1]
Alexandre Sousa[1]
Nuno Coimbra[2]
Conceição Leal[2]
Joaquim Abreu de Sousa[1]

Afiliação:
[1]Service of Surgical Oncology of the Portuguese Institute of Oncology of Porto, FG EPE. [2]Service of Pathologic Anatomy of the Portuguese Institute of Oncology of Porto, FG EPE

Autor para correspondência:
Cátia Raquel Lopes Ribeiro
Rua Gonçalo Mendes da Maia, nº 835, 3º C,
4425-656 Pedrouços Maia
Email: catia_r_ribeiro@hotmail.com
Tfno.: 91508 95 82

Resumo

Objetivos: A biópsia de gânglio sentinela (BGS) está indicada quando se realiza uma mastectomia total por CDIS. Quando a mastectomia é efetuada após uma ou mais tentativas de cirurgia conservadora mamária (CCM), a necessidade de efetuar BGS é questionável. O objetivo deste trabalho foi determinar a taxa de *upgrade* histológico e os resultados da BGS nas doentes submetidas a totalização de mastectomia por CDIS.

Metódos: Estudo retrospetivo de uma série de casos de doentes submetidas a totalização de mastectomia e BGS por CDIS depois de pelo menos uma tentativa de CCM, entre 2008-2016.

Resultados: Foram analisados 1071 casos e selecionados 81 que cumpriam os critérios de inclusão. A mediana de idades foi de 55 anos. O diagnóstico foi realizado por exames de rastreio em 88.6% dos casos. Microcalcificações foram a apresentação mais frequente (78,8%). A totalização de mastectomia foi efetuada depois de 1 tentativa de CCM (mediana = 1). As margens de ressecção foram positivas em 46,9% dos casos. Foi identificada doença residual na peça de mastectomia em 65,4%. A taxa de upgrade pós-mastectomia foi de 4,9% (1 caso com microinvasão e 3 casos com foco de invasão). A mediana de GS isolados foi de 2 (0-5) e a taxa de metastização ganglionar (MG) foi nula.

Conclusões: Nesta amostra, a taxa de upgrade histológico foi baixa. Nos casos de upgrade a taxa de metastização ganglionar foi nula. Estes achados sugerem que o estadiamento ganglionar pode ser omitido com segurança nas doentes com CDIS submetidas a totalização de mastectomia depois de tentativa CCM.

Palavras-chave: CDIS, mastectomia, câncer de mama, biopsia, câncer de mama conservador

Abstract

Goals: Sentinel lymph node biopsy (SLNB) is indicated when a mastectomy is performed by Ductal Carcinoma In Situ (DCIS). When mastectomy is performed after one or more attempts of breast conservative surgery (BCS), the need to perform SLNB is questionable. The goal of this study was to determine the histological upgrade rate and SLNB results in this specific group of patients.

Methods: Retrospective study of a case series of patients submitted to total mastectomy and SLNB by CDIS after BCS between 2008 and 2016.

Outcomes: We analysed 1,071 cases and selected 81 that fulfilled the inclusion criteria. The median age was 55 years. The diagnosis was made by screening tests in 88.6% of the cases. Microcalcifications were the main presentation (78.8%). The mastectomy totalisation was performed after one attempt of BCS due to positive or

inadequate margins. The resection margins were positive in 46.9% of the cases. Residual disease in the mastectomy specimen was identified in 65.4%. The post-mastectomy upgrade rate was 4.9% (one case with microinvasion and three cases with invasion). The median number of sentinel nodes (SN) isolated were 2 (0-5) and the rate of lymph node metastasis was null.

Conclusions: *In this sample, the histological upgrade rate was very low. We didn´t find lymph node metastasis in any case, even in those cases with upgrade to invasive carcinoma. These findings suggest that lymph node staging can be safely omitted in DCIS patients submitted to mastectomy after attempted BCS.*

Keywords: *DCIS, mastectomy, breast cancer, biopsy, breast conservative surgery*

Introduction

Breast cancer is the most frequent malignancy in women in developed countries and the incidence is still increasing. A breast cancer will be diagnosed in one of every eight women at some time during their life.[1]

In a screening breast cancer program 18% of the carcinomas diagnosed are ductal carcinoma *in situ (DCIS)*.[2,3] Treatment of DCIS consists in breast conservative surgery (BCS) or mastectomy, depending on the extension of the DCIS and convenience of the patient, with or without immediate breast reconstruction.

Ductal carcinoma *in situ* cannot give rise to axillary metastases by definition. However, it is well demonstrated that there is a rate of positive sentinel lymph nodes in patients with the pre--operative diagnosis of DCIS that ranges from 0 to 18.6%.[4]

The indications for a sentinel lymph node biopsy (SLNB) in patients with pure DCIS has been a matter of debate and are based on the risk for invasive breast cancer. Breast cancer guidelines still advise sentinel lymph node biopsy in patients with DCIS on core biopsy at high risk of invasive cancer or in case of mastectomy.[5] Similar to other authors,[6,7] we do not routinely offer SLNB in DCIS patients undergoing BCS. Sentinel lymph node biopsy is usually performed in a second stage surgery if definitive histopathology shows invasive cancer. A variable number of patients initially treated with BCS with pathologic findings of DCIS alone will do a mastectomy due to inadequate margins. We have questioned the need of an SLNB in this scenario. Assuming that the major part of the lesion has already been removed, the expected upgrade to invasive carcinoma should be very low and the rate of axillary metastasis even lower. Current data about this specific cohort of patients are limited to the *Melissa Pilewskie* work published in 2016.[8]

The aim of this study was to determine if the omission of the sentinel node biopsy is safe at the time of the mastectomy for DCIS in patients previously submitted to BCS.

Methods

Patient medical records were reviewed to identify patients treated at our institution with diagnosis of DCIS, from January 2008 to December 2016. In this search, 1071 patients with the diagnosis of CDIS were identified. Patients aged under 18 years with a diagnosis of invasive or microinvasive disease prior to mastectomy or those who underwent SLNB at a prior breast conservative surgery, were excluded from this study. After applying these criteria, our study sample was limited to 81 cases.

Microinvasive disease was defined as the extension of cancer cells beyond the basement membrane into adjacent tissues with no more than 1 mm in diameter. Positive margins were defined as ink on the tumor and insufficient margins were defined as ≤ 2 mm. A sentinel lymph node with isolated tumor cells (ITC) were considered a positive sentinel node.

Patients data, tumor characteristics, treatment, type and time of recurrence were extracted. Statistical analyses were performed using Statistical Package for the *Social Sciencesâ* (SPSS), version 21.0 (IBM Corporation, Armonk, NY, USA). Nominal variables are presented as frequency or percentage and continuous variables as media or median. Descriptive analyses were performed using the t-test for continuous variables and Chi-squared test (or Fisher's exact test when appropriate) for categorical or nominal variables. All p values were two-sided, and $p < 0.05$ was considered statistically significant. Log-rank test and Cox regression analysis were used to conduct univariate and multivariate analyses to identify the risk factors of survival.

Outcomes

From an initial number of 1071 patients, we selected 81 patients that had an indication to mastectomy and SLNB due to positive or insufficient margins following at least one attempt of BCS.

Clinicopathologic features of the entire cohort are shown in Table 1. All patients were female, with a median age of 55 years (range 36–82 years). The majority of the patients 88.6% (n = 70) were referred to our hospital from the national screening breast cancer program. Most the patients (78.8% [n = 63]) had microcalcifications on the imaging study.

About 65% (n = 52) of the patients had an pathological size of the lesions greater than 20 mm but less than 50 mm; 18.8% (n = 15) had lesions > 50 mm; 11.3% (n = 9) had lesions between 10–20 mm and 5% (n = 5) lesions smaller than 10 mm.

Approximately, 42.6% (n = 29) of the lesions were located in the external quadrants (25% UEQ; 13.2% TEQ and 4.4% IEQ). The remaining lesions were distributed in 17.6% (n = 12) in a central location, 20.6% (n = 17) in the inner quadrants and 19.1% (n = 13) in the upper quadrant transition.

Ductal carcinoma *in situ* of intermediate and high grade was found in 35 patients (43.2%) and 39 patients (48.1%) respectively. The comedonecrosis was found in 53 patients (67.9%). The most common pathology showed cribiform pattern in 34.2% (n = 26) of the cases. Mixed, micropapillary and solid patterns were found in 28.9%, 14.5% and 10.5% of cases, respectively. Most of the patients had positive hormone receptors

Table 1. Clinicopathologic features of the entire cohort (n = 81).	
Median age (range), years	**55 (36–82)**
Primary means of diagnosis DCIS	% (n)
Physical examination	11.4% (9)
Mammography	88.6% (70)
Missing	2
Imaging presentation	
Microcalcifications	78.8% (63)
Asymmetric density	5.0% (4)
Nodule	10.0% (8)
Others	6.3% (5)
Missing	1
Biopsy type	
Microbiopsy	87.6% (71)
Vacuum biopsy	4.9% (4)
Surgical	7.4% (6)
DCIS histology on lumpectomy	
Micropapillary	14.5% (11)
Papillary	7.9% (6)
Cribriform	34.2% (26)
Solid	10.5% (8)
Mixed	28.9% (22)
Others	3.9% (3)
Missing	5
Pathological lesion size	
1–10 mm	5.0% (5)
>10–20 mm	11.3% (9)
>20–50 mm	65.0% (52)
>50 mm	18.8% (15)
Missing	1
Nuclear grade	
Low	8.6% (7)
Intermediate	43.2% (35)
High	48.1% (39)
Comedonecrosis	
Yes	67.9% (53)
No	32.1 (25)
Missing	3
DCIS HR status	
Positive	73.2% (41)
Negative	26.8% (15)
Missing	25
DCIS ER status	
Positive	83.9% (47)
Negative	16.1% (9)
Missing	25
DCIS PR status	
Positive	73.2% (41)
Negative	26.8% (15)
Missing	25

Data are expressed as % (n) unless otherwise specified.

DCIS – ductal carcinoma *in situ*; ER – oestrogen receptor; HR – hormone receptors; PR – progesterone receptor.

73.2% (n = 41). The oestrogen receptor was positive in 83.9% of the cases and the progesterone receptor was positive in 73.2%.

The median number of BCS attempts prior to mastectomy was one (range one to three) Table 2. Mastectomy after BCS was done in 38 patients (46.9%) due to positive margins and in 43 patients (53.1%) due to insufficient margins. Residual disease was found in 53 patients (65.4%), being *in situ* disease in 49 patients (92.5%), microinvasive disease in 1.9% (n = 1) and foci of invasive carcinoma in 5.6% (n = 3). A positive margin was found to be a predictor of residual disease.

Pathological upgrade in the breast lesion was found in four patients (4.9%), which corresponds to three invasive carcinomas and one microinvasive carcinoma. No lymph node metastasis was found in any of the 81 cases (Table 2).

A subgroup analysis was performed between the group without histological upgrade and those with histological upgrade. The purpose of this analysis, obviously limited by the difference in cases between the two groups, was to find clinicopathological differences that justified the presence of upgrade. From the univariate analysis performed, we verified that all pathological upgrades were found in cases with DCIS > 20 mm in diameter, a micropapillary subtype was present in two of these patients and all patients were hormone receptor-positive. In the subgroup of patients without histological upgrade, only 17% (13) had lesions < 20 mm and 8.2% (5) of the cases had micropapillary subtype (Table 3).

The mean number of lymph nodes removed was two (zero to five) and no positive nodes were found, including ICT. Axillary lymph node dissection (ALND) was performed in two patients: in one patient because the sentinel node was not found, and in another patient for a false positive lymph node in the intraoperative examination (Table 2).

After a median follow-up of 51 months (0–108) there were no records of recurrences or deaths.

Discussion

Breast cancer treatment has dramatically changed in the last decade. A large study from Netherlands that included more than 900 patients concluded that SLNB should no longer be performed in patients diagnosed with DCIS undergoing BCS.[7]

Data from the International Breast Cancer Study Group (IBCSG)23-01 trial carried out in women with micrometastases in the Sentinel Node (SN), showed that there is no outcome benefit in performing a completion axillary clearance.[9] These findings were in accordance with the ACOSOG Z-0011 trial, which showed that there is no benefit in clearing the axillary nodes when up to two SNs are involved provided that whole breast radiotherapy is administered.[10] These data led the breast surgical oncology community to further limit axillary surgery.

A recent study showed that patients with a T1–T2 invasive breast cancer and at least three metastatic lymph nodes do not benefit from ALND after SLNB for specific and overall survival.[11] In 2014, Donker published the *AMAROS trial*. This trial showed comparable axillary control for patients with

Table 2. Surgical procedures and pathology results of the entire cohort (n = 81).	
Number of BCS prior to mastectomy	
1	82.7% (67)
2	16.0% (13)
≥ 3	1.2% (1)
Margin status of final BCS prior to mastectomy	
Positive	46.9% (38)
Close	53.1% (43)
Residual disease on mastectomy	
No	34.6% (28)
Yes	65.4% (53)
*Positive margins**	66.0% (35)
Close margins	34.0% (18)
DCIS	92.5% (49)
Microinvasive carcinoma	1.9% (1)
Invasive Carcinoma	5.6% (3)
	OR:18 CI 95% (3.9-92.7)
Any upgrade to invasive carcinoma	4.9% (4)
Final in-breast pathology	
DCIS	95.0% (77)
Microinvasive carcinoma	1.2% (1)
Invasive Carcinoma	3.7% (3)
Number of isolated SN	
0	1.2% (1)
1	35.8% (29)
2	42.0% (34)
3	11.1% (9)
≥ 4	9.9% (8)
Axillary surgery	
SLNB alone	97.5% (79)
SLNB and ALND**	1.2% (1)
ALND	1.2% (1)
Axillary pathology	
pN0	100% (81)

Data expressed as % (n) unless otherwise specified.

ALND – axillary lymph node dissection; BCS – breast-conserving surgery; DCIS – ductal carcinoma *in situ*; SLNB – sentinel lymph node biopsy; SN – sentinel node.

*Positive margins predicting residual disease (p < 0.001).

**Indication for ALND was in one patient because the sentinel node was not found and in the another patient for a false positive lymph node in an intraoperative imprint cytology not confirmed after pathologic evaluation.

T1–T2 primary breast cancer and clinical negative axilla with surgery or radiotherapy.[12] As there is no advantage in performing ALND even when the SN is positive, doubts can be raised on the real need of even performing SNB in patients with early breast cancer. In fact, there are some ongoing prospective, multicenter trials trying to give an answer to this question, such as the ongoing clinical trial *omitting sentinel node procedure in breast cancer patients undergoing breast conserving therapy*.[13,14,15] We also cannot forget the morbidity associated with every surgery. Despite a strong reduction in morbidity since the abandonment of the axillary dissection for nodal staging in patients with early breast cancer and a clinically negative axilla, the complication rate associated with the SLNB procedure is underestimated.[16]

The lymphoedema will develop in 21% of women treated for breast cancer. It is four times more likely when axillary clearance is performed compared with the SLNB. However, it is still a problem in SLNB patients and seems to increase over time, at least up to 24 months after surgery.[1] Also, shoulder and arm impairments among sentinel node-negative patients occur in variable rates and cannot be neglected. A considerable number of patients still suffer from those impairments more than 2 years after surgery.[17] Two well-known major trials, ALMANAC

Table 3. Comparison of clinical and pathologic features of DCIS among patients with and without an upgrade to invasive carcinoma (univariate analysis).

Clinical and pathologic features	Without Upgrade n = 77	With Upgrade n = 4	p value
Age (median)	52	46	p = 0.04
Primary means of diagnosis DCIS			
Physical examination	13.4% (10)	0	p = 0.6
Imaging	86.7% (65)	100% (4)	
Missing	2		
Micropapillary subtype	8.2% (5)	66.7% (2)	p = 0.03
Nuclear grade			
Low	7.8% (6)	25.0% (1)	p = 0.2
Intermediate	44.2% (34)	25.0% (1)	
High	48.1% (37)	50.0% (2)	
Lesion size			
1–10 mm	5.2% (4)	-	
> 10–20 mm	11.8% (9)	-	-
> 20–50 mm	63.2% (48)	100% (4)	
> 50 mm	19.7% (15)	-	
Missing	1	-	
Oestrogen-positive receptors	82.7% (43)	100% (4)	p = 0.5
Progesterone-positive receptors	71.2% (37)	100% (4)	p = 0.3
Number of BCS attempts			
1	81.8% (63)	100% (4)	p = 0.7
2	16.9% (13)	0	
> ou = 3	1.3% (1)	0	
Status of margins prior to mastectomy			
Close	54.5% (42)	25.0% (1)	p = 0.3
Positive	45.5% (49)	75.0% (3)	

Data are expressed as % (n) unless otherwise specified
BCS – breast-conserving surgery; DCIS – ductal carcinoma in situ.

and NSABP B-32, demonstrated persistent long-term problems with arm function, lymphoedema, and paresthesia following a sentinel node biopsy. In the ALMANAC trial, patients reported arm swelling (7%) and numbness (8.7%) and in the NSABP B-32 trial, arm numbness and impaired shoulder abduction was experience by 8.1% and 13.2% of the patients, respectively.[16,18]

SLNB is also being questioned in the subset of patients with microinvasion found on the final pathology report because of the relatively low number of positive sentinel nodes in those patients.[19,20,21,22]

Personalising the care of cancer patients is difficult given the unclear oncologic benefit and comorbidities associated with some procedures. In this new era the decision-making process for adjuvant treatment is becoming increasingly dependent on the tumor biological features rather than on the axillary staging. This vision imposes the need to reduce invasive axillary procedures.

Melissa Pilewskie and colleagues, continue to advocate sentinel node biopsy at completion mastectomy in patients with DCIS who underwent previous BCS. In their study, a histological upgrade rate of 8.6% was identified, 6.4% (n = 15) in the primary tumor and in 2.1% (n = 5) due to the presence of axillary metastasis in the sentinel node (three micrometastases and two macrometastases). However, in two of the five cases of positive sentinel node there was no invasive carcinoma in the previous pathologic evaluation, so we have to consider an insufficient pathologic evaluation. It should also be taken in account that three axillary dissections were performed and none of them had residual disease, causing increased morbidity.[8]

In contrast, our study showed a very small histological upgrade in patients submitted to mastectomy following at least one attempt at breast-conserving surgery (4.9%), and all the cases corresponding to primary tumor pathology.

Although there was a small number of cases in our cohort, the sentinel node biopsy did not alter the therapeutic strategy defined by the primary tumor characteristics. If we only consider the patients who had a histological upgrade, all were hormonal receptor-positive, thus also allowing adjuvant hormonotherapy.

Conclusion

In conclusion, taking into account our results and the growing evidence that small volume axillary node disease has no impact on disease-free survival and overall survival, and the increasing role of biology in the decision-making process for adjuvant therapy, is safe to omit the indication for SLNB in patients with DCIS patients submitted to mastectomy after attempted BCS.

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