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Annals of Clinical Pathology

Research Article

Reducing the Use of Sentinel Lymph Node Biopsies and the Upstage Rate in Patients with a Ductal Carcinoma in Situ Biopsy, We Are Not There Yet

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Submitted: 07 February 2026

Accepted: 07 April 2026

Published: 08 April 2026

ISSN: 2373-9282

Keywords
- Ductal carcinoma in situ
- Sentinel lymph node biopsy
- EUSOMA
- Quality Indicator

Abstract

In February 2024 the EUSOMA introduced a new quality indicator for patients with ductal carcinoma in situ (DCIS) treated by breast conserving surgery (BCS). The proportion of patients without a Sentinel Lymph Node Biopsy (SLNB) was set at 90% with a minimum of 80%. Additionally, it was suggested that the upstage rate can be as low as 7-11% The purpose of this study was to evaluate the SLNB rate, the upstage rate, and metastasis rate in a large cohort of both BCS and mastectomy treated patients.

Patients aged <18 years, with a DCIS biopsy were selected from the nationwide automated pathology archive (PALGA) and the Netherlands Cancer registry. Cut-off values, at which the proportion of patients without a SLNB would be less than 80%, were defined based on upstage rate and metastasis rate using previously published prediction models.

Of 2269 patients, 1526 were treated with BCS. Of these, 50% did not have a SLNB, while the upstage rate was 13.2% (vacuum-assisted biopsies (VAB) 10.6%, core-needle biopsies (CNB) 20.4%). The metastasis rate was 1.0% (VAB 0.7%, CNB 2.1%). In 743 patients treated by mastectomy 2.7% did not have a SLNB, the upstage rate was 26% (VAB 19%, CNB 35%) and the metastasis rate was 4.4% (VAB 3%, CNB 6 %). At a cut-off value of 16.8% in the upstage model and of 3.9% in the metastasis model the target of more than 80% of patients without a SLNB can be achieved for patients treated by BCS or mastectomy

The use of SLNB in patients with DCIS biopsy treated by BCS is well above the target set by EUSOMA. Prediction models may be helpful to further reduce the use of SLNB. The universal use of VAB will further reduce the upstage rate and metastasis rate. Although the risk of upstaging and metastasis is higher in patients undergoing mastectomy compared to those treated by BCS, the risk of metastasis is low and also in these patients the SLNB rate can be reduced.

INTRODUCTION

Patients with a needle biopsy diagnosis of ductal carcinoma in situ (DCIS) are at risk of upstaging to invasive cancer in the surgical specimen. A meta-analysis reported a pooled estimate of 25.9% of patients upstaged to invasive cancer [1]. As far as we know, the lowest reported upstage rate is 14% [2]. Because of the risk of upstaging, several international guidelines recommend a sentinel lymph node biopsy (SLNB) in selected high risk patients treated by breast conserving surgery (BCS) [3-5]. Although there is a considerable overlap in what these guidelines consider risk factors, it is often unclear how many risk factors should be present to label a patient as high risk or if the risk factors are equally important [6]. Some guidelines like the ASCO guideline even recommend that a SLNB can be omitted in patients treated with BCS [7,8].

The recently updated EUSOMA set of quality indicators for early non-metastatic breast cancer introduces a new indicator for the use of SLNB in patients with a DCIS biopsy [9]. In patients who underwent BCS, the target is that 90% should not have had a SLNB, with a minimum of 80%. One argument for this low target of SLNB usage is that the risk of upstaging to invasive cancer can be as low as 7-11%. Based on a study by Zetterlund et al., it is also stated that the metastasis rate in patients with DCIS is less than 1% [10]. However, this study reports the metastasis rate in patients with a final diagnosis of DCIS, so by definition patients with a DCIS biopsy that is upstaged to invasive cancer are

excluded. Furthermore, the EUSOMA did not set a target for the SLNB rate in patients treated by mastectomy.

In the past, our study group has studied two large cohorts of patients with a DCIS biopsy and developed and validated prediction models for the upstage rate and the metastasis rates [11-13]. In these studies, data from patients treated by BCS and mastectomy were combined and we did not report the SLNB rate. The aim of the present study was to analyze the upstage, SLNB and the metastasis rates separately for patients treated by BCS or mastectomy. In addition, we investigated whether the prediction models we have developed could be helpful in reducing the use of the SLNB: at what risk of upstaging or metastasis is the use of SLNB reduced to the minimum target of 80% set by the EUSOMA? Furthermore, it has been known for years that the upstage rate is influenced by the type of biopsy device: core needle or vacuum-assisted [1]. Therefore, we stratified for the biopsy device to determine the influence on upstage rate.

PATIENTS AND METHODS

The present analysis is based on the cohort we previously used for the validation of a prediction model for upstaging [13,14]. In short, 2269 patients >18 years of age with a biopsy diagnosis of DCIS between July 2016 and March 2019 were selected from the Dutch Pathology Registry (PALGA) including the results of the operation specimen. Additional clinical data were obtained by linkage to the Netherlands Cancer Registry.

Three outcomes; SLNB rate, the upstage rate, and the metastasis rate, were calculated separately for patients treated with BCS or mastectomy. We further explored the effect of the type of biopsy core needle biopsy or vacuum assisted biopsy, on the three outcomes.

The risk of upstaging and metastasis were determined using pre-developed prediction models. These prediction models can be found online (www.evidencio.com, Meurs et al). A cut-off value for the risk of upstaging or metastasis at which the target of at least 80% of patients not undergoing SLNB, was found by trial and error. Since the EUSOMA quality indicator makes a distinction between BCS and mastectomy, we did this separately for both groups.

RESULTS

Of the 2269 patients included in the study, 1562 (69%) were treated with BCS and 743 (31%) with mastectomy (Table 1). Patients undergoing BCS were more often screen-detected and more often had a vacuum assisted biopsy compared to patients undergoing a mastectomy. They less often had a palpable lesion, a lower BI-RADS score and a lower DCIS grade compared to patients undergoing a mastectomy.

Table 1. Characteristics of patients treated by BCS or mastectomy

Variable	Value	BCS		Mastectomy		p-value
		N	(%)	n	(%)	
Age						
	<= 58	717	(47%)	371	(50%)	0.19
	>= 59	809	(53%)	372	(50%)	
Detection						<0.001
	Screening	1139	(75%)	391	(53%)	
	Otherwise	387	(25%)	352	(47%)	
Palpable						<0.001
	No	1373	(90%)	521	(70%)	
	Yes	153	(10%)	222	(30%)	
BI-RADS score						<0.001
	1-3	88	(6%)	29	(4%)	
	4	1348	(88%)	591	(79%)	
	5	90	(6%)	123	(17%)	
Type of biopsy						<0.001
	True cut	388	(25%)	300	(40%)	
	VAB	1124	(74%)	437	(59%)	
	Other/ unknown	14	(1%)	6	(1%)	
Grade						<0.001
	Low	218	(14%)	45	(6%)	
	Intermediate	680	(45%)	274	(37%)	
	High	628	(41%)	424	(57%)	
Suspect invasive						0.31
	No	1497	(98%)	724	(97%)	
	Yes	29	(2%)	19	(3%)	

Overall, the SLNB rate was 64%, the upstage rate was 17% and the metastasis rate was 2%. The SLNB rate was significantly lower in BCS versus mastectomy treated patients (50% versus 94%, p<0.001). The upstage rate in patients treated with BCS was significantly lower compared to those treated with mastectomy (13.2% vs 26.0%, p < 0.001). In addition, the metastasis rate in patients treated with BCS was significantly lower compared to those treated with mastectomy (1.0% vs 4.4%, p < 0.001).

A further analysis of the upstage rate in patients treated by BCS demonstrated that this was 10.6% for patients diagnosed by vacuum-assisted biopsy and 20.4% in patients diagnosed by core-needle biopsy (Table 2). The metastasis rate was 1.0% in the whole group of patients treated by BCS, but 2.1% in the subgroup in which DCIS was diagnosed by core needle biopsy and 0.7% in those diagnosed by vacuum assisted biopsy.

A further analysis of the upstage rate in patients treated with mastectomy demonstrated that this was 19% for patients diagnosed by vacuum-assisted biopsy and 35% in patients diagnosed by core-needle biopsy (Table 3). The metastasis rate was 4.4% in the whole group of patients

Table 2. Upstage and metastasis rates in patients treated by BCS according to the biopsy type (n = 1526)

Outcome		True cut		VAB		Other/unknown		p-value
		N	(%)	N	(%)	n	(%)	
Upstaging								<0.001
	No	309	(79.6%)	1005	(89.4%)	10	(71.4%)	
	Yes	79	(20.4%)	119	(10.6%)	4	(28.6%)	
Metastasis								<0.001
	No	380	(97.9%)	1116	(99.3%)	14	(100%)	
	Yes	8	(2.1%)	8	(0.7%)	0	(0%)	

Table 3. Upstage and metastasis rates in patients treated by mastectomy according to the biopsy type (n = 743)

Outcome		True cut		VAB		Other/unknown		p-value
		N	(%)	N	(%)	N	(%)	
Upstaging								0.092
	No	194	(65%)	352	(81%)	4	(67%)	
	Yes	106	(35%)	85	(19%)	2	(33%)	
Metastase								0.029
	No	281	(94%)	424	(97%)	5	(83%)	
	Yes	19	(6%)	13	(3%)	1	(17%)	

treated by mastectomy, 3% in those diagnosed by vacuum assisted biopsy and 6% in those diagnosed by core needle biopsy.

Using our upstage and metastasis risk prediction models, it was possible to find a cut-off value to ensure that the percentage of patients who do not undergo a SLNB is at least 80%. In patients treated by BCS, the cut-off value would be 16.8% in the upstage model and 3.9% in the metastasis model. This would result in 4 out of 16 metastases being found in the upstage model and 8 out of 16 in the metastasis model.

In patients treated by mastectomy the same cut-off values of 16.8% in the upstage model and 3.9% in the metastasis model could be used. In both risk prediction models 24 out of 33 metastases would be found.

Additional calculations for the target of 90% of patients without a SLNB including patients treated by BCS or mastectomy can be found in the Supplementary Appendix.

A secondary SLNB is not possible in patients treated by mastectomy, therefore another consideration in selecting patients for a SLNB could be to find 80% or more of the metastases. This target can be achieved by setting the cut-off value at 15.0% in the upstage model and at 3.5% in the metastasis model. In both prediction models this would result in the detection of 27 out of 33 metastases. The reduction in SLNB rate would be 37.9% in the upstage model and 46.9% in the metastasis model. Additional data on the upstage rate and different cut-off values can be found in the Supplementary Appendix (Figures 1,2).

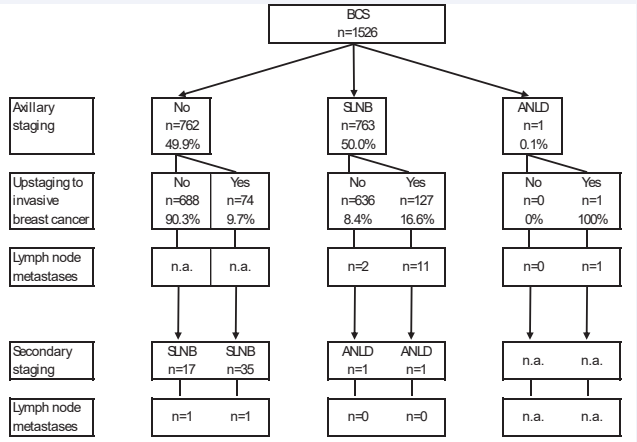

Figure 1 Flow diagram of patients with a DCIS biopsy treated by BCS.

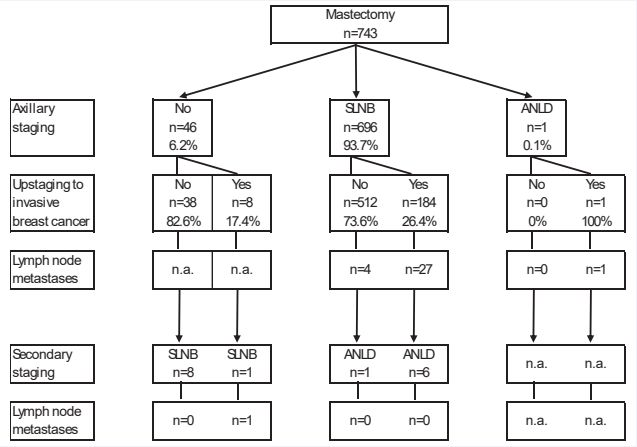

Figure 2 Flow diagram of patients with a DCIS biopsy treated by mastectomy.

DISCUSSION

The objective of this study was to determine the use of SLNB in patients with DCIS biopsy treated with BCS or mastectomy in a large, nationwide cohort of patients. We found that 50% of patients treated by BCS did not have a SLNB, well above the target of 90% and the acceptable limit of 80% set by the EUSOMA [9]. In patients treated by BCS, registry based studies have found that between 81% and 44%of patients did not have a SLNB , all above the 90% target set by the EUSOMA [15-18]. These studies used the final diagnosis of DCIS, the biopsy diagnosis was not available, but nevertheless they indicate that there is an overuse of SLNB. The upstage rate in patients treated by BCS was 13.2%, higher than the 7-11% considered achievable by EUSOMA and metastasis rate was 1.0%. The results in patients treated by mastectomy differed from the BCS with a SLNB rate of 94%, an upstage rate of 26.0% and a metastasis rate of 4.4%.

In a previous population based study, we reported

an upstage rate of 20% and a metastasis rate of 4.4% in the development cohort of our metastasis prediction model [11]. In the validation cohort the upstage rate was 18% and the metastasis rate was 2.2% [13]. Over the last two decades, meta-analyses and systematic reviews reported metastasis rates of 7.4%, 9.8%, 5.95% and 4.9% in patients with a DCIS biopsy [19-21]. In patients with a final diagnosis of DCIS the metastasis rate was 5.0% and 3.02% [20, 21]. One study based on a final diagnosis of DCIS reports metastasis rates lower than 1% [10].

In the present study we found a clear difference in metastasis rate and upstage rate between patients undergoing BCS or mastectomy. The difference in the metastasis rate between patients undergoing BCS and those undergoing mastectomy was also found by van Roozendaal et al., who reported a rate of 3.5% and 7%, respectively [19]. The differences in upstage rate and metastasis rate between patients treated by BCS or mastectomy can be explained by patient selection. Patients treated by mastectomy were less often screen-detected and less often had a vacuum assisted biopsy compared to patients undergoing BCS. They more often had a palpable lesion, a higher BI-RADS score and a higher DCIS grade compared to patients undergoing BCS. All these factors have been identified as risk factors for upstaging and lymph node metastasis [6-14].

An important finding of our study is that vacuum-assisted biopsy was used to diagnose DCIS in only 74% of the patients undergoing BCS and in 60% of the patients undergoing mastectomy. This resulted in significantly lower upstage rates and metastasis rates compared to DCIS diagnosed by core needle biopsy in both patients treated by BCS and those treated by mastectomy. These differences can be easily explained by the difference in the amount of tissue obtained by the two procedures, vacuum- assisted biopsy yielding significantly more tissue. The superiority of vacuum-assisted biopsy in the diagnosis of DCIS well established for quite some time [1]. The equipment used for vacuum-assisted biopsy is somewhat more expensive and the procedure takes longer, which may explain why it is not always used in the diagnosis of DCIS. In addition, selection of the type of biopsy procedure is based on radiological features, which may be equivocal.

Our results confirm that the risk of metastasis in patients undergoing BCS, and also in those undergoing mastectomy, is very low supporting a policy of limited use of a SLNB. However, the EUSOMA recommendations for patients undergoing BCS offer little guidance on how to reduce the use of a SLNB and several guidelines recommend to always perform a SLNB in patients undergoing a mastectomy. We and others have developed prediction models for upstaging, and we have also developed a prediction model for SLNB metastasis [2-20]. In this study we therefore explored whether the use of these prediction models could be an aid in safely reducing the use of SLNB, By setting different cut-offs in these models we were able to find a cut-off value that would result in at least 80% of patients not undergoing a SLNB. For patients undergoing BCS, this would result in 4 out of 16 metastases being detected in both prediction models, so 12 out of 1562 patients, 0.1% will have undetected metastasis. For patients undergoing mastectomy, this would result in 24 out of 33 metastases being detected by both prediction models, so 11 out of 743 patients, 1.4% will have undetected metastases. These numbers are significantly lower than the 13.7% in the control arm who underwent SLNB in early breast cancer patients randomized to SLNB or no axillary staging [21]. Nevertheless, these authors were unable to demonstrate a difference in five-year distant disease-free survival. Also, no differences were observed in locoregional relapses [21]. Further reductions in the use of SLNB are achievable by using higher cut-offs and will still result in metastasis rates that are low compared to the metastasis rate in the study by Gentilini [21]. Therefore, selection of patients for a SLNB based on these prediction models seems to be safe, not only in patients undergoing BCS, but also in those undergoing mastectomy.

We conclude that the use of SLNB in patients with DCIS biopsy treated by BCS is well above the target set by EUSOMA. Prediction models may be helpful to further reduce the use of SLNB. The universal use of vacuum-assisted biopsies will further reduce the upstage rate.

SUPPLEMENTARY INFORMATION

The online version contains a supplementary appendix.

ACKNOWLEDGEMENTS

The authors thank the Dutch Pathology Databank in the Netherlands and the Netherlands Comprehensive Cancer Organisation for the data from their registries.

FUNDING

This work was supported by a grant from the Albert Schweitzer Hospital, grant number 2020-01.

ETHICS APPROVAL

This study was approved by the privacy committee and the scientific committee of PALGA (LZV 2019-57) and the Privacy Review Board of IKNL (K19.199).

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