

# Active surveillance in the management of Ductal Carcinoma In Situ: the radiologist's point of view

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**Simple Summary:** A diagnosis of ductal carcinoma in situ, made on biopsy, is often followed by surgery or radiotherapy because of the risk of an upgrading disease upon subsequent surgical specimens, finding invasive carcinoma. In order to select which patients can be spared overtreatments and alternatively followed with active surveillance, we retrospectively reviewed 2173 vacuum assisted breast biopsies. Our goal was to demonstrate if complete removal of the lesion by biopsy, documented by mammograms, can be a valid criterion to select the patients that can be spared further treatments. The results of our study demonstrate a significant lower upgrading rate of disease when the lesion is completely removed. So, performing a mammogram to document the absence of residual lesion following VABB, allows to reduce overtreatments and to select which patients can be followed with an active surveillance, sparing unjustified public health costs.

**Abstract:** (1) Background: Considering highly selected patients with ductal carcinoma in situ (DCIS), active surveillance is a valid alternative to surgery. Our study is aimed at showing the reliability of post-biopsy complete lesion removal, documented by mammogram, as additional criterion to select these patients. (2) Methods: 2173 Vacuum Assisted Breast Biopsies (VABB) documented as DCIS have been reviewed. Surgery has been performed in all cases. We retrospectively collected the reports of post-VABB complete lesion removal and the histological results of the biopsy and surgery. We calculated the rate of upgrade of DCIS identified on VABB upon excision for patients with post-biopsy complete lesion removal and for those showing residual lesion. (3) Results: We observed 2173 cases of DCIS: 408 classified as low grade; 1262 as intermediate grade; 503 as high grade. The overall upgrading rate to invasive carcinoma was 15.2% (330/2173). The upgrade rate was significantly lower (8.2%) when considering patients showing mammographically documented complete removal of the lesion. (4) Conclusion: The absence of mammographically documented residual lesion following VABB is associated to a lower upgrading rate of DCIS to invasive carcinoma

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on surgical excision and should be considered when deciding the proper management DCIS diagnosis.

**Keywords:** Ductal carcinoma in situ (DCIS); Invasive Breast Carcinoma; Underestimation; Upgrade Rate; Vacuum assisted breast biopsy (VABB); Breast Microcalcifications; Active Surveillance.

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## 1. Introduction

Breast cancer is the most common cancer diagnosed in the female population, accounting for approximately 15.2%-30% of all new cancer cases among women [1].

Ductal carcinoma in situ (DCIS) of the breast represents a heterogeneous group of neoplastic lesions confined to the breast ducts and lobules, without showing invasive features nor metastatic potential [2].

About 25% of all breast cancer cases are ductal carcinoma in situ [3], thus their diagnostic and therapeutic management represents an important health challenge with fundamental public health implications.

DCIS is usually diagnosed by imaging because it is often clinically occult [4]. Its incidence has rapidly increased from 1980 considering the dramatic improvement in diagnosis and screening imaging tools, mostly mammography which plays a central role, as a majority of DCIS is diagnosed by microcalcifications.

Nowadays, approximately 98% of patients with DCIS undergo surgery, often associated with radiotherapy [5]. However, it is now clear that most of them rarely progress spontaneously to invasive cancer, indeed the mortality rate is as low as 4% [6]. The risk of progression seems to be related the grade of the disease, being high grade tumour associated with a worse prognosis [7,8]. Besides, according to some studies, a higher aggressiveness is due to multifocality as well as to aberrant branching and lobularization, defined as neoductogenesis [9,10]. So, the identification of these patterns at imaging and histology could help in distinguishing intrinsic aggressiveness and tailoring the therapy accordingly.

Therefore, we can assume that aggressive treatment of DCIS, especially in patients with comorbidities, can be considered a form of overtreatment, as well as unjustified public health costs, particularly during the COVID 19 pandemic [11].

Four prospective international study protocols (LORIS, COMET, LORD and LORETTA) are currently in place to evaluate non-invasive treatment strategies for DCIS [12-16]. The main proposals consist in including selected patients in protocols based on active surveillance with or without associated endocrine therapy according to specific inclusion criteria, such as the nuclear grade of DCIS and biopsy technique (Table 1).

**Table 1.** Main aspects of the four prospective international study protocols (LORIS, COMET, LORD and LORETTA).

Study	LORIS [13]	COMET [14]	LORD [15]	LORETTA [16]
Country	UK	USA	EU	Japan
Year of activation	2014	2017	2017	2017
Accrual target (number of patients)	932	1200	1240	340
Minimum age at diagnosis (years)	48	40	45	40
Comedonecrosis	Excluded	Allowed	Excluded	Excluded
Hormone receptor status	Any	HR positive only	any	HR positive only

<b>Size of the lesion</b>	Any	Any	Any	<2.5cm
<b>Type of guide for biopsy</b>	Stereotactic (vacuum assisted)	Stereotactic (vacuum assisted)	Stereotactic (vacuum assisted)	Stereotactic and ultrasound (vacuum assisted)
<b>Endocrine therapy</b>	Optional	Optional	Not allowed	Mandatory

The effectiveness of active surveillance can be improved by reducing biopsy-related diagnostic underestimation: presurgical biopsy proven DCIS may be upgraded to invasive carcinoma on submitted surgical specimens.

However, data regarding DCIS diagnostic underestimation rate are quite controversial: according to an important meta-analysis performed by Brennan et al, up to 26% of patients with biopsy proven DCIS reveal a synchronous invasive carcinoma on surgical specimens [17].

The primary purpose of our observational multicentre retrospective study is to determine the rate of upgrade of DCIS identified on Vacuum Assisted Breast Biopsy (VABB) upon excision.

The secondary objective of the study is to prove a correlation, if it exists, between the post-biopsy complete removal of the lesion and the lower likelihood to find an invasive carcinoma on subsequent surgical specimen.

In order to do this, the residual tumour rate found on surgical specimen was compared with imaging of mammogram performed post VABB but before subsequent surgery.

## 2. Materials and Methods

We reviewed all cases of breast biopsies with DCIS diagnosed on VABB at our Departments of Pathology from January 1st, 2000 to December 31st, 2018 and subsequent surgical excision performed in two centres.

Since VABB provides a better diagnostic performance than core needle biopsy [18], we selected patients submitted to this procedure using a 12G needle.

During the considered period of this study, we have been using a subcategorization of DCIS according to the so-called DIN system (Ductal Intraepithelial Neoplasia) as previously published [19]. Briefly, DIN1C corresponds to low grade DCIS, DIN2 to intermediate, DIN3 to high grade, according to nuclear morphologic features of the neoplastic cells [20,21].

Patients younger than 40 years of age, those with concomitant invasive carcinoma or past personal history of breast cancer and those showing DCIS with comedonecrosis were excluded from the study.

All these data have been retrospectively collected.

By using mammogram before surgery, we recorded the absence or the presence of post-VABB residual lesion and we compared the outcomes of these two groups of patients.

The upstage rate of DCIS to invasive carcinoma following surgical excision was always recorded.

### 2.1. Statistics

The collected data were compared using the compare proportions test. A p-value <0.05 was used to determine statistically significant differences.

## 3. Results

A total number of 2173 vacuum assisted breast biopsies were performed under stereotactic guidance showing DCIS: 408 cases were low grade (DIN1C); 1262 cases were intermediate grade (DIN2), and 503 cases were high grade (DIN3). The mean age of the

patients was 62 years (range 32-84 years). The overall mean diameter of the lesions was 20 mm. Table 2 summarizes clinicopathologic characteristics of the patients.

**Table 2.** Patients characteristics.

	DIN1C	DIN2	DIN3	Overall
<b>Patients number</b>	408	1262	503	2173
<b>Age at VABB, mean (years)</b>	50 (40-82)	54 (43-87)	49 (44-85)	54 (40-87)
<b>Mean diameter of the lesion (mm)</b>	22 (5-75)	20 (7-60)	25 (4-80)	20 (5-80)
<b>BIRADS</b>				
<b>BIRADS 3</b>	10 (2.4%)	2 (0.2%)	0 (0%)	12 (0.5%)
<b>BIRADS 4a</b>	308 (75.6%)	952 (75.5%)	10 (1.9%)	1270 (58.4%)
<b>BIRADS 4b</b>	60 (14.7%)	248 (19.6%)	102 (20.2%)	410 (18.9%)
<b>BIRADS 4c</b>	27 (6.6%)	50 (3.9%)	345 (68.7%)	422 (19.4%)
<b>BIRADS 5</b>	3 (0.7%)	10 (0.8%)	46 (9.2%)	59 (2.7%)
<b>Absence of residual disease post-VABB</b>				
<b>Absence of residual disease post-VABB</b>	159 (39%)	420 (33.3%)	206 (41%)	785 (36.1%)
<b>Family history</b>	230 (56.3%)	754 (59.7%)	330 (65.6%)	1314 (60.5%)

Taken as a whole, 15.2% (330/2173) of DCIS were upgraded to invasive cancer on surgical excision.

We observed post-VABB complete removal of the lesion in 785 out of 2173 (36.1%) patients. By considering this subgroup, we reported 65 cases of invasive carcinoma on surgical specimen and thus, 8.3% (65/785) of DCIS were upgraded to invasive cancer. The mean diameter of the lesion removed with the biopsy was 20 mm.

These data led to the first observation: patients showing complete removal of the lesion experienced a significantly lower upgrade rate compared to those showing mammographically detectable residual tumour after VABB ( $p$ -value < 0.01).

Data considering the three diagnostic categories (DIN1C, DIN2 and DIN3) are summarized in Table 3.

**Table 3.** Diagnostic underestimation rate comparison between cases with and cases without residual lesion post biopsy.

		Comments	<i>p</i> -value for testing differences between the two proportions
<b>Absence of residual disease post biopsy (DIN1C)</b>		Percentage of upgrading rate	
	<b>Final surgical evaluation</b>		

					from DCIS to invasive disease =	(Absence and presence of residual disease)
<b>VABB result</b>	Negative	DIN1C	IN	Total	5.6%	<b><i>p = 0.002</i></b>  <i>statistical significance</i> <b>0.05</b>
DIN1C	19	131	9	159		
<b>Presence of residual disease post biopsy (DIN1C)</b>					Percentage of upgrading rate from DCIS to invasive disease =	
<b>Final surgical evaluation</b>						
<b>VABB result</b>	Negative	DIN1C	IN	Total	12%	
DIN1C	43	176	30	249		
<b>Absence of residual disease post biopsy (DIN2)</b>					Percentage of upgrading rate from DCIS to invasive disease =	<b><i>p &lt; 10<sup>-8</sup></i></b>  <i>statistical significance</i> <b>0.001</b>
<b>Final surgical evaluation</b>						
<b>VABB result</b>	Negative	DIN2	IN	Total	7.8%	
DIN2	49	338	33	420		
<b>Presence of residual disease post biopsy (DIN2)</b>					Percentage of upgrading rate from DCIS to invasive disease =	
<b>Final surgical evaluation</b>						
<b>VABB result</b>	Negative	DIN2	IN	Total	18.7%	
DIN2	34	650	158	842		
<b>Absence of residual disease post biopsy (DIN3)</b>					Percentage of upgrading rate from DCIS to invasive disease =	<b><i>p &lt; 10<sup>-4</sup></i></b>  <i>statistical significance</i> <b>0.001</b>
<b>Final surgical evaluation</b>						
<b>VABB result</b>	Negative	DIN3	IN	Total	11.1%	
DIN3	14	169	23	206		
<b>Presence of residual disease post biopsy (DIN3)</b>					Percentage of upgrading rate from DCIS to invasive disease =	
<b>Final surgical evaluation</b>						
<b>VABB result</b>	Negative	DIN3	IN	Total	25.9%	
DIN3	31	189	77	297		
<b>Absence of residual disease post biopsy (Overall)</b>					Percentage of upgrading rate from DCIS to invasive disease =	<b><i>p &lt; 10<sup>-13</sup></i></b>  <i>statistical significance</i> <b>0.001</b>
<b>Final surgical evaluation</b>						
<b>VABB result</b>	Negative	DIN	IN	Total	8.2%	
Overall	72	638	65	785		
<b>Presence of residual disease post biopsy (Overall)</b>						

VABB result	Final surgical evaluation				Percentage of upgrading rate from DCIS to invasive disease = 19%
	Negative	DIN	IN	Total	
Overall	108	1015	265	1388	

VABB: Vacuum Assisted Breast Biopsy; IN: Invasive Neoplasia; DIN: Ductal Epithelial Neoplasia

### 3.1. DCIS subcategories

#### 3.1.1. DIN1C (Low grade DCIS)

- We observed that 408 patients received the diagnosis of DIN1C (low grade DCIS): 9.6% (39/408) of them were upgraded to invasive cancer. The overall mean diameter of the DIN1C lesions was 22 mm.
- We reported post-VABB complete removal of the lesion in 159 out of 408 patients with DIN1C diagnosis. Among them, we reported 9 cases of invasive carcinoma on surgical specimen and thus, 5.7% (9/159) of low grade DCIS cases with no residual lesion were upgraded to invasive cancer.
- Patients with diagnosis of low grade DCIS showing complete removal of the lesion experienced a significantly lower upgrade rate when compared to those showing mammographically detectable residual tumour after VABB (p-value < 0.019).

#### 3.1.2. DIN2C (Intermediate grade DCIS)

- We observed that 1262 patients received the diagnosis of DIN2 (intermediate grade DCIS): 15.1% (191/1262) of them were upgraded to invasive cancer. The overall mean diameter of the DIN 2 lesions was 20 mm.
- We reported post-VABB complete removal of the lesion in 420 out of 1262 patients with DIN2 diagnosis. Among them, we reported 33 cases of invasive carcinoma on surgical specimen and thus, 7.8% (33/420) of intermediate grade DCIS cases with no residual lesion were upgraded to invasive cancer.
- Patients with diagnosis of intermediate grade DCIS showing complete removal of the lesion experienced a significantly lower upgrade rate compared to those showing mammographically detectable residual tumour after VABB (P-value < 0.01).

#### 3.1.3. DIN3C (High grade DCIS)

- We observed that 503 patients received the diagnosis of DIN3 (high grade DCIS), 19.9% (100/503) of them were upgraded to invasive cancer. The overall mean diameter of the DIN 3 lesions was 25 mm.
- We reported post-VABB complete removal of the lesion in 206 out of 503 patients with DIN3 diagnosis. Among them, we reported 23 cases of invasive carcinoma on surgical specimen and thus, 11.2% (23/206) of high grade DCIS cases with no residual lesion were upgraded to invasive cancer.
- Patients with diagnosis of high grade DCIS showing complete removal of the lesion experienced a significantly lower upgrade rate compared to those showing mammographically detectable residual tumour after VABB (p-value < 0.01).

#### 4. Discussion

Considering that most of DCIS will never progress to invasive breast cancer during a patient's lifetime, surgical therapy and radiotherapy of DCIS, especially in patients with comorbidities, can be considered a form of overtreatment, without taking into account unjustified health and social care costs.

Surveillance, Epidemiology, and End Results (SEER) data shows that the 20-year breast cancer-specific mortality rate in patients with DCIS is as low as 3.3% [11,22]. On the other side, according to a significant meta-analysis, 25.9% (18.6–37.2%) of presurgical cases diagnosed as DCIS have been upgraded to invasive carcinoma upon excision [17].

In this study, we tried to minimize the risk of diagnostic underestimation by applying strict inclusion criteria. In particular, in our series, all cases were biopsied by VABB with at least a 12G needle; patients younger than 40, or patients with previous history of breast cancer were excluded.

Our overall upgrading rate of 15.2% was in line with other previous studies [23-25] that have reported upgrading rates in the range 11–25% (Table 4).

**Table 4.** Upgrading rates to invasive carcinoma of breast biopsies in different studies.

References	No. pts	Years	Biopsy type	Upstaging rate to invasive cancer
Brennan et al. (meta-analysis of 52 studies) [17]	7350	1996-2011	Variable	26% overall 21% non-high grade 32% high grade
Soumian et al. [23]	225	2001-2010	VABB	18% overall 10% low grade 23% high grade
Pilewskie et al. [24]	296	2009-2012	Variable	8% low grade 22% intermediate grade
Grimm et al. [25]	307	2008-2015	VABB	17% overall 7% low grade 7% intermediate grade 23% high grade
Current study	2173	2000-2018	VABB	15.2% overall 9.6% low grad 15.1% intermediate grade 19.3% high grade
Current study (post-biopsy removal of the lesion)	2173	2000-2018	VABB	8.2% overall 5.6% low grade 7.8% intermediate grade 11.1% high grade

Furthermore, in order to reduce the diagnostic underestimation rate as much as possible, we took into account additional parameters such as the post-biopsy complete removal of the lesion [26] information not reported in other studies and the diameter of the lesion, information evaluated only in Loretta trial (diameter <25mm) [16].

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The results of our study show that if the lesion is completely removed during biopsy, the overall diagnostic underestimation rate is significantly lower. Indeed, DCIS patients showing complete removal of the lesion experienced a significantly lower upgrade rate to invasive cancer compared to those showing mammographically detectable residual tumour after VABB (respectively 8.2% vs 15.2%).

Therefore, we strongly believe that this last parameter should be considered as a possible selection criterion to enrol DCIS patients in surveillance protocols.

As far as we know, this study has one of the largest number of biopsies considered in a single retrospective study, but the main limitation is its retrospective nature. Moreover, involved patients do not perfectly match inclusion criteria of LORIS, LORETTA, COMET and LORD protocols.

The absence of mammographically documented residual lesion following VABB is associated to a lower upgrading rate of DCIS to invasive carcinoma on surgical specimens and should be taken into account when deciding the proper management of patients with ductal carcinoma in situ diagnosis.

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