Published in final edited form as:

Ann Surg Oncol. 2017 November ; 24(12): 3534–3540. doi:10.1245/s10434-017-6018-9.

Surgical upstaging rates for vacuum assisted biopsy proven DCIS: implications for active surveillance trials

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Abstract

Purpose: To determine invasive cancer upstaging rates at surgical excision following vacuum assisted biopsy of DCIS among women meeting eligibility for active surveillance trials.

Methods: Patients with vacuum assisted biopsy proven DCIS at a single center from 2008–2015 were retrospectively reviewed. Imaging and pathology reports were interrogated for the imaging appearance, tumor grade, hormone receptor status, and presence of comedonecrosis. Subsequent surgical reports were reviewed for upstaging to invasive disease. Cases were classified by eligibility criteria for the COMET, LORIS, and LORD DCIS active surveillance trials.

Results: Of 307 DCIS diagnoses 15 (5%) were low, 95 (31%) intermediate, and 197 (64%) high nuclear grade. The overall upstage rate to invasive disease was 17% (53/307). There were 81 patients eligible for the COMET Trial, 74 for the LORIS trial, and 10 for the LORD Trial, although LORIS trial eligibility also includes real time multiple central pathology review, including elements not routinely reported. The upstaging rates to invasive disease were 6% (5/81), 7% (5/74), and 10% (1/10) for the COMET, LORIS, and LORD Trials respectively. Among upstaged cancers (N=5), four tumors were Stage IA invasive ductal carcinoma and one was Stage IIA invasive lobular carcinoma; all were node negative.

Conclusion: DCIS upstaging rates in women eligible for active surveillance trials are low (6–10%) and in this series, all those with invasive disease were early stage, node negative. The careful patient selection for DCIS active surveillance trials carries a low risk of missing occult invasive cancer and additional studies will determine clinical outcomes.

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Disclosures: None

Introduction

Ductal carcinoma *in situ* (DCIS) is a common form of non-invasive breast cancer representing approximately 20–30% of all new breast cancer diagnoses.^{1,2} Although the natural history of DCIS is poorly understood because almost all patients undergo surgical excision, there is a growing understanding that DCIS is a heterogeneous disease process.^{3–6} It is estimated that 47% to 86% of untreated DCIS cases will never progress to invasive disease, prompting overtreatment concerns.^{1,4,5,7–9} Furthermore, it is unknown whether long-term disease outcome is adversely impacted if lower grade DCIS does in fact progress to invasive disease. As a result, there is strong interest in active surveillance strategies which avoid surgery and radiation therapy for patients with DCIS deemed to have a low likelihood of progression to invasive cancer.

There are currently three prospective randomized controlled active surveillance trials underway that are comparing experimental arms to standard treatment. The Low Risk DCIS (LORD) Trial in Europe is testing imaging follow up alone versus standard treatment; the Low RISK DCIS (LORIS) Trial in Europe and the Comparison of Operative to Monitoring and Endocrine Therapy for low-risk DCIS (COMET) Trial in the United States allow for endocrine therapy in the imaging follow up cohort.^{10–14} Identifying low risk patients for active surveillance trials is a critical component for the successful execution of these active surveillance trials. Patient selection criteria are designed to include those at low risk for progression to invasive disease and to exclude patients with occult invasive disease at initial presentation.

The goal of this study is to determine the invasive cancer upstaging rates at surgical excision for women diagnosed with DCIS on vacuum assisted core needle biopsy, to compare these rates according to the differing eligibility criteria for each trial, and to model the impact of differential upstaging rates on patient outcomes.

Materials and Methods

Institutional Review Board approval with a waiver of informed consent was obtained for this HIPAA-compliant retrospective study. We searched our medical record system to identify all cases of DCIS presenting as screen detected or incidental calcifications diagnosed by vacuum assisted core needle biopsy from January 1, 2008 through December 31, 2015 (n=373). Tumors with missing hormone receptor status (i.e., inadequate sample available for testing, n=22), no surgical excision (n=27), or synchronous invasive ductal carcinoma (i.e., DCIS plus invasive ductal carcinoma identified on biopsy, n=17) were excluded. Patients with atypia bordering on DCIS or DCIS with the suggestion of microinvasive disease were not identified by our search criteria. Patient demographic information including age, race, personal cancer history, and family history of breast cancer were recorded.

All patients underwent stereotactic biopsies with a 9-gauge vacuum-assisted biopsy device (Suros ATEC, Hologic, Bedford, MA) guided by a fellowship trained breast imager. Six to 12 core specimens were typically collected and radiographs confirmed that the targeted calcifications had been successfully sampled. Pathology reports from the initial core needle

biopsy and subsequent surgical excision were reviewed by specialist breast pathologists for tumor grade, estrogen receptor (ER), progesterone receptor (PR), and if invasive cancer was present human epidermal growth factor receptor-2 (HER2). For cases with missing receptor status on initial needle biopsy, the results from the surgical excision were used. The presence or absence of comedonecrosis was noted. Mammogram reports were reviewed for an associated mass, asymmetry, or architectural distortion. Surgical pathology reports were reviewed for upstaging to invasive disease.

Univariate analysis was performed to compare demographic and pathology variables to the nuclear grade upgrade and invasive disease upstaging rates. Multivariable logistic modeling was then performed based on the predictive variables of the univariate analysis. Cases were classified according to published eligibility criteria from the COMET, LORIS, and LORD trials as outlined in Table 1. The LORIS trial has a two stage eligibility process, whereby pathology slides from patients meeting the eligibility criteria in Table 1 are then reviewed in real time by two expert DCIS pathologists for the following: low nuclear grade or lower half of intermediate nuclear grade, no comedo-type necrosis, no more than occasional mitoses (1 per 3 duct cross section), and not any marked nuclear pleomorphism (less than 2.5 red blood cells in diameter). Only patients who meet central review criteria are eligible to be randomized; thus the upstaging rates evaluated here apply to those patients who would have been eligible for registration and not necessarily for randomization. Nuclear grade upgrade and invasive disease upstaging rates were calculated for cases that met published eligibility criteria for each active surveillance trial.

A previously established computational risk projection model estimated the impact of differential upstaging rates (7%, 15%, and 25%) on patient outcomes in a hypothetical active surveillance scenario.¹⁵ In brief, the model combines a continuous-time Markov chain model of the natural history of breast cancer with outcome data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database of the United States (1999–2011) to estimate the median 10-year disease-specific cumulative mortality and corresponding 95% projection range. The simulated active surveillance scenario was based on a diagnosis with low to intermediate nuclear grade DCIS at age 60 years, regular follow-up screening for detection of invasive disease (every 6-months, 80% sensitivity), and usual care treatment (as reported in SEER) upon detection of a cancer. Simulations were performed in R (Foundation for Statistical Computing, Vienna, Austria) and results were visualized in MatLab (The MathWorks, Inc, Natick, MA).

Results

Overall Study Cohort

There were 307 cases for analysis with patient demographics and DCIS characteristics listed in Table 2. The mean age was 61.3 years (range: 33.5–86.7 years); two thirds were Caucasian women (64%, 198/307) and one third (31%, 96/307) were in black women. DCIS cases were most commonly high grade (62%, 191/307), ER positive (81%, 249/307), and PR positive (70%, 216/307) with 51% (157/307) of cases containing comedonecrosis. Among cases of low and intermediate grade DCIS the upgrade rate to a higher nuclear grade at surgical excision was 12% (13/110). The upstage rate from DCIS to invasive disease for the

total cohort was 17% (53/307): 7% (1/14) for low grade, 7% (7/88) for intermediate grade, and 23% (46/151) for high grade DCIS. The upstage rate for ER positive DCIS was 14% (36/249), versus 31% (18/58) for ER negative DCIS. Among cases of ER negative, high grade DCIS the upstage rate was 33% (17/51). Upgrade and upstage rates by demographics and pathology variables are shown in Table 3. High nuclear grade, ER negative, and PR negative status were associated with upstaging to invasive disease (all $p < 0.01$).

Trial eligible patients

Based on published eligibility criteria (Table 1) there were 81 patients eligible for the COMET Trial, 74 for the LORIS Trial, and 10 for the LORD Trial (Table 2). The upgrade rate to a high nuclear grade DCIS was 7% (6/81) for COMET, 7% (5/74) for LORIS, and 10% (1/10) for LORD eligible cases. The upstage rate to invasive disease was 6% (5/81) for COMET, 7% (5/71) for LORIS, and 10% (1/10) for LORD eligible cases. Among these upstaged cases, there was one case of low grade DCIS upstaged to Stage IA IDC (T1aN0M0); this case was trial-eligible for all three active surveillance studies. There were four upstaged cases of intermediate grade DCIS included in both the COMET and LORIS groups: three cases of Stage IA IDC (T1a or b N0 M0) and one case of Stage IIA (T2N0M0) invasive lobular cancer. All upstaged cases were node negative and HER2 negative. There was no upgrading of nuclear grade. The characteristics of each COMET-eligible upstaged case are shown in eTable 1.

Modeled patient outcomes

The projected median 10-year breast cancer-specific cumulative mortality for the *active surveillance strategy* for a 60-year old woman with low to intermediate nuclear grade DCIS, was 1.4% (95%-PR: 0.9–2.6) for a 7% upstaging rate, 2.0% (95%-PR: 1.5–3.2) for a 15% upstaging rate, and 2.8% (95%-PR: 2.3–3.8) for a 25% upstaging rate, (Figure 1). The SEER-based estimate of the 10-year disease-specific cumulative mortality for *usual care* was 1.4% (95%-CI: 0.8–1.9), and the 10-year mortality due to other causes of death was estimated to be 6.1% (95%-CI: 4.9–7.2). For the COMET and LORIS trials with an upgrade rate closest to 5% this may equate to a 1.3–2% mortality at 10 years, compared to 1.4% for usual care and surpassed by death from other causes of 6.1% at 10 years.

Discussion

This study provides insights into the upstaging rates to invasive cancer for patients with newly diagnosed DCIS who meet published active surveillance trial eligibility criteria. Our overall upstaging rate of 17% was consistent with previous investigators who have reported upstaging rates for vacuum assisted core needle biopsies of 11–25%; however, typically higher upstaging rates are reported when cases of DCIS that present as masses or palpable findings are included.^{16–18} Following the application of trial eligibility criteria, the upstaging rates dropped to 6%, 7%, and 10% for the COMET, LORIS, and LORD Trials respectively. All upstaged cases were early stage, node negative, ER positive, PR positive and HER2 negative, features of a long term good prognosis. For the three active surveillance trials, the primary outcomes are based upon diagnosis of invasive cancer; thus it is important to exclude as many patients with occult invasive disease during enrollment. The low rates of

upstaging in our study indicate that a sufficient number of patients with occult invasive disease will be initially excluded during patient selection for active surveillance trials to allow for safe testing of the primary study objectives.

Although there are no published series of upstaging based upon COMET or LORD eligibility criteria,^{16,19} Soumian et al., as part of a preliminary audit of locally reported low grade DCIS, found that among LORIS eligible patients the upstaging rate to invasive disease was 0% (Table 4).¹⁶ In contrast, Pilewskie et al. reported upstaging rates of 20% among LORIS eligible patients, although this study differed from the LORIS trial as it was not limited to patients undergoing vacuum assisted sampling only.¹⁹ Of note, the LORIS trial requires central pathology review to exclude additional patients, an important criterion which could not be captured retrospectively in either the Pilewskie or the current study. For context, a recent meta-analysis of 7350 patients from 52 studies, unrelated to active surveillance, reported a median DCIS upstaging rate of 26.0% (IQR: 18.6%–37.2%), emphasizing the need to apply stringent eligibility criteria for any active surveillance trials.¹⁷ As expected, the application of eligibility criteria result in lower upstaging rates.

These variable upstaging rates are due in part to differences in study demographics and biopsy techniques. The 0% upstaging reported by Soumian et al. is due in part to the inclusion of only low grade DCIS in the analysis.¹⁶ In the present study, there was only one upstaged case of low grade DCIS eligible for all three trials, but the total number of low grade DCIS cases was small (n=15) which makes it difficult to draw definitive conclusions on this population and in particular the LORD trial. Moreover, the biopsy technique is likely a major cause of the higher upstaging rate (20%) reported by Pilewskie et al. as a vacuum assisted biopsy technique was not required, and only 48% of patients had documentation of a 8 or 9-gauge biopsy.¹⁹ In contrast, all subjects in our study underwent a 9-gauge vacuum assisted biopsy as both wider bore needles and vacuum assistance are associated with reduced underestimation rates.¹⁷ Notably, the LORIS and LORD Trials require a pre-defined number and size of vacuum-assisted biopsies. For the LORIS trial at least six 12-gauge vacuum-assisted core biopsies are required and for the LORD trial at least six 8–9 gauge or twelve 10–11 gauge biopsies are required. Furthermore, the COMET and LORD trials require that at least two sites be sampled for lesions exceeding 4 cm to reduce undersampling. Finally, variable upstaging rates may be due to differences in pathologists' DCIS interpretations.²⁰ In recognition of this issue, the COMET trial requires concordance among two clinical pathologists. In contrast, the LORIS trial has instituted a two stage process, where designated pathology criteria determine eligibility for registration, but only those who fulfill strict real-time central pathology review requirement are eligible for randomization. The rate of registered patients in LORIS who are deemed not eligible for randomization based on centralized pathology review will be evaluated in a scheduled interim analysis, and is thus not available at this time.

There are notable differences between the individual trial inclusion/exclusion criteria, which change the pool of eligible patients. The LORD Trial includes only low nuclear grade DCIS. In a recent analysis of 57,222 cases of DCIS from the SEER registry, low grade DCIS was present in only 16% of cases.²¹ However, reported rates of low grade DCIS are higher in other countries, including a rate of 27% in the Netherlands.²² The COMET Trial requires

ER and/or PR positive disease due to the allowance of endocrine therapy in the active surveillance arm. Of note, both ER and PR negative status were predictive of upstaging in our study, thus these may be useful active surveillance exclusion criteria even if endocrine therapy is not utilized. In this study sample, there were more patients that were eligible for the COMET Trial (n=81) than the LORIS Trial (n=74), but there were minimal differences in the upstaging rates (6% versus 7% respectively) as the same five cases of upstaging were present in both groups.

Patient outcomes of active surveillance will depend in part on the risk of missing concurrent invasive disease at diagnosis and on the frequency and sensitivity of follow-up screens. The upstaging rate was previously shown to have a substantial impact on the projected 10-year disease-specific mortality when modeling the outcomes of an active surveillance approach for all DCIS.¹⁵ Repeating the risk projections for patients diagnosed with low to intermediate grade DCIS only, the models predicted a negligible difference in disease-specific mortality between active surveillance and usual care for an upstaging rate of 7% and lower. This finding emphasizes that the risk of active surveillance can be mitigated by thorough baseline assessment at diagnosis of DCIS to rule out invasive cancer. Due to the study design, we were unable to comment on the impact that additional imaging modalities may have on upstaging, but this is clearly an important area that merits further investigation.

This study is limited by the retrospective design. Although there was no centralized pathology or radiology re-review, all cases were originally interpreted by specialized breast pathologists and specialist breast radiologists at a single large academic medical center. The retrospective design has the greatest impact on assessment of eligibility according to the LORIS criteria, since only the initial *registration* criteria could be examined and the full *eligibility* criteria, including the centralized pathology review, would likely affect the upstaging rate in LORIS. The use of a 9 gauge vacuum assisted biopsy device and the acquisition of 6–12 samples may completely remove small DCIS lesions thus reducing the likelihood of upgrading/upstaging compared to prior investigators who have reported on the use of different needle gauges.

In conclusion, women with DCIS who meet eligibility criteria for the COMET and LORD Trials have low rates (7%) of upstaging to early stage, node negative invasive disease at surgical excision. Modeling the long-term impact of this level of upstaging using SEER data revealed minimal impact on breast cancer specific survival. In aggregate, these three prospective randomized trials will determine whether active surveillance impacts disease and patient reported outcomes. For now, the low rates of upstaging and a minimal projected effect on survival should allow clinicians to feel comfortable to accrue patients to trials of active surveillance for DCIS to safely test their primary trial objectives of progression to invasion, breast cancer specific survival, and overall survival.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments:

We are grateful for the feedback from Adele Francis for the interpretation of results and manuscript editing. The authors have no financial conflicts of interest to disclose.

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Synopsis

DCIS upstaging rates among women eligible for active monitoring trials are low (6–10%) and those with invasive disease were early stage, node negative. Careful patient selection for DCIS active surveillance trials carries a low risk of missing occult invasive cancer.

Figure 1. Cumulative mortality after diagnosis with low to intermediate nuclear grade DCIS at age 60 years: active surveillance (AS) disease-specific projections vs usual care (UC) disease-specific and competing risks.

The model-based, projected disease-specific cumulative mortality (DSCM) for the AS strategy (median: blue solid line; 95% projection range: blue band) is compared with the Surveillance, Epidemiology, and End Results (SEER)-based DSCM for UC (point estimate: red dotted line; 95% confidence interval: red band) and the cumulative mortality because of competing risks (point estimate: green dash-dotted line; 95% confidence interval: green band) for three different upstaging rates of 7% (A), 15% (B) and 25% (C). All parameters as in [Ryser et al., JNCI, 2016], except for a restricted probability of progression to invasive disease (prior range: 10%–40%) to reflect the exclusion of lesions with high nuclear grade.

Table 1.

Inclusion and exclusion criteria for the COMET, LORIS, and LORD trials.

	COMET	LORIS*	LORD
Inclusion criteria			
Age (years)	40	46	45
Nuclear grade	Low and intermediate	Low and intermediate	Low
Morphology	Calcifications only	Calcifications only	Calcifications only
Hormone receptor status	ER and/or PR positive, plus HER2 negative if performed	N/A	N/A
Biopsy technique	VACB <i>and/or</i> surgical biopsy	At least 12 gauge VACB <i>and/or</i> surgical biopsy	6 samples with 8–9 gauge <i>or</i> 12 samples with 10–11 gauge VACB
Exclusion criteria			
History of cancer	Exclude if invasive breast cancer	Exclude if invasive breast cancer or ipsilateral DCIS	Exclude if any cancer except in situ of the cervix or basal carcinoma of the skin
Symptomatic	Exclude	Exclude	Exclude
Comedonecrosis	Exclude	Exclude	N/A
Synchronous invasive cancer	Exclude	Exclude	Exclude
Bilateral DCIS at presentation	Include	Include	Exclude
High risk	Include	Exclude if high risk per NICE guidelines ^{2,3}	Exclude if family with BRCA 1/2 mutation
History of chemoprevention	Exclude	N/A	N/A

Criteria deemed not applicable (N/A) are not mentioned in the inclusion or exclusion criteria of the study protocols. DCIS: ductal carcinoma in situ. LORD: Low Risk DCIS. LORIS: Low Risk DCIS. COMET: Comparing Operative to Medical Endocrine Therapy for low-risk DCIS. NICE: National Institute for Health and Care Excellence. VACB: vacuum assisted core biopsy

* Initial eligibility for registration criteria only; patients are subsequently deemed eligible for randomization based on confirmation of low risk disease (low and low to intermediate grade) by central pathology review.

Table 2.

Patient demographics and DCIS characteristics for the entire study population and cases eligible for the COMET, LORIS, and LORD trials (eligibility criteria for each trial are listed in table 1).

	Entire population (n=307) No. (%)	COMET (n=81) No. (%)	LORIS (n=74) No. (%)	LORD (n=10) No. (%)
Age (years, mean [range])	60.3 (33.5–86.7)	61.3 (44.1–86.7)	62.5 (44.1–86.7)	63.1 (51.5–80.6)
Race				
Caucasian	198 (64)	54 (67)	52 (70)	6 (60)
Black	96 (31)	27 (33)	22 (30)	4 (40)
Other	13 (5)	0 (0)	0 (0)	0 (0)
ER positive	249 (81)	80 (99)	71 (96)	10 (100)
PR positive	216 (70)	77 (95)	68 (92)	10 (100)
Nuclear grade				
Low	15 (5)	12 (15)	12 (16)	10 (100)
Intermediate	95 (31)	69 (85)	62 (84)	0 (0)
High	197 (64)	0 (0)	0 (0)	0 (0)
Comedonecrosis	157 (51)	0 (0)	0 (0)	0 (0)
Upgrade to high grade DCIS	10 (3)	6 (7)	5 (7)	1 (10)
Upstage to invasive disease	53 (17)	5 (6)	5 (7)	1 (10)

Data are expressed as n (%) unless otherwise specified. LORD: Low Risk DCIS, LORIS: Low Risk DCIS, COMET: Comparing Operative to Medical Endocrine Therapy for low-risk DCIS, ER: estrogen receptor, PR: progesterone receptor

Table 3.

Upgrade and upstage rates by demographic and pathology results.

	Upgrade rate to a higher nuclear grade ^{***}	p value	Upstage rate from DCIS to invasive disease	p value
Total	12% (13/110)		18% (54/307)	
Age		0.34		0.78
50 years	18% (3/17)		19% (11/57)	
>50 years	11% (10/93)		17% (43/250)	
Race		0.66		0.86
Caucasian	10% (7/71)		18% (35/198)	
Black	14% (5/37)		17% (16/96)	
Other	50% (1/2)		21% (3/14)	
Nuclear grade		0.09		<0.01 *
Low	27% (4/15)		7% (1/15)	
Intermediate	9% (9/95)		7% (7/95)	
High	N/A		23% (46/197)	
ER		0.55		<0.01 *
Positive	11% (11/103)		14% (36/249)	
Negative	29% (2/7)		31% (18/58)	
PR		0.51		<0.01 *
Positive	10% (10/98)		11% (24/216)	
Negative	25% (3/12)		33% (30/91)	

Data are expressed as row percentage with fraction in parentheses.

*
p value less than 0.05.***
Among cases of low or intermediate nuclear grade at core needle biopsy. ER: estrogen receptor. PR: progesterone receptor. N/A: not applicable.

Table 4.

Comparison of upstaging rates in the literature with attention to active surveillance trials.

Reference	N	Years	Biopsy type	Upstaging rate to invasive cancer	Comments
Brennan et al. ¹⁷	7350	1996–2011	Variable [*]	26% overall: 21% non-high grade and 32% high grade	Meta-analysis of 52 studies. [*] Includes non-image, stereotactic, US, and MRI guided biopsies.
Sourmian et al. ¹⁶	225	2001–2010	VAB	18% overall: 10% low and 23% high grade 0% among low grade and LORIS eligible [*]	LORIS trial in practice includes both low and lower half of intermediate grade
Pilewskie et al. ¹⁹	296	2009–2012	VAB [*]	8% low and 22% intermediate grade 20% among LORIS eligible [*]	VAB “was routinely used” but not an inclusion criteria
Current study	307	2008–2015	VAB	17% overall: 7% low, 7% intermediate, and 23% high grade 6% among COMET eligible [*] 7% among LORIS eligible [*] 10% among LORD eligible	

VAB: vacuum assisted biopsy, LORD: Low Risk DCIS, LORIS: Low Risk DCIS, COMET: Comparing Operative to Medical Endocrine Therapy for low-risk DCIS.

^{*} Note that LORIS eligible patients might not be eligible for randomization based upon real-time central pathology review criteria.