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Active Surveillance for Atypical Ductal Hyperplasia and Ductal Carcinoma In Situ

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Abstract

Atypical ductal hyperplasia (ADH) and ductal carcinoma in situ (DCIS) are relatively common breast lesions on the same spectrum of disease. Atypical ductal hyperblasia is a nonmalignant, high-risk lesion, and DCIS is a noninvasive malignancy. While a benefit of screening mammography is early cancer detection, it also leads to increased biopsy diagnosis of noninvasive lesions. Previously, treatment guidelines for both entities included surgical excision because of the risk of upgrade to invasive cancer after surgery and risk of progression to invasive cancer for DCIS. However, this universal management approach is not optimal for all patients because most lesions are not upgraded after surgery. Furthermore, some DCIS lesions do not progress to clinically significant invasive cancer. Overtreatment of high-risk lesions and DCIS is considered a burden on patients and clinicians and is a strain on the health care system. Extensive research has identified many potential histologic, clinical, and imaging factors that may predict ADH and DCIS upgrade and thereby help clinicians select which patients should undergo surgery and which may be appropriate for active surveillance (AS) with imaging. Additionally, multiple clinical trials are currently underway to evaluate whether AS for DCIS is feasible for a select group of patients. Recent advances in MRI, artificial intelligence, and molecular markers may also have an important role to play in stratifying patients and delineating best management guidelines. This review article discusses the available evidence regarding the feasibility and limitations of AS for ADH and DCIS, as well as recent advances in patient risk stratification.

Key words: atypical ductal hyperplasia; ductal carcinoma in situ; invasive ductal carcinoma; active surveillance; de-escalation.

Introduction

Decreased mortality and early detection of breast cancer through screening mammography have been well established, but the balance between the benefits and harms of screening mammography is an ongoing discussion (1,2). One of the unintended harms is the detection of either a high-risk lesion or a noninvasive cancer that would not have been found and would not otherwise come to attention in the woman's lifetime if not for screening and the subsequent overtreatment of such a lesion (3). Atypical ductal hyperplasia (ADH), a high-risk lesion, and ductal carcinoma in situ (DCIS), a noninvasive cancer, are two biopsy findings that are undergoing investigation for possible active surveillance (AS) (4). Under current guidelines, treatment for both lesions often involves surgical excision because of the possibility of upgrade to invasive cancer after surgery or risk of progression to invasive breast cancer (IBC) for DCIS if not excised (5). In an effort to minimize unintended harms and overtreatment, current management with surgical excision is being re-evaluated because this may not be optimal for all patients.

Key Messages

- Atypical ductal hyperplasia (ADH) and ductal carcinoma in situ (DCIS) are commonly encountered in breast imaging and are on the same spectrum of disease, on which ADH is a high-risk lesion that increases the risk of invasive breast cancer in both breasts and DCIS is a nonobligate precursor to invasive breast cancer.
- There is concern that current treatment guidelines for ADH and DCIS may constitute overtreatment in some cases, and there is interest in pursuing active surveillance (AS) with imaging for certain patients who are deemed to be at low risk, with multiple AS clinical trials for DCIS currently underway.
- In the future, MRI, artificial intelligence, and biomarkers may have an important role in informing management decision-making by improving patient risk stratification.

Extensive research has identified many potential histologic, clinical, and imaging factors that may predict ADH and DCIS upgrade and thereby help clinicians select which patients should have surgery and which may be appropriate for AS. The aims of this review article are to provide an update on the evidence for AS for ADH and low-grade DCIS (LGDCIS) and discuss recent advances in MRI, artificial intelligence, and molecular markers, which may also have an important role in stratifying patients and delineating best management guidelines.

Histopathology

The ADH and DCIS spectrum describes intraductal epithelial proliferative breast lesions that typically develop in the terminal duct lobular unit (TDLU) and display varying degrees of atypia. This spectrum includes ADH, ADH bordering on DCIS (ADH-BD), LGDCIS, and intermediate- and high-grade DCIS. Subtle histologic differences in architectural pattern, cytologic monotony and uniformity, nuclear features, lesion extent, and size and number of involved ducts are used to distinguish these closely related entities (6). However, subjectivity and differences in interobserver interpretation remain a diagnostic challenge and potential limitation (7,8).

Histologically, ADH is an intraductal clonal epithelial proliferation and is similar to LGDCIS in many ways, including both cell type and molecular marker expression. In fact, ADH is diagnosed when a lesion contains some but not all of LGDCIS-defining features (9). Both ADH and LGDCIS are characterized by cytological atypia with monomorphic, evenly spaced small, round cells and abnormal architecture, exhibiting solid, cribriform, or micropapillary growth patterns (10). If the atypical cells involve ≤2 mm, ≤2 spaces, or a portion of a duct, the lesion is diagnosed as ADH. These histologic criteria are somewhat arbitrary, but they have been developed with the goal of optimizing reproducibility and interobserver agreement (11). However, some lesions are truly borderline and do not conform to these criteria. For example, a lesion may be classified as ADH-BD if there are atypical cells involving >2 mm but still only a portion of a duct. This diagnosis is also known to be subjective and to have substantial interobserver variability (12,13).

Intermediate- and high-grade DCIS are differentiated from the previously mentioned lesions by the presence of abnormal, large nuclei with prominent nucleoli and frequent mitosis and may exhibit comedonecrosis (4).

Natural History and Clinical Implications

Atypical ductal hyperplasia is classified as a high-risk lesion and is associated with an approximate fivefold increase in breast cancer risk within five years of diagnosis, with the risk imparted on either breast. Patients with ADH have a lifetime breast cancer risk between 15% and 20% (14). Furthermore, ADH is also associated with other known risk factors. Patients with a first-degree relative with a history of breast cancer have a 10-fold increase in breast cancer risk. In addition, ADH is more common in BRCA mutation carriers and in other patients who are known to be at increased risk (15,16).

Hartmann et al longitudinally followed a cohort of patients with atypical ductal and/or lobular hyperplasia and reported that, in the first five years after a diagnosis of ADH, patients were more likely to develop an ipsilateral breast cancer than in later years (17). However, more than five years after the ADH diagnosis, patients were at continued increased risk for breast cancer, including in the contralateral breast. Specifically, 20.5% (143/698) of women with ADH developed breast cancer during a mean follow-up period of 12.5 years, and 25% of these breast cancers were node-positive. These results support that ADH is a generalized high-risk lesion.

Although the role of ADH as a high-risk lesion is well established, genetic and immunohistochemical similarities between ADH and DCIS suggest that ADH is likely also a precursor to LGDCIS and to low-grade estrogen receptor (ER)–positive breast carcinoma (18). For example, both ADH and DCIS are usually ER- and progesterone receptor (PR) positive and human epidermal growth factor receptor (HER2) negative. In addition, both lesions lack expression of cytokeratin 5/6 (CK 5/6) (6). However, it is not thought that lesions predictably progress along this spectrum (19). Instead, progression is likely a much more complex process, and several models have been proposed, including the independent lineage model, in which DCIS and IBC cells separately evolve from distinct normal breast cells; the evolutionary bottle neck model, in which multiple clones evolve from a single normal breast cell, with one subclone achieving invasion; and the multiclonal invasion model, in which multiple clones evolving from a single normal breast cell achieve invasion (20). It is also proposed that changes in the microenvironment ultimately allow for invasion (21).

Although DCIS is a heterogeneous lesion on pathology, from low- to intermediate- to high-grade, all grades of DCIS

are generally accepted to represent nonobligate precursors to IBC, and it is cited that approximately 40% of DCIS lesions progress to IBC (22). One piece of evidence supporting DCIS as a nonobligate precursor to IBC comes from several small studies that detail the outcomes of women with biopsy-proven DCIS who did not undergo treatment (other than biopsy) or who underwent delayed treatment after long-term follow-up (23–25). Notably, one such study found that, after following 28 women with biopsy-proven low-grade DCIS over a median follow-up period of 31 years, 39.2% (11/28) had developed IBC in the same breast and quadrant as the original biopsy. Five of these women died of metastatic breast cancer (24).

Multiple studies have established that poor prognostic factors for DCIS include younger patient age, larger lesion size, and comedo morphology (26–28). The histologic grade of DCIS also plays a role in the behavior of lesions and outcome at long-term follow-up. A study of women with DCIS and more than 40-year follow-up showed that the natural history of LGDCIS differs from intermediate- and high-grade DCIS (4). This concept is supported by data from a study comparing the detection rates of different grades of DCIS over time in a screening mammography program. While detection rates of high-grade DCIS remained high throughout the multiple screening rounds, detection rates of LGDCIS decreased, suggesting that low-grade and high-grade DCIS have different patterns of progression (29).

Current Challenges in Diagnosis

Atypical ductal hyperplasia is commonly encountered in breast imaging and is diagnosed in 3%–4% of image-guided core-needle biopsies and in up to 12%–17% of breast biopsies for calcifications on mammography (30–34). Ductal carcinoma in situ represents about 20%–25% of breast cancers detected on screening mammography (35). There has been an increase in DCIS diagnosis since the introduction of screening mammography, and although there has been a corresponding decrease in subsequent invasive interval cancers, this relationship has not been linear (36).

Some argue that a subset of diagnoses of DCIS represent "overdiagnosis," a term that has been used to describe indolent lesions that will never become symptomatic during a patient's lifetime (3). Studies attempting to quantify rates of "overdiagnosis" are limited for many reasons, including variability in background incidence of breast cancer, patient population age and relative risk, and follow-up duration. Therefore, these studies report wide ranges of invasive cancer "overdiagnosis." However, a recent review cited that reasonable "overdiagnosis" rates are likely between 1% and 10% for women aged 40–80 and lower if specifically evaluating "overdiagnosis" of invasive cancer and in women in their 40s (3).

Although the controversies around the concept of "overdiagnosis" are complicated and beyond the scope of this review, overtreatment of such cases constitutes the main harm and is a burden for patients, physicians, and the health care system.

Current Challenges in Management

Previously, treatment guidelines for both entities have always included surgical excision because of the well-established risk that a subset of ADH and DCIS lesions diagnosed by needle biopsy are upgraded to invasive cancer after surgery and the risk of progression of DCIS to invasive cancer if not excised (37,38). These potential risks have led some to argue that AS and/or risk-reduction strategies alone would represent undertreatment of these lesions.

Management of ADH diagnosed by needle biopsy is challenging, and there is currently no consensus in the literature. To combat the dilemma of overtreatment versus undertreatment, there has been extensive research to identify a subset of patients who may be safely observed. Despite substantial variability in the literature, the American Society of Breast Surgeons recommends surgical excision for biopsy-proven ADH in most clinical scenarios. However, a patient may be safely observed if the ADH is small in volume and if it is completely excised at time of needle biopsy. These cases require multidisciplinary discussion since accurate radiologic-pathologic correlation, in addition to breast cancer risk assessment, are critical for appropriate patient selection (39). The National Comprehensive Cancer Network (NCCN) guidelines have not changed and continue to recommend surgical excision for all ADH lesions (40).

The vast heterogeneity of DCIS makes development of optimal treatment strategies very difficult. The goal of treatment is to prevent subsequent invasive cancer. In particular, there is controversy involving de-escalation of treatment in elderly patients with LGDCIS and indications for endocrine and radiotherapy (41). Currently, NCCN guidelines recommend either breast-conserving therapy with negative margins followed by radiation therapy or total mastectomy with or without sentinel lymph node biopsy. Patients may be eligible for endocrine therapy if they have ER-positive DCIS and receive breast-conserving therapy or do not receive radiation therapy. Patients should also receive risk-reduction counseling (42).

Byng et al studied patient and oncologist preferences for LGDCIS treatment strategies and confirmed that patients have a strong preference for AS and avoiding surgery (43). This study collected treatment preferences for LGDCIS, including AS, from 172 women in the Netherlands with recently diagnosed LGDCIS and 30 oncologists involved in DCIS treatment. A discrete choice experiment was used to determine the relative importance of different treatment options by using a conditional logit model (43). Although not generalizable to all patients, these results indicate that patients are interested in AS options.

As will be discussed further, there are multiple ongoing clinical trials investigating AS for a select group of patients with DCIS, which would spare patients treatment-related

morbidity, with treatment only initiated if progression is identified during long-term surveillance.

Upgrade Risk

There is a wide range of ADH upgrade rates to malignancy in the literature, with studies reporting between 15% and 48% (44,45). A meta-analysis of 6458 pure ADH lesions diagnosed by image-guided biopsy reported an upgrade rate to DCIS of 20% for lesions that were surgically excised and 2.8% for lesions managed with follow-up, and an upgrade rate to invasive ductal carcinoma (IDC) of 9% for lesions that were surgically excised and 3.4% for lesions managed with follow-up (38). The upgrade rate for ADH-BD lesions is significantly higher. Pawlowski et al (46) prospectively identified patients with ADH-BD and found that these patients had an upgrade rate of 40% after surgical excision. Many retrospective studies have investigated risk factors for upgrade, with variable results (Table 1). Factors significantly associated with ADH upgrade include ≥3 foci and/or multiple cores with ADH involvement, suspicious histologic features, larger lesion size, incomplete removal of calcifications/mammographic presence of residual lesion, positive family history of breast cancer, core-needle biopsy (CNB) with smaller needle gauge, suspicious imaging features, increased age, palpability, and presence of an additional high-risk lesion such as radial scar or papilloma (44,45,47–61).

Conversely, factors associated with ADH non-upgrade are equally important to help identify patients at lower risk. Multiple retrospective studies have identified factors significantly associated with ADH non-upgrade, including <3 foci, coexisting columnar cell lesions, small size, complete removal with no residual calcifications, less suspicious imaging features, negative family or personal history of breast cancer, and age <50 years (Figure 1) (62–65). Using this extensive volume of retrospective data, multiple predictive models and nomograms have been proposed, many of which have been independently validated (53,61,66–72). The goal of these studies is to spare unnecessary surgery for selected patients by identifying a subset of patients who can be safely observed.

As is the case with ADH, there is a wide range of DCIS upgrade rates to invasive cancer in the literature, with studies reporting between 0 and 59% (37). Retrospective studies that have investigated risk factors for upgrade are shown in Table 1 (73–81). A meta-analysis of 7350 DCIS lesions reported a pooled upgrade rate of 25.9%. This meta-analysis found that factors associated with DCIS upgrade include biopsy device, imaging guidance, size, grade, suspicious mammographic features, and palpability (37). Some studies have identified high-grade DCIS as a risk factor for upgrade (Figure 2) (82–84).

Factors that may lead to upgrade of ADH and DCIS after imaging-guided biopsy are likely multifactorial. It is well established that biopsies can result in undersampling (22). Undersampling is particularly a problem for ADH because histologic diagnosis is especially difficult and is tied to volume and extent of atypia (9).

ADH Surveillance Studies

Multiple retrospective studies have investigated whether surveillance is a safe option in a select group of patients with ADH (Table 2). In most studies, the lesions that were observed tended to be small, involve fewer ducts and foci, be completely or mostly removed by biopsy, and have less suspicious imaging features (85–95). Although most of these studies are limited by small sample size, the upgrade rate was relatively low at 4.4%, suggesting that ADH diagnosed by needle biopsy may be managed with AS rather than surgery in some cases. However, because the meta-analysis by Schiaffino et al (38) did find a pooled upgrade rate of greater than 2% regardless of biopsy features, these authors argue that ADH diagnosed by needle biopsy should be excised. However, because a 2% threshold is used to determine whether a lesion should undergo biopsy or not, perhaps a higher threshold can be used to determine whether a lesion should undergo surgery or not. Figure 3 shows an example of a patient diagnosed with ADH after a stereotactic core biopsy of calcifications, who chose not to undergo surgical excision and was found to have IDC one year later.

There are very little prospective data following ADH lesions, but the studies that have been performed support the notion that AS for patients with ADH who satisfy specific criteria is a viable option (Table 3). Caplain et al (96) applied management guidelines established in Forgeard et al's (88) retrospective study to a prospective series of 124 patients. The management guidelines called for excision of lesions ≥21 mm, follow-up of lesions <6 mm with complete removal of microcalcifications, follow-up of 6–21-mm lesions with ≤2 ADH foci, and excision of 6–21-mm lesions with >2 ADH foci. Caplain et al (96) found that, when these guidelines were applied, the upgrade rate was 28% for the group for which excision was recommended, and there were no cases of upgrade for the patients who underwent excision when follow-up was recommended. In addition, of the cases that were followed, two cancers occurred during the follow-up period. One patient developed an IDC in the contralateral breast two years after the ADH diagnosis, and the other patient developed a malignant event at three years in the same breast but in a different quadrant (96).

A recent prospective study had similar promising results. Kilgore et al (97) prospectively observed 309 patients who were determined to be at low risk for upgrade. The observed ADH lesions involved <3 TDLUs, were well sampled (>50% removal of calcifications), and had no mass lesion or architectural distortion and no necrosis. The authors found no significant differences in the rates of breast cancer between the operative and nonoperative groups within this subset of low-risk patients (7.3% vs 4.4%, respectively, $P = 0.2$).

Table 1. Review of Selected Retrospective Studies From 2009 to 2021 Evaluating Image-guided Biopsy-diagnosed Atypical Ductal Hyperplasia (ADH) and Ductal Carcinoma In Situ (DCIS) Upgrade and Non-upgrade Demonstrates Variable Results

First Author (Reference No.)	Year	Lesions, *N*	Biopsy Method	Upgrade, *n* (%)	Upgrade to DCIS, *n* (%)	Upgrade to IBC, *n* (%)	Key Factors Associated With Upgrade	Key Factors Associated With Non-upgrade
ADH studies								
Kohr (49)	2010	101	VAB	20 (19.8)	17 (16.8)	3 (3)	≥3 foci	
Rageth (50)	2019	207	VAB & CNB	NR (39)	NR	NR	CNB, multifocality on VAB, absence of calcs	
Khoury (44)	2016	100	VAB	15 (15)	12 (12)	3 (3)	Increased no. of involved cores	
Allison (52)	2010	97	VAB	20 (20.6)	16 (16.4)	4 (4.1)	Suspicion for DCIS on histology: nuclear features ≥3 foci	
Linsk (53)	2018	151	CNB	25 (16.6)	18 (11.9)	7 (4.6)	Large lesion size, residual lesion	
Badan (56)	2016	12	VAB & CNB	5 (41.7)	5 (41.7)	0	CNB	
Gümüş (57)	2012	150	VAB & CNB	41 (27.3)	28 (18.7)	13 (8.7)	>7 mm, CNB, smaller gauge, suspicious on imaging	
Jang (45)	2008	44	VAB & CNB	21 (47.7)	12 (27.3)	9 (20.5)	CNB, smaller gauge	
Hodorowicz-Zaniewska (58)	2018	72	VAB	21 (29.2)	10 (13.9)	11 (15.3)	Lesion visible on US and mammo, BI-RADS 5	
Chae (59)	2009	45	CNB	10 (22.2)	8 (17.8)	2 (4.4)	Age ≥50 years	
Hong (60)	2011	124	CNB	56 (45.2)	43 (34.7)	13 (10.5)	Age ≥50 years, >15 mm, arch distortion on mammo	
Kim (61)	2012	85	CNB	31 (36.4)	27 (31.7)	4 (4.7)	Age ≥50 years, palpability, presence of calcs, >15 mm	
Karkowski (48)	2021	200	VAB and CNB	33 (16.5)	30 (15)	3 (1.5)	Presence of papilloma	
Chen (63)	2019	143	CNB	48 (34.3)	33 (23.1)	15 (10.5)		Presence of CCL and lower no. ADH foci
McGhan (62)	2012	114	CNB and VAB	20 (17.5)	14 (12.3)	6 (5.3)	Age ≥50 years, presence of mass, shorter core	Age <50 years, focal atypia, no residual calcs
Nicosia (64)	2021	141	VAB	NR (NR)	NR (29.1)	NR (7.8)		Complete removal, size ≤15 mm, BI-RADS ≤4a, age <50 years
Kim (65)	2020	50	VAB	8 (16)	5 (10)	3 (6)		Presence of mass, absence of calcs

Table 1. Continued

First Author (Reference No.)	Year	Lesions, *N*	Biopsy Method	Upgrade, *n* (%)	Upgrade to DCIS, *n* (%)	Upgrade to IBC, *n* (%)	Key Factors Associated With Upgrade	Key Factors Associated With Non-upgrade
DCIS studies								
Shin (73)	2019	80	CNB	27 (33.8)	NR	NR	Final BI-RADS category, DCIS grade on biopsy	
Park (74)	2014	86	CNB	27 (31.4)	NR	NR	Palpability, nipple discharge, <5 core specimens, mammo lesion ≥25 mm, mammo mass ≥40 mm, US mass ≥2 mm, MRI size ≥30 mm, hetero or rim enhancement on MR	
Yoon (75)	2020	206	VAB and CNB	94 (45.6)	50 (24.3)	44 (21.4)	Irregular mass, clustered ring or clumped NME on MRI, PR–, high Ki-67	
Cheung (76)	2020	131	VAB	NR	NR	23 (17.6)		Calcs <11.5 mm, ≥90% calc removal
Lamb (77)	2021	78	CNB	17 (21.8)	4 (5.1)	13 (16.7)	Older age, first degree relative with hx of breast ca	
Sá (78)	2021	86	CNB	21 (24.4)	7 (8.2)	14 (16.3)	Presence of mass, US-guided CNB	
Krischer (79)	2020	58	VAB	4 (13)	NR	NR	High-grade DCIS	
Nicosia (80)	2021	2173	VAB	330 (15.2)	NR	NR		No residual lesion on mammo
Allen (81)	2017	51	CNB	10 (19.6)	NR	NR	Fewer no. of cores, smaller biopsy needle gauge	

Abbreviations: ca, cancer; calcs, calcifications; CCL, columnar cell lesions; CNB, core-needle biopsy; hetero, heterogeneous; hx, history; IBC, invasive breast carcinoma; mammo, mammogram; mIDC, microinvasive ductal carcinoma; mm, millimeter; NME, non-mass enhancement; NR, not reported; PR–, progesterone receptor negative; VAB, vacuum-assisted biopsy.

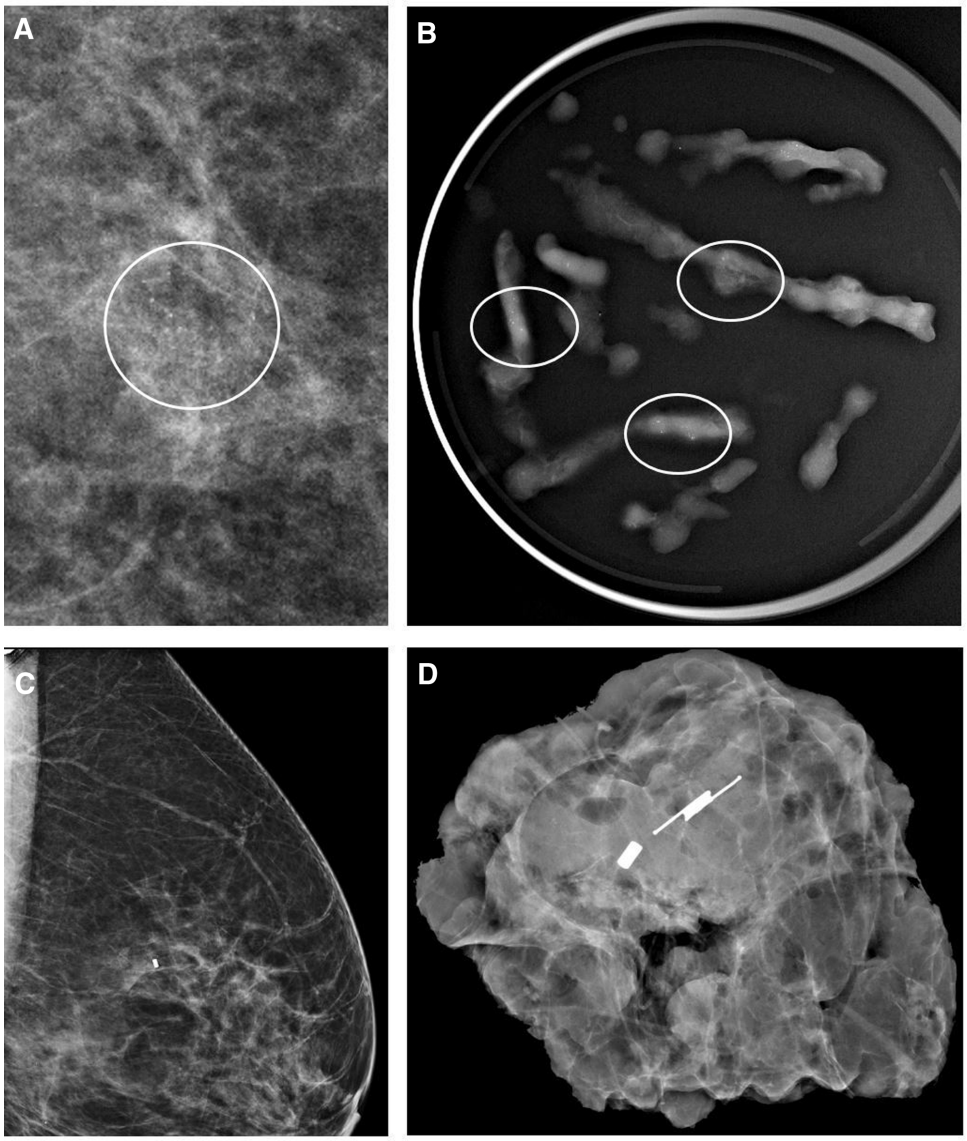

Figure 1. Images of 58-year-old woman with atypical ductal hyperplasia (ADH) diagnosed by stereotactic biopsy, which was not upgraded after surgery. **A:** Spot magnification lateromedial view of the left breast at 2:00 at middle depth demonstrates grouped punctate and amorphous calcifications (circle). Stereotactic biopsy specimens (**B**) demonstrate sampling of calcifications (circle), and post-procedure mammogram (**C**) shows biopsy clip in the appropriate position. Pathology yielded ADH. **D**: Surgical excision specimen includes a biopsy marker, a SAVI SCOUT reflector (Merit Medical Systems, Inc, South Jordan, UT, USA), without residual calcifications. Surgical pathology yielded fibrocystic change.

Ongoing DCIS Clinical Trials and Interval Data

Several studies have suggested that AS is a reasonable alternative to surgery in select patients with DCIS, which has provided the rationale for clinical trials (98). For example, a comparative mortality analysis in patients over the age of 65 revealed that, although patients who underwent AS for DCIS had higher all-cause and breast-cancer-specific mortality, this effect declined after accounting for baseline comorbidities (99). Ryser et al (100) developed a computational risk projection model to estimate the disease-specific cumulative mortality of AS and to compare this estimate with the projected outcome disease-specific cumulative mortality with usual care. The authors found that AS could be a feasible management option for some patients, particularly older age groups and those with mortality risks. As expected, the effectiveness of AS would be considerably improved by reducing the rate of upgrade.

Currently, there are multiple active prospective randomized clinical trials exploring AS for DCIS. These studies all share similar primary objectives of determining the incidence of ipsilateral invasive cancer in patients with DCIS undergoing AS. However, the trials all have different inclusion and exclusion criteria, AS monitoring, and study designs (Table 4).

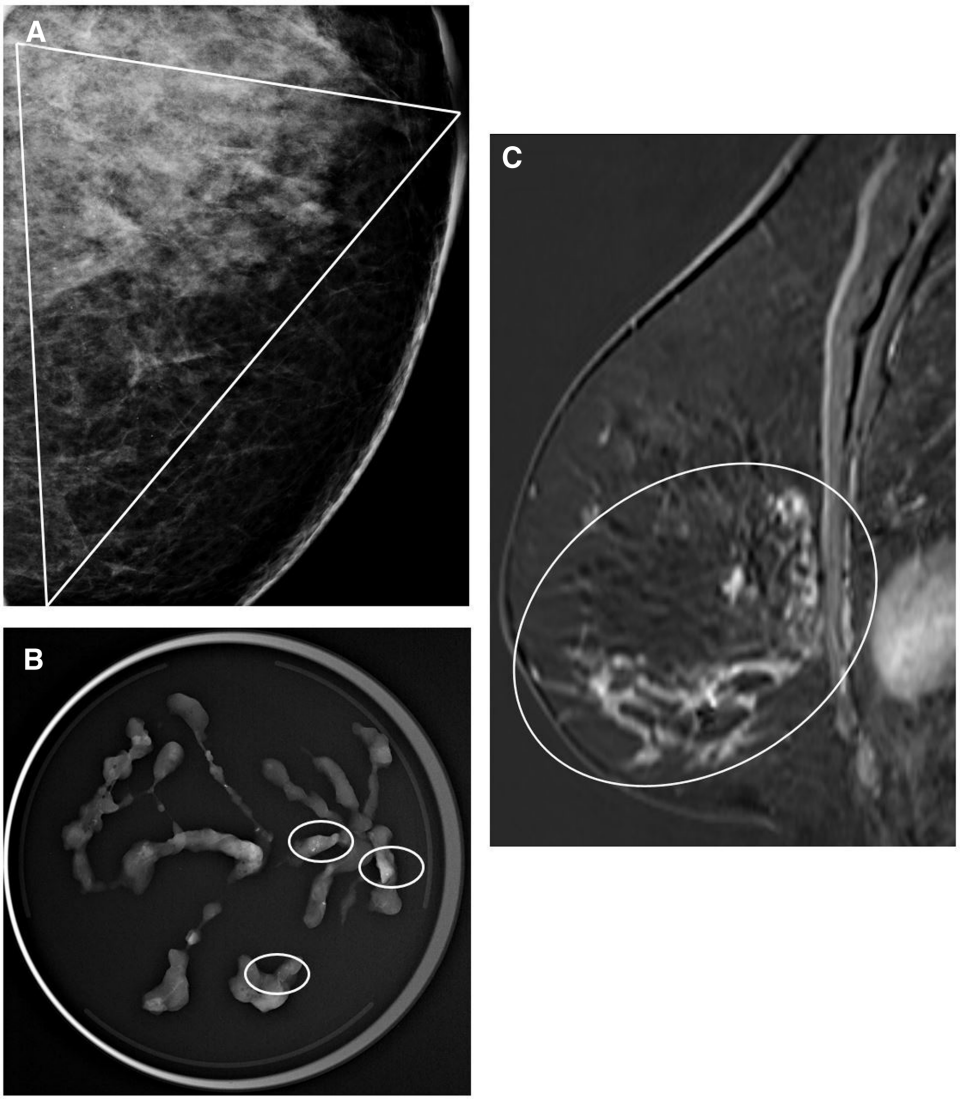

Figure 2. Images of 48-year-old woman with intermediate- to high-grade ductal carcinoma in situ (DCIS) diagnosed by stereotactic biopsy, which was upgraded to grade 2 invasive ductal carcinoma (IDC) at excision. **A:** Spot magnification views of the medial breast demonstrate fine pleomorphic calcifications, extending approximately 6 cm in anteroposterior dimension (triangle). **B:** Stereotactic biopsy specimens demonstrate calcifications (circles) and yielded DCIS. **C:** Sagittal T1 post-contrast subtraction MRI demonstrated segmental non-mass enhancement (circle) in the left breast from the 6 to 9 o'clock positions. Patient underwent left mastectomy, with surgical pathology yielding a 2-cm grade 2 IDC.

Inclusion criteria vary in patient age, imaging and pathology features, biopsy method, and hormone receptor status, among other variables. Study arms also vary (101–105).

The Comparison of Operative versus Monitoring and Endocrine Therapy (COMET) trial notably does include patients with pathology findings of ADH-BD, positive surgical margins, and comedonecrosis, features that are excluded in the LORETTA and LORIS trials. The COMET trial is also unique because the AS arm includes optional endocrine therapy and allows patients to switch study arms if they are randomized to a study arm that is not their preference (43). Studies applying the COMET eligibility criteria to DCIS lesions have calculated an upgrade rate to high-grade DCIS from 7% to 10.9% and to invasive cancer from 6% to 22% (106–110).

In the low-risk DCIS (LORIS) trial, the investigators notably do include ADH cases that were downgraded from DCIS following a consensus pathology review. Unlike the COMET trial, the AS arm in LORIS is not offered endocrine therapy (103). Studies applying the LORIS eligibility criteria to DCIS lesions calculated an upgrade rate to high-grade DCIS from 5% to 7% and to invasive cancer from 0 to 24% (106–108,110–113).

The low-risk DCIS (LORD) trial initially only included LGDCIS but was later amended to also include intermediate-grade DCIS to improve accrual. In an additional effort to improve accrual, although participants were initially randomized to one of the two study arms, participants are now allowed to choose which arm of the study to join based on preference (43). Included DCIS cases must be ER+/HER2–.

Table 2. Review of Retrospective Studies from 2003 to 2018 Investigating Active Surveillance for Atypical Ductal Hyperplasia (ADH) Demonstrates a Low Upgrade Rate (4.4%)

First Author (Reference no.)	Year	Features of Observed Lesions	Observed Lesions, *N*	Biopsy Method	Upgrade, *n* (%)	Upgrade to DCIS, *n* (%)	Upgrade to IBC, *n* (%)
Amitai (85)	2018	Absent enhancement on MRI	18	VAB and CNB	0	0	0
Latronico (89)	2018	Imaging/pathologic features, patient declined surgical excision	12	VAB and CNB	1 (8.3)	0	1 (8.3)
Schiaffino (94)	2018	4–11 mm, BI-RADS 4b	65	VAB	1 (1.5)	1 (1.5)	0
Menen (90)	2017	<3 TDLUs involved, >90% removal of calcifications, and no necrosis OR no mass lesion or architectural distortion, and >50% of calcifications removed with adequate sampling	125	NR	7 (5.6)	NR	NR
Ancona (86)	2011	BI-RADS 3, 4 mm–6 mm, complete calc removal	79	VAB	6 (7.6)	2 (2.5)	4 (5.1)
Nguyen (91)	2011	Removal of the majority of calcifications, limited involvement by ADH, or patient declined surgical excision	19	VAB	0	0	0
Villa (95)	2011	Surgery not recommended to patient, patient comorbidity, patient declined surgical excision	35	VAB	1 (2.9)	1 (2.9)	0
Forgeard (88)	2008	≤2 ADH foci, more freq complete calc removal, smaller average size	135	VAB	4 (3.0)	3 (2.2)	1 (0.7)
Bedei (87)	2006	BI-RADS 4, 2–20 mm, more freq complete calc removal	19	VAB	1 (5.3)	1 (5.3)	0
Wu (92)	2006	NR	1	CNB	0	0	0
Zhao (93)	2003	NR	14	VAB & CNB	2 (14.3)	NR	NR
Total			522		23 (4.4)		

Abbreviations: calc, calcifications; CNB, core-needle biopsy; DCIS, ductal carcinoma in situ; freq, frequent; IBC, invasive breast carcinoma; NR, not reported; obs, observed; rec, recommendation; VAB, vacuum-assisted biopsy.

In this trial, the AS arm is also not offered endocrine therapy (101). Studies applying the LORD eligibility criteria to DCIS lesions reported an upgrade rate to high-grade DCIS of 10% and to invasive cancer from 5% to 25% (106,108,110).

The LORETTA trial does not include cases with comedonecrosis but is the only trial to include DCIS with a mass present on imaging. Iwamoto et al (110) applied the LORETTA eligibility criteria to DCIS lesions and reported an upgrade rate to invasive cancer of 12%.

There have been multiple interval studies retrospectively simulating these trials for ADH and DCIS using the same eligibility criteria, with results indicating that patients undergoing AS remain at risk for occult invasive cancer. These findings raise the question of whether more stringent criteria should be developed to limit the possibility of a patient with pre-existing invasive cancer entering an AS trial (106–112).

Inclusion of ADH Lesions in Clinical Trials

The argument to include ADH lesions in clinical trials is supported by the fact that a portion of women with ADH will be upgraded to low- or intermediate-grade DCIS on surgical excision and therefore may have been eligible for a clinical trial based on other clinical, imaging, and histologic factors (38). In addition, as previously mentioned, the distinction between ADH and LGDCIS on needle biopsy is somewhat arbitrary (22).

Data from a 10-year prospective observational study performed by Farshid et al (114) followed women with screening-detected, biopsy-proven ADH. In their cohort, 24% would meet eligibility criteria for DCIS AS trials. However, on final surgical pathology, 9% had invasive cancer, 6% had high-grade DCIS, and 6% had necrotizing, intermediate-grade DCIS, which would lead to a relatively high upgrade rate. However, extrapolation of their findings is limited because they did not use the specific eligibility criteria from any active DCIS trial in their inclusion criteria. In fact, the authors included many patients who would have been excluded from most clinical trials, including patients with mass lesions and HER2+ cancer.

More recently, Khoury et al (10) applied the COMET eligibility criteria to 165 cases of ADH and DCIS spectrum lesions in their pathology database from January 2007 to December

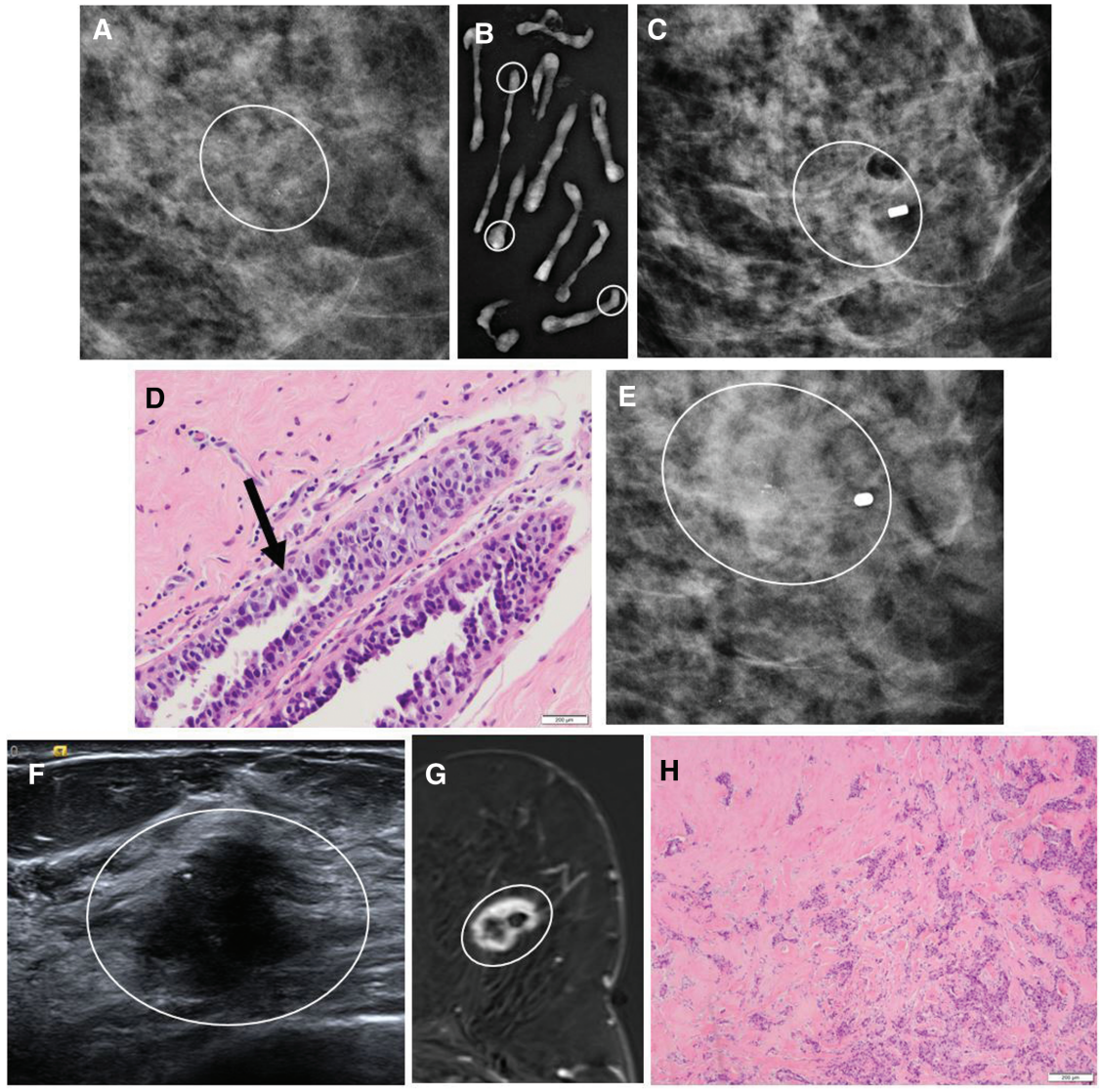

Figure 3. Images of 54-year-old woman with atypical ductal hyperplasia diagnosed by stereotactic biopsy who did not undergo surgical excision and later developed an invasive ductal carcinoma (IDC). **A:** Left lateromedial (LM) spot compression magnification view demonstrates grouped calcifications in the left breast at 1 o'clock at anterior depth (circle). **B:** Stereotactic biopsy specimens demonstrated sampling of calcifications (circle). **C:** Post-procedure LM view demonstrates biopsy clip in appropriate position with residual calcifications. **D:** Histology shows one duct with atypical cells (arrow) growing in a Pagetoid spread (H&E). **E:** One year later, spot compression magnification LM view demonstrates the biopsy marker, now with increased calcifications and an associated developing asymmetry (circle). **F:** US demonstrated an irregular hypoechoic mass (circle) corresponding to the calcifications and developing asymmetry. US-guided core-needle biopsy yielded IDC. **G:** Axial T1 post-contrast subtraction MRI demonstrates a 2.1-cm irregular enhancing mass (circle) with associated central susceptibility artifact from the biopsy marker. **H:** Histology image (H&E) from surgical pathology shows IDC, grade 3, estrogen receptor positive, human epidermal growth factor receptor positive. Abbreviation: H&E, hematoxylin and eosin.

2017 and found that a total of 9 (5.5%) lesions were upgraded. Based on these findings, ADH and ADH-BD have lower upgrade rates than DCIS, and opening an AS clinical trial for women with these diagnoses is recommended by the authors.

Improving Management Decision-making Strategies

MRI

Studies have provided mixed evidence on whether dynamic contrast-enhanced (DCE)-MRI features are helpful in predicting malignant upgrade of ADH, and generalization is limited by small sample sizes. Linda et al (115) performed a prospective study of 169 high-risk lesions, including 16 ADH lesions, which were evaluated with preoperative DCE-MRI and subsequently excised. The authors found a 25% ADH upgrade rate (4/16), and a negative MRI, defined as BI-RADS 1–3, had a negative predictive value (NPV) of 90%. However, even though this NPV was relatively high, the authors concluded that a negative MRI is not helpful in cases of ADH and that all ADH lesions should be excised. In contrast, a similarly designed study performed by Tsuchiya

Table 3. Review of Prospective Studies Investigating Active Surveillance for Atypical Ductal Hyperplasia (ADH)

First Author (Reference no.)	Year	Lesion Features Recommended for Observation	Observed Lesions, *N*	Biopsy Method	Median Follow-up (Years)	Index Site Cancers	Other Cancers	*P*-value
Caplain (96)	2014	<6 mm with complete calc removal, follow-up 6–21 mm for ≤2 ADH foci	55	VAB	2.5	0	2	NR
Kilgore (97)	2021	<3 TDLUs, >50% removal of calc, no mass or architectural distortion, and no necrosis	309	CNB and VAB	5.2	3	6	0.2

Abbreviations: calc, calcifications; CNB, core-needle biopsy; NR, not reported; TDLU, terminal duct lobular unit; VAB, vacuum-assisted biopsy.

et al (116) with 17 ADH lesions reported an upgrade rate of 52.9% (9/17) and found MRI to be useful in that MRI demonstrated suspicious non-mass enhancement (NME) at the site of biopsy in all upgraded patients. The authors of this study reported an NPV of 100%.

Larger studies by Amitai et al (85) and Bertani et al (85,117) had consistent findings. Bertani et al (117) found that, of 68 ADH lesions with an upgrade rate of 25% (17/68), suspicious enhancement was seen on DCE-MRI for 94.1% (16/17) of malignant lesions. Furthermore, the only malignant lesion without suspicious enhancement was a 4-mm LGDCIS. Therefore, these authors suggest that, after a needle biopsy diagnosis of ADH, malignancy can be ruled out in most cases if there is no suspicious enhancement at the biopsy site on DCE-MRI.

The findings of Yoon et al (75) support that these conclusions are likely applicable to DCIS lesions as well. Their study retrospectively analyzed 206 DCIS lesions, of which 50 (24.3%) were upgraded to microinvasive cancer and 44 (21.4%) to invasive cancer. Both mass enhancement and NME were independent predictors of DCIS upgrade. Specifically, suspicious features such as irregular shape, noncircumscribed margins, heterogeneous or rim-enhancing masses, clumped or clustered ring-enhancing NMEs, and high peak enhancement were significantly associated with histologic upgrade.

Ultrafast (UF)-MRI is a relatively novel imaging technique, and early data are promising for its utility in predicting upgrade risk of DCIS. Studies have indicated that time-to-enhancement (TTE) may help to differentiate DCIS from invasive cancer, with invasive cancers having shorter TTE than in situ cancer (Figures 4 and 5) (118). Other features that may be derived from UF-MRI that have been shown to be significantly different in DCIS and invasive cancer include maximum slope (MS), maximum enhancement (ME), and time interval between arterial and venous visualization (118,119).

Building off these results, Heo et al (120) retrospectively investigated whether UF-MRI with DCE-MRI could predict histologic upgrade risk of DCIS to invasive cancer. The authors found that DCIS lesions that were upgraded to invasive cancer had significantly larger lesion size on MRI, higher MS, and higher ME than the non-upgrade group. Furthermore, the interobserver agreement for UF-MRI parameters was excellent. Mori et al (121) investigated whether UF enhancement, shape, and texture parameters could be helpful in distinguishing LGDCIS from intermediate- or high-grade DCIS, as well as from DCIS lesions upgraded to invasive cancer. The authors reported that five shape and seven texture features were significantly different in LGDCIS when compared to non-low-grade lesions or upgraded DCIS lesions, whereas enhancement features were not. More studies are needed to confirm these findings and confirm whether clinically available UF-MRI features, such as TTE, can be used to predict upgrade and help stratify patients. Currently, there is a paucity of data regarding the role of UF-MRI in evaluation of ADH upgrade.

Artificial Intelligence

Artificial intelligence (AI) is a very active area of research in breast imaging, with many studies investigating the ways in which AI can be clinically useful. Multiple studies have demonstrated that there is potential for machine learning models to help predict upgrade risk of high-risk lesions, such as ADH, to cancer (122,123). Ha et al (124) developed a convolutional neural network algorithm using 298 unique images of mammographic calcifications of known surgically confirmed non-upgraded ADH and DCIS cases. Their model had an aggregate sensitivity of 84.6% and specificity of 88.2%, and the authors hypothesized that a larger data set would likely improve their prediction model. Recently, the same team prospectively validated their algorithm using a new data set of 280 unique mammographic images of calcifications not used in training of their AI algorithm and reported a sensitivity of 63.9% and a specificity of 93.7% in distinguishing pure ADH from DCIS (125). Lo Gullo et al (126) had a similar goal but attempted to use DCE-MRI features in their machine learning model. However, the authors did not find any significant associations between the DCE-MRI features and upgrade status.

There have also been studies evaluating whether machine learning can predict the upgrade risk of DCIS to invasive

Table 4. Comparison of Multiple Ongoing Low-risk Ductal Carcinoma In Situ (DCIS) Clinical Trials

Trial (Reference nos.)	Country	Current Key Inclusion Criteria	Current Key Exclusion Criteria	Goal Accrual	AS Monitoring	Follow-up (Years)	Primary End Point	Design
LORD (101,107,109,111)	International, led by BOOG and EORTC	Age ≥45 y, asymptomatic, screen-detected, low- or intermediate-grade DCIS diagnosed on VAB of calcs, ASA 1–2, life expectancy >5 y, ER+,HER2-	Hx of DCIS or IBC, *BRCA*1/2 carrier, synchronous IBC, LCIS, Paget disease, nonoperative candidate	1240	Annual digital mammo	10	10 y ipsilateral invasive breast cancer free %	Two arms: standard treatment according to local policy and AS
COMET (43,102,107–111)	United States	Age ≥40 y, new DCIS without hx of DCIS or IBC on CNB, VAB, or surgery, ECOG 0–1, histology reviewed by 2 pathologists, ER+ and/or PR+, HER2– if performed	High-grade DCIS, male gender, synchronous IBC, mass, symptomatic DCIS, pregnancy, prior endocrine therapy	1200	Clinical exam q 6m for a min of 5 y and q 12 m thereafter, for up to 7 y. Ipsilateral mammo q 6 m and contralateral mammo q 12 m	2,5,7	Ipsilateral IBC rate in women undergoing GCC compared with AS	Two arms: guideline concordant care and AS ± endocrine therapy
LORIS (103,112,113)	United Kingdom	Age ≥46 y, asymptomatic, screen-detected low- or intermediate-grade DCIS, VAB	Mass, hx or current IBC, hx of ipsilateral DCIS, high-risk	NR	Annual mammo	10	Ipsilateral invasive breast cancer free survival time	Two arms: standard treatment according to local protocol and AS
LARRIKIN (104)	Australia and New Zealand	Age ≥55 y, asymptomatic, screen-detected low- or intermediate-grade DCIS, <25 mm ER/PR+, HER2–, no comedonecrosis	NR	470	Clinical reviews q 6m and annual mammo	NR	Ipsilateral breast cancer-free survival	Two arms: surgery ±RT and AS
LORETTA (106,111)	Japan	Age 40–75 y with ER+, low-risk DCIS	Synchronous or metachronous cancer, pregnancy, hx of DVT/PE	340	NR	5, 10 y	5 y cumulative incidence of ipsilateral IBC	Single arm: Endocrine therapy alone

Abbreviations: AS, active surveillance; ASA, American Society of Anesthesiologists; BOOG, Dutch Breast Cancer Research Group; calcs, calcifications; ECOG, Eastern Cooperative Oncology Group; EORTC, European Organization for Research and Treatment of Cancer; GCC, guideline concordant care; H&P, history and physical; hx, history; IBC, invasive breast carcinoma; LCIS, lobular carcinoma in situ; m, months; mammo, mammogram; NR, not reported; q, every; RT, radiation therapy; VAB, vacuum-assisted biopsy.

cancer. Hacking et al (127) investigated a series of 44 DCIS lesions with an associated mammographic mass, which is known to be a risk factor for upgrade. This study used a machine learning model to predict DCIS upgrade based on stromal computational signatures derived from pathology slides and was successful in predicting mass-forming

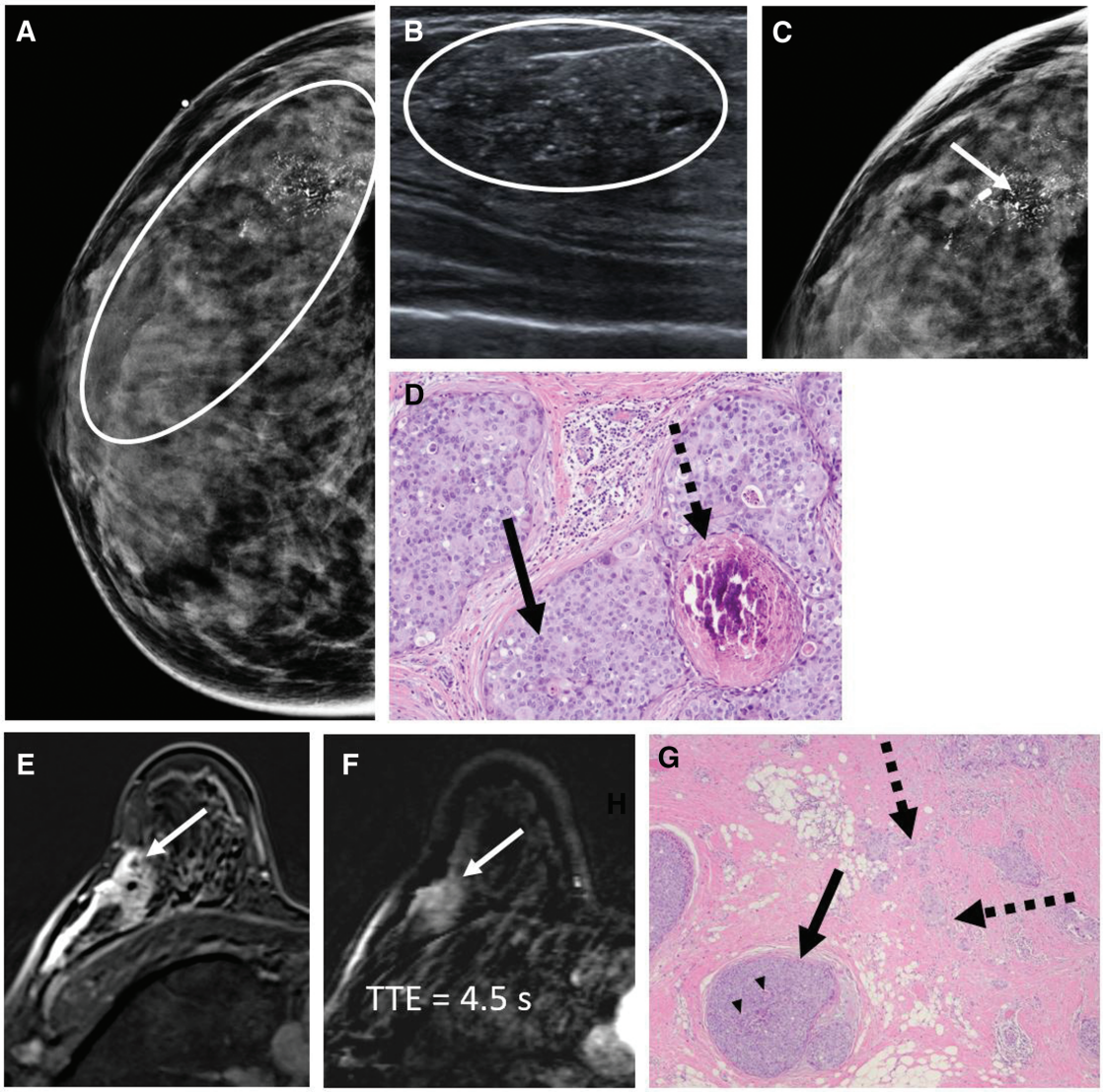

Figure 4. Images of 31-year-old woman who presented with a palpable lump in the right breast, diagnosed with high-grade ductal carcinoma in situ (DCIS) by US-guided core-needle biopsy, which was upgraded to poorly differentiated invasive ductal carcinoma (IDC) after surgical excision. **A:** Diagnostic mammogram right craniocaudal (CC) view demonstrates segmental fine pleomorphic, fine linear, and coarse heterogeneous calcifications (circle) at 9 to 11 o'clock that correspond to the area of palpable concern (BB marker). **B**: US demonstrates a corresponding ill-defined hypoechoic mass with numerous echogenic foci corresponding to mammographic calcifications (circle) in the right breast at 11 o'clock. **C:** Post-procedure right CC view demonstrates biopsy marker in the appropriate position with residual calcifications (arrow). **D:** Histology (H&E, 10×) shows high-grade DCIS with ducts filled with a solid proliferation of tumor cells (solid arrow) showing marked nuclear pleomorphism and prominent nucleoli. One of the ducts (dashed arrow) demonstrates central necrosis with calcifications. **E:** Axial T1 post-contrast subtraction MRI demonstrates an irregular enhancing mass (arrow) containing the biopsy marker in the right breast at 11 o'clock, corresponding to the biopsy-proven malignancy. **F:** Corresponding ultrafast MRI demonstrates a short time to enhancement (TTE) of 4.5 seconds for the mass (arrow). **G:** Surgical pathology (H&E, 4×) showed DCIS and IDC. The DCIS shows a solid proliferation of neoplastic cells within circumscribed and dilated ducts (solid arrow). Foci of single cell necrosis (arrowheads) are present in the DCIS. The invasive carcinoma shows small groups of tumor cells infiltrating mammary stroma. The groups of IDC show a haphazard, infiltrative appearance (dashed arrows) without a normal lobulocentric arrangement. Abbreviation: H&E, hematoxylin and eosin.

DCIS upgrade to invasive cancer with high sensitivity and specificity.

Studies have also investigated whether US, mammography, and MRI features can be used in machine learning models to predict DCIS upgrade. Qian et al (128) developed a deep learning model trained on US images of DCIS, DCIS upgraded to microinvasive DCIS, and DCIS upgraded to IDC. The area under the receiver operating characteristic (ROC) curve (AUC) of their models ranged from 0.724 to 0.804. Their best model achieved a sensitivity of 73.3%, specificity of 75.0%, and accuracy of 74.2%. A larger retrospective study by Hou et al (129) investigated whether

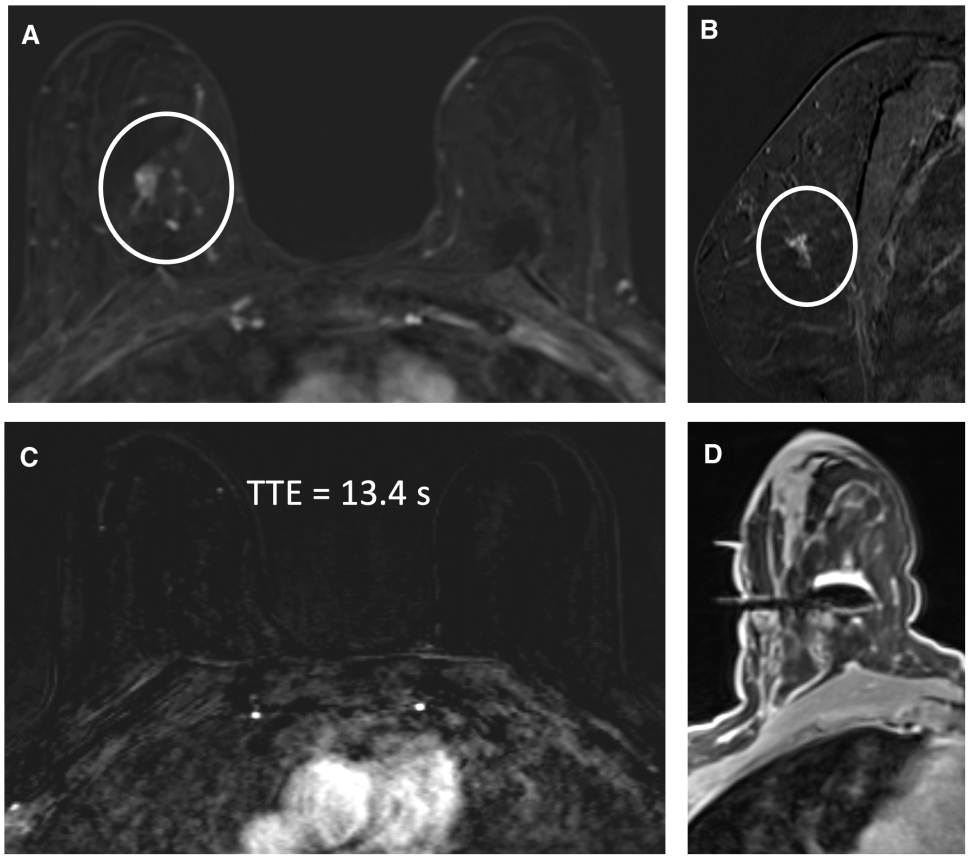

Figure 5. Images of 55-year-old woman with a strong family history of breast cancer found to have clumped non-mass enhancement (NME) on annual surveillance MRI with no mammographic or sonographic correlate. T1 post-contrast subtraction axial (**A**) and sagittal reconstruction (**B**) MRI show clumped NME (circles) in the right breast at 2 o'clock, 5 cm from the nipple. **C:** Corresponding ultrafast-MRI TWIST image at time to enhancement (TTE) of 13.4 seconds shows no early enhancement. **D:** T1 post-contrast axial MRI shows post-biopsy changes (arrow) at site of clumped non-mass enhancement. Histology showed intermediate nuclear grade ductal carcinoma in situ (micropapillary, papillary, solid, and cribriform patterns). Surgical pathology showed no upgrade. Abbreviation: TWIST, time-resolved angiography with interleaved stochastic trajectories.

mammography features could be used to predict upgrade risk. This study included 700 DCIS lesions, which all presented as pure asymptomatic calcifications diagnosed by stereotactic biopsy, with 114 lesions upgraded to IBC after surgery. After training their machine learning model using mammographic radiomic and clinical features, their best model was able to help predict upgrade with an AUC of 0.71 (95% CI: 0.62, 0.79), and for a fixed high sensitivity (90%), their model achieved a specificity of 22% and NPV of 92%. Lee et al (130) retrospectively investigated whether support vector machine trained with DCE-MRI radiomic features could predict DCIS upgrade. This study included 349 DCIS lesions diagnosed by CNB, and radiomic features were extracted from the post-contrast T1 DCE-MRI sequence. Using the test set, their model achieved a sensitivity of 73.3%, a specificity of 70%, an accuracy of 76.7%, and an AUC of 0.767.

Large prospective studies are needed to provide further support for the role machine learning models may play in identifying patients with ADH and LGDCIS who may be appropriately managed with AS.

Molecular Tests

As previously described, ADH and DCIS are very similar in molecular marker expression. For DCIS in particular, part of the variability in clinical progression may be due to the molecular and microenvironmental diversity within DCIS (131). It is likely that specific genetic mutations, transcriptional changes, and microenvironmental and molecular features may be used to potentially predict upgrade of these lesions. Developing greater understanding of these differences at the molecular level would be useful for management decisions (32). Figure 6 summarizes the major biomarkers currently undergoing investigation and key findings of relevant studies (132–134).

Enhancer of zeste homolog 2 (EZH2) is a catalytic protein that regulates gene expression and is known to play a role in oncogenesis. Overexpression of EZH2 has been hypothesized to be an independent predictor of upgrade for both ADH and DCIS. This relationship was first suggested by studies showing that transgenic mice overexpressing EZH2 are more likely to develop intraductal epithelial hyperplasia. Furthermore, in women, EZH2 is also

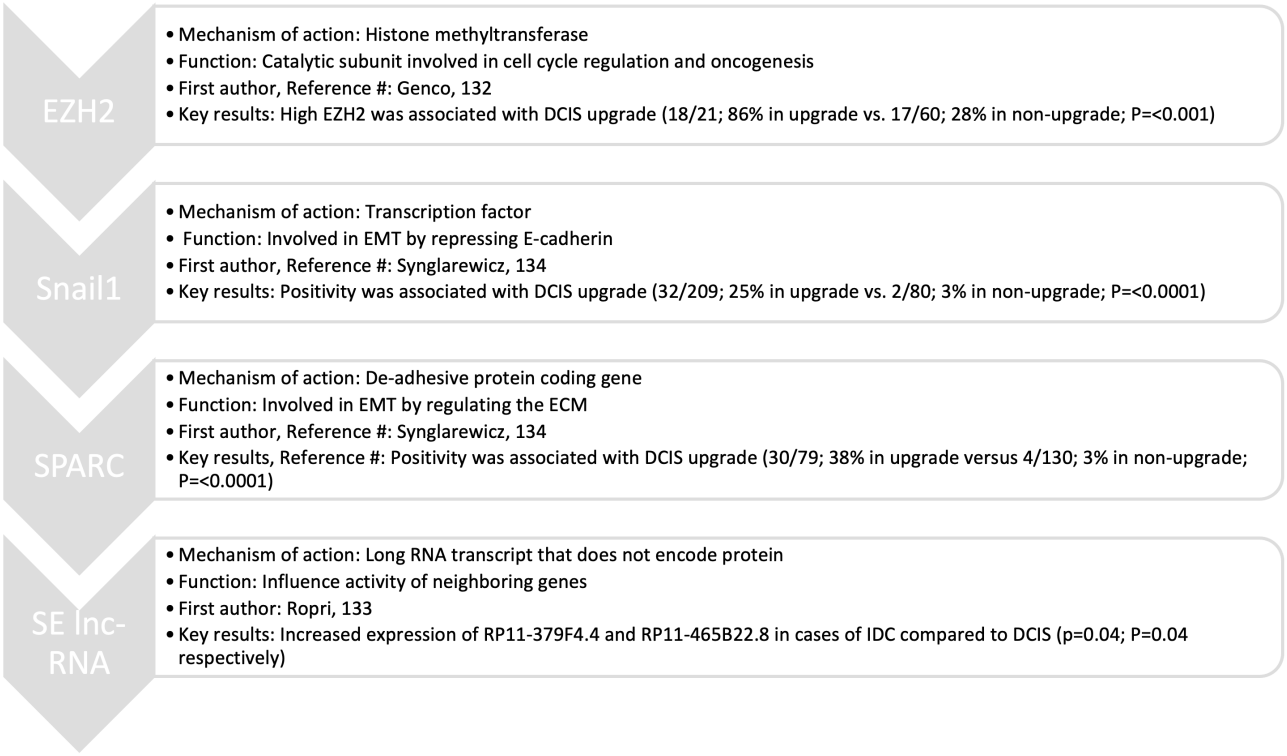

Figure 6. Summary of major biomarkers currently undergoing investigation as potential predictors of atypical ductal hyperplasia (ADH) and ductal carcinoma in situ (DCIS) upgrade. Abbreviations: #, number; dx, diagnosed; ECM, extracellular matrix; EMT, epithelial-mesenchymal transition; EZH2, enhancer of zeste homolog 2; IDC, invasive ductal carcinoma; SE lnc, super enhancer long-noncoding; SPARC, secreted protein acidic and rich in cysteine.

upregulated in the normal breast epithelium surrounding ADH and DCIS lesions, in BRCA1 carriers, and in biologically aggressive forms of breast cancer such as triple-negative and HER2-positive cancers (135). Recently, Genco et al (132) retrospectively compared EZH2 expression in women with CNB-diagnosed DCIS subsequently upgraded to invasive cancer and in women with surgically confirmed DCIS. In keeping with their hypothesis, the authors found that increased EZH2 expression was significantly associated with both DCIS upgrade and other histologic markers of aggressiveness.

Epithelial-mesenchymal transition (EMT) is a phenomenon by which epithelial cells temporarily take on a mesenchymal morphology, which allows the cell to migrate and potentially invade surrounding tissue. EMT is known to occur in cancer progression, invasion, and metastasis. Therefore, increased expression of factors essential for EMT, including EMT enhancers, regulators, and key molecules in related pathways, are thought to be related to more aggressive cancer subtypes. Recently, Synglarewicz et al (134) showed that postoperative upgrade of non-mass DCIS diagnosed by stereotactic biopsy was associated with expression of EMT biomarkers Snail1 and secreted protein acidic and rich in cysteine (SPARC). Furthermore, double-positive DCIS (positive for both Snail1 and SPARC) had a higher risk of invasive cancer than single-positive DCIS, and, even more encouragingly, the authors did not find any cases of double-negative DCIS upgraded to invasive cancer after surgery.

Super enhancers (SEs) are known to play a role in malignancy and are expressed differently in breast tumor cells than in normal breast parenchyma. Super enhancer function is regulated by long-noncoding RNAs (lncRNAs). Therefore, differences in SE lnc-RNA expression have also been identified as a possible functional determinant of progression from DCIS to invasive cancer. Ropri et al (133) analyzed patient samples and identified two SE-lncRNAs, RP11-379F4.4 and RP11-465B22.8, as possible predictors of progression of DCIS to invasive cancer through regulation of the expression of their nearby genes (RARRES1 and miR-200b, respectively). More research to fully elucidate the molecular information of ADH and DCIS at the DNA, RNA, and protein levels is needed. In the future, it may be possible to develop biomarkers of progression to invasive cancer, which would be helpful in guiding management decisions.

Conclusion

The goal in managing ADH and DCIS spectrum lesions is avoiding both overtreatment and undertreatment. This goal presents a challenging dilemma, and decision-making requires multidisciplinary input. There is a vast amount of

research on this topic, including multiple ongoing clinical trials for active surveillance of LGDCIS, aiming to delineate best practices for ADH and low-grade DCIS. There is a strong argument that ADH should be included in these clinical trials. Based on available research, criteria that should be included in selecting patients appropriate for AS are presence of an additional high-risk lesion, histologic features including molecular markers, imaging features including MRI evaluation, lesion size, and biopsy modality. In the future, as there are advances in MRI, AI, and molecular testing, this stratification may also be aided by machine learning models, DCE-MRI and UF-MRI features, and molecular profiles.

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Conflict of Interest Statement

None declared.

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