# With DCIS, where does the real risk lie?

## Karen Titus

**December 2015—When a pathologist makes a diagnosis of DCIS,** few people greet the news happily. Not patients, not surgeons, not radiation oncologists. Depending on the particulars of the case, pathologists might also feel cheerless. Typically, the only winners are uncertainty and its sidekick, fear.

DCIS diagnosis is straightforward in most cases, but at either end of the spectrum it's less so, says Dr. Stuart Schnitt. "There's no substitute for having face-to-face, real-time conversations with clinicians related to the care of these patients with borderline or equivocal lesions."

While it's not difficult to distinguish between cases of high-grade and low-grade ductal carcinoma in situ, telling low-grade DCIS from atypical ductal hyperplasia often is. "The toughest distinction that I encounter is a borderline lesion between those two," says David Hicks, MD, professor of pathology and laboratory medicine and director of surgical pathology, University of Rochester (NY) Medical Center.

There's plenty at stake for everyone involved. In such cases, pathologists are asked to be seers as much as scientists, as they try to predict the future malignant potential of a lesion and help surgeons and radiation oncologists choose the best treatment. "They look to us to have all the answers, and we do the best we can. In some cases it's clear; in others it's murky," says Dr. Hicks. "In one sense, we're looking at cells as if they're a crystal ball and we're trying to predict the future."

Given that, pathologists might be tempted to add to their reports lines from Robert Frost's famous, slightly regretful poem about picking a path through the woods: "Both that morning equally lay…/I took the one less traveled by,/and that has made all the difference."

The need to understand where DCIS might be headed has only grown more critical with the advent of screening mammography in recent decades. DCIS represents some 20 percent of breast cancers identified through screening. There has even been talk, off and on, about removing the word "carcinoma" from diagnoses, and

concerns about overdiagnosis and overtreatment of DCIS run high.

“I talked with a radiation oncologist recently about this,” says Dennis Sgroi, MD, professor of pathology, Harvard Medical School, and co-director of breast pathology, Massachusetts General Hospital. “I said, ‘Would you not agree we are probably overtreating?’ He said, ‘Yes—but we just don’t know how to stratify patients. If we can come up with a way, that would be great.’ They would like to give less radiation.”

The question is clear, says Dr. Sgroi. “Can we come up with something that allows us to stratify patients into less aggressive treatment?”

Dr. Simpson

“In current practice there’s a lot riding on getting the diagnosis of DCIS correct, because atypical ductal hyperplasia is excised and the patient is followed,” says Jean Simpson, MD, president, Breast Pathology Consultants, Nashville, Tenn., and adjunct professor of pathology, University of South Alabama, Mobile. “And if a diagnosis of DCIS is made, often patients will receive radiation.”

There are good reasons to steer patients away from unnecessary treatment. Many of them fall into the you-can-kill-a-fly-with-a-grenade-but-why-not-try-a-flyswatter-first? category.

But just as pathologists can find it difficult to make a diagnosis in borderline cases, clinicians and patients can find it hard to understand the risks of DCIS.

Stuart Schnitt, MD, explains why. Treating DCIS isn’t treating cancer—it’s prophylactic treatment. And even when clinicians try to downplay the cancer angle, by reminding patients DCIS means they have a type of precancer, the treatments they’re offered typically erase that notion. They’re basically the same options—radiation, surgery—given to patients with invasive cancer. Says Dr. Schnitt: “No wonder patients are confused.”

The term LCIS is not nearly as explosive, despite the common “carcinoma” denominator. Dr. Schnitt, director of the Division of Anatomic Pathology, Beth Israel Deaconess Medical Center, and professor of pathology at Harvard Medical School, attributes that to the fact that LCIS is managed by either observation or observation and chemoprevention, which are less doomful than DCIS treatments.

Even as physicians ponder drastic approaches to treating DCIS, another undercurrent remains: What about the case that looks harmless but then develops into an invasive cancer? It mirrors current debates about immigration and terrorists: Everyone fears the dangerous one that gets through.

**Given the many possibilities in play,** DCIS might be described by a faux Latin phrase: *ductal est ductile*.

The diagnosis is actually straightforward in most cases, says Dr. Schnitt, but at either end of the spectrum matters can get tricky. On the high end, it can be hard to tell pure, high-grade DCIS from a DCIS with foci of microinvasion. At the low end, as noted, it can be difficult to distinguish limited forms of low-grade DCIS from ADH.

Dr. Sgroi

There are also occasional cases of intermediate nuclear-grade DCIS that are difficult to distinguish from usual ductal hyperplasia, Dr. Schnitt says. Other differential diagnostic issues include distinguishing DCIS from LCIS, and even distinguishing DCIS from frankly invasive cancers; as Dr. Schnitt notes, sometimes the latter can present in a nested pattern that mimics DCIS.

Trying to decide if there's microinvasion associated with DCIS can be challenging, says Dr. Simpson. While immunohistochemistry can help identify areas of microinvasion, with high-grade DCIS, the myoepithelial markers may be decreased or absent. In such cases, "good quality H&E stained slides can help," she says. "And the good news is that the prognosis of microinvasive carcinoma is essentially equivalent to DCIS without microinvasion."

But the most problematic area remains solving the low-grade DCIS/ADH riddle. "There are no hard definitions of where that difference is," says Dr. Sgroi. "Some people say it has to involve two ducts. Some say that it's two millimeters." Given that ambiguity, Dr. Sgroi says he looks at the two entities as a continuum, a notion that has molecular support. "ADH is basically identical to DCIS from a gene expression standpoint," he says. But interestingly, DCIS is molecularly similar to invasive cancer as well. "Nearly identical. So it's a bit more complex than we realized."

With DCIS, it's not strictly a matter of where it's headed. It's also a matter of how it got there. What is the pathologist working with?

"A lot of the cases we encounter are in core needle biopsies, which provide limited sampling," says Dr. Schnitt. "I've seen a lot of cases in consultation where a pathologist made the diagnosis of low-grade DCIS on a core biopsy, based on very, very limited volume of abnormality." The next step typically is surgery—sometimes an excision, but sometimes a mastectomy or bilateral mastectomy, he says. "In some of these cases, there is no DCIS in the excision or mastectomy specimen, and this creates a huge problem."

Part of the difficulty is that the distinction relies on the extent of involvement, agrees Dr. Simpson, who chairs the CAP Cancer Committee. A core biopsy might lead to an ADH diagnosis, while the lesion may be shown, on excision, to be DCIS. Says Dr. Simpson: "That's not a false-negative. That's a sampling issue." Notwithstanding, she recounts a recent conversation she had with a surgeon whose patient was in that very situation and who was sure the pathologists had erred. "They missed it," the patient told the surgeon.

These aren't isolated incidents. "It's probably the area that's gotten the most publicity," says Dr. Schnitt. From what he's read, he adds, nuance has been absent in the lay press discussions. "Basically, a lot of people talk about the inability of pathologists to reliably distinguish DCIS from ADH."

That's not the real issue, he says. Most pathologists are good at distinguishing extensive examples of low-grade DCIS from ADH. The problem is distinguishing limited examples of low-grade DCIS from ADH. "There are published

criteria that people use to distinguish them," says Dr. Schnitt. "But I think in the end, in many cases it's subjective. Pathologists have their own way of approaching things, depending on where they were trained, what sort of pathology school they adhere to, and how easy it is in a particular case to apply the criteria."

To surmount such problems, Dr. Schnitt says that at his institution, he and his colleagues try not to overdiagnose low-grade DCIS on the limited samples afforded by core needle biopsy, which is advice given in the WHO Blue Book recommendations, he notes. When pathologists encounter a borderline lesion in a core sample and are uncertain whether it represents ADH or low-grade DCIS, they should recommend an excision.

The short-term consequences of getting this call correct might "not be as critical as reports in the media would have us believe," says Dr. Simpson. If a pathologist is on the fence between the two diagnoses, the core biopsy should be viewed similarly to a frozen section, she says, in that it should prompt the surgeon's next step. "And in the case of low-grade ductal carcinoma in situ versus ADH, the next step is an excision."

The long-term issues are more concerning, Dr. Schnitt says. "There's no question in my mind that a lot of what we detect as either incidental findings or small areas of microcalcifications on mammogram probably would never come to harm the patient." That's been confirmed, he says, in a small number of follow-up studies of DCIS, which were retrospectively identified in breast biopsies previously categorized as benign, where the majority of patients did not develop invasive breast cancer. Even in cases where invasive breast cancer does occur, "We don't know the size or the extent of the original DCIS lesion, or the adequacy of the excision," Dr. Schnitt says.

Adds Dr. Sgroi: "If you talk to clinical colleagues, they'll tell you they're probably overtreating a lot of patients with radiation that they don't need. Yet it's hard to argue with a 97 and 99 percent success rate."

**Rather than argue with success rates, then, it** might make sense to reconsider how they talk about DCIS.

Dr. Masood

Shahla Masood, MD, would like to do a full-blown renovation on the topic. Dr. Masood, professor and chair, Department of Pathology and Laboratory Medicine, University of Florida College of Medicine, Jacksonville, says recent studies confirm what has been evident for many years—that low-grade DCIS is genetically different from high-grade DCIS. "But for some reason we have not paid attention to this." With worries about overcalling and overtreating DCIS back in the spotlight, there's an opportunity to make significant changes to how patients are approached. "High-grade ductal carcinoma in situ, clearly these are the cases that require cancer therapy," she says. "And the cases that are non-high-grade, the atypical hyperplasia, just call them borderline breast disease." In that scenario, the surgeon would follow up the core biopsy with an excision to ensure no invasive cancer has been overlooked. "Then we put that patient on close surveillance."

"This is not a new concept," she says. "People have been talking about it for years." It's time for pathologists to act, an argument she also makes in an editorial scheduled for publication in the January 2016 issue of *The Breast Journal*.

The reason pathologists have struggled to distinguish low-grade DCIS from ADH is that they're almost the same disease. "So abandon those two terms and replace that with 'borderline breast disease.'"

Won't clinicians find that an unsatisfying category? "It's a matter of how much pathologists want to educate their colleagues," Dr. Masood says. She has been using the term "borderline breast disease" at her institution for several years. "In those circumstances, they know very well this is on the spectrum of disease. They accept it, and this has worked quite well. We need to gradually educate our colleagues. It's not something that's going to happen overnight."
She compares the current state of affairs to earlier approaches to LCIS. "This is not different," she says. "People used to do bilateral mastectomy for lobular carcinoma in situ. And then they found out it wasn't necessary."

**Language matters.**

Dr. Sgroi, like Dr. Masood, says there may be value in using the B word. And, similar to Dr. Masood's experience, he says his surgical colleagues don't seem to have a problem with it.

"There are times when we'll call something severely atypical, bordering on DCIS," says Dr. Sgroi. "If we find severely atypical ADH bordering on DCIS at the margin, it's not uncommon for us to call the clinician and say, 'Listen, we're worried about this. You may want to consider doing a re-excision." In cases like this, he says, the laboratory supplies a discussion as much as it provides answers. "We try to approach it in more of a working relationship with our clinical colleagues." As with quoting the Bible, context is everything. The diagnosis is one thing; how clinicians interpret it might be something else.

Dr. Sgroi emphasizes the need for pathologists to know their local practice patterns. At Massachusetts General, he says, it would be unlikely for a surgeon to proceed to a mastectomy based on a core biopsy. But that's not the case everywhere. "If you have a surgeon who's going to do that, you'd probably pick up the phone and suggest an excision."

Might a name change be appropriate?

Dr. Schnitt says he's not opposed to using something less provocative than "DCIS," but wonders how effective it might be, especially since any patient who searches the Internet for information about her disease will likely come across the word "carcinoma" anyway. It may take several generations for "DCIS" to leave the lexicon, he predicts.

While agreeing that words such as "borderline breast disease" may be helpful, Dr. Schnitt offers another perspective. At an American Cancer Society meeting he attended several years ago, a patient advocate was "strongly opposed to a name change. I was absolutely shocked." In her words—Dr. Schnitt still remembers them clearly—a name change would be "duplicitous and patronizing to women." Her fear was that watering down the terminology might lead some patients to be undertreated; her solution was to change the way clinicians communicated risk to patients.

Dr. Simpson doesn't mince words. "Removing the C word is not going to change the biological behavior of the diseases." Instead, she'd like to see physicians steer the conversations toward letting patients know DCIS is a spectrum of diseases and explaining the implications of their particular type of DCIS.

She likes the idea of using "borderline" as needed in core biopsy when only a portion of the lesion is sampled. She wonders if pathologists, under pressure from clinical colleagues to be specific with their diagnoses, will be reluctant to do so. "But the surgeons I've spoken with would, I think, prefer this approach. Because they're the ones who are faced with talking to patients." Such conversations are fraught when, for example, a diagnosis of a small example of low-grade DCIS is made on core, and then there's no material left in the ensuing excision. "Because a diagnosis of DCIS has been rendered, the patient is pretty much relegated to getting radiation." That bell can't be unrung. Having to explain that to patients is challenging; a "borderline" case might be easier to understand, she suggests.

That's not to say DCIS shouldn't be diagnosed on core biopsies, Dr. Simpson hastens to add. But in situations

where the lesion either hasn't been adequately sampled or some features are not fully present, "I think it's better to err on the side of caution," she says.

Dr. Hicks says he's become more conservative over the years. When faced with the tough call between ADH and low-grade DCIS, he keeps in mind that most patients do extremely well. "When I'm in that gray zone on a core biopsy, and I'm trying to make that distinction, I often think, what do I think this patient needs?"

Dr. Hicks

When making an ADH diagnosis on core, Dr. Hicks says he can upgrade up to 30 percent of cases to something more significant, such as DCIS or even an invasive cancer. It's important, therefore, to do an excision in those cases. "I'd rather err on the side of undercalling something on the needle core biopsy and further evaluating it on excision than labeling a patient with cancer and then seeing on excision that nothing more significant has been left behind."

And yet he acknowledges another side to being conservative. If treatment becomes more conservative, and women receive radiation in fewer cases, "Everyone is fearful of the case where you err on the side of being conservative and then the patient comes back with an invasive cancer." Cue litigious nightmares, although as Dr. Hicks points out, those can also be triggered by treating patients unnecessarily.

There's another apprehension at play, says Dr. Hicks. "All pathologists fear reviewing breast excision or a breast core and calling something ADH, and then having the patient go off to Memorial [Sloan Kettering] and they say, 'Oh, no, no, this is low-grade DCIS.' Is that a mistake? I don't know. It's a difference of opinion. That's somebody seeing something a little differently."

At the University of Rochester Medical Center, he and his colleagues review borderline lesions at a daily breast pathology consensus meeting. "We don't always agree, so if there is not consensus, we'll do additional work to sort it out. Sharing cases that are unclear, sending it out for outside second opinions, is always wise," says Dr. Hicks.

Conversations within the hospital's walls are equally vital. Says Dr. Sgroi, "What I always say to my residents is, 'Why do we have this biopsy?'" In other words, what is the indication? Calcifications? Architectural distortion? A mass? What are the clinical indications? "It's our job to try to correlate what they're [radiologists] finding with what we're finding."

Dr. Hicks agrees. "The pathologist needs to be aware of what the imaging findings are," he says. "What was the radiologist targeting? And then make sure what's seen on the slides correlates with the radiology. We can't read these things in isolation." In fact, he says, "I've heard pathologists say, 'It's the radiologist's responsibility to say if this correlates or not.' But in my view, it's jointly held." Indeed, many institutions have radiologic-pathologic correlation conferences to review imaging and core biopsies. "These are useful. Both sides become more informed" about the challenges their colleagues face.

**Dr. Schnitt is convinced that as** more patients are treated by specialists who better understand the spectrum of risks, those risks will become clearer to patients.

Still, even the best-informed physicians and patients may find risk to be a malleable concept.

Data are in the eyes of the beholder. In studies that have looked at women with so-called favorable DCIS, who are

treated with excision alone, “perception of the data really varies with what you think is a low risk of local recurrence,” says Dr. Schnitt. The ECOG 5194 study, for example, looked at patients with DCIS who had either a low- or intermediate-grade lesion or a high-grade lesion, all of whom were treated with lumpectomy alone. The patients in the low-/intermediate-grade arm had a roughly 15 percent recurrence rate at about 10 years, says Dr. Schnitt. “Is that high, or is that low?” he asks.

Similarly, in the RTOG 9804 study, patients with low-risk DCIS were randomized to get either excision alone or excision and radiation therapy. Patients who were treated with excision and radiation therapy had an ipsilateral local failure rate of 0.9 percent at seven years, while those treated with excision alone had a 6.7 percent rate of local recurrence.

Again, Dr. Schnitt asks: “Is the 6.7 percent recurrence rate at seven years in the excision-alone arm of that trial high, or is that low?” That projects to about a 10 percent local recurrence rate at 10 years. “You can look at that and say, one in 10 patients will develop a local recurrence at 10 years. The other way of looking at it is to say, in 10 years, 90 percent of patients won’t have an ipsilateral breast event.”

Labeling those events high or low risk depends greatly on patients’ perception and willingness to accept varying degrees of risk. “If you tell women that they have a one in 10 chance of getting a recurrence in 10 years, some will say, ‘Oh my god, that’s awfully high,’” says Dr. Schnitt. “Others will say, ‘I’m willing to take that chance to preserve my breast for 10 years without having radiation therapy.’”

Women don’t necessarily evaluate those risks alone. Surgeons can influence those perceptions. “And in fact, we know there’s differences among surgeons in their perception of DCIS,” says Dr. Schnitt. And not just surgeons. At an NIH State of the Science meeting on DCIS several years ago, Dr. Schnitt recalls a radiologist telling audience members, “We need to think about DCIS as a caged tiger”—a frightening image, to say the least.

Even if clinicians are convinced small examples of DCIS can be treated with excision alone, patients may be less sure. Says Dr. Simpson: “Some would like to avoid radiation. But patients’ response to the diagnosis is certainly varied.”

Pathologists can play a role in guiding perceptions of risk. Tumor boards in particular are a good place to have those discussions, says Dr. Schnitt. But again, there are limits. “In my experience, no matter how careful you are at wording a diagnosis, there’s no way you could ever anticipate how some people might interpret it.” He recalls the “Clinicians are from Mars and pathologists are from Venus” article published years ago (Powsner SM, et al. *Arch Pathol Lab Med.* 2000;124:1040–1046). Recalling that paper, Dr. Schnitt says, “It was shocking to me how often clinicians would misinterpret what the pathologist thought were fairly straightforward reports and diagnoses.”

He also cites a study done by Ann Partridge, MD, MPH, of Dana-Farber Cancer Institute, that showed that more than 25 percent of patients with DCIS were concerned about its spreading to other parts of their bodies. In such patients, says Dr. Schnitt, “it’s clear that clinicians haven’t done a good job of explaining to patients what they have. There’s a lot of fault to spread around.”

Pathologists could cut the Gordian knot if they could figure out how to stratify risk. What might help?

While some studies hint that certain morphologic features are associated with an increased risk or progression to invasion—including positive margins, comedonecrosis, and high grade—not all demonstrate a link. After decades of research in this area, “I think we’ve pushed routine morphology about as far as we can go,” says Dr. Schnitt.

Biomarkers are an obvious place to start looking, but so far, says Dr. Schnitt, none, including ER and HER2 and Ki67, are ready for clinical use for risk stratification. And some physicians are eyeing the Oncotype DCIS assay, a multigene test that provides a risk score for recurrence, similar to the Oncotype DX test used for invasive breast cancer.

In addition to looking at more obvious targets, such as biology and molecular characteristics of DCIS, researchers are also looking at the microenvironment in which DCIS exists, including the myoepithelial cells that surround the

ducts and the microenvironment of the surrounding stroma. It's possible that DCIS that is associated with myoepithelial cell abnormalities is more likely to progress. In one study, DCIS cases having low CD10 expression were more likely to progress than those without this change, says Dr. Schnitt. Another study has pointed to elevated myoepithelial cell levels of a specific integrin, αvβ6, that might be associated with increased risk of progression.

Dr. Schnitt and his colleagues are trying to better understand the genomic landscape of DCIS. "I think we have a very good understanding now, through the TCGA [The Cancer Genome Atlas], of the genomic landscape of invasive cancer," he says. "We do know, based on using surrogate immunohistochemical markers, that all of the molecular subtypes that we see in invasive breast cancer are seen in DCIS, including luminal A, luminal B, HER2 enriched, and basal-like. So it certainly seems that the molecular phenotype of these lesions is established early in the course of their development, probably at the DCIS stage." But whether that adds information beyond routine morphology is not entirely clear.

There's another mystery for women undergoing breast-conserving therapy—what's the appropriate margin? It may differ for patients who are undergoing radiation therapy versus those undergoing excision alone. In fact, a consensus conference on that very topic, jointly sponsored by the American Society of Clinical Oncology, the Society of Surgical Oncology, and the American Society for Radiation Oncology, was scheduled to be held in Chicago Nov. 20–21. Dr. Schnitt, who planned to attend, compared it to a similar consensus conference on margins for invasive breast cancer. Those guidelines "have changed the way patients with invasive cancer are treated," he says. "We hope that whatever guidelines we come up with in November will standardize the required margin width for patients with DCIS and improve patient care."

In his own laboratory, Dr. Sgroi says he's trying to find an approach for identifying biomarkers to identify patients at low risk for recurrence.
Some 15 years ago, he says, he began wrestling with the vexing problem of DCIS risk stratification. He recalls the frustration vividly. "I didn't think that study would ever be done, one that would answer the questions and not harm patients in the process," says Dr. Sgroi. "That's the key." He recalls being involved with a study years ago, in which patients with low- and intermediate-grade DCIS were treated with excision only. Patients had a 16 percent recurrence rate, which was found to be unacceptable. "If we now take some of these biomarkers and apply them to that type of strategy, I bet we can improve on that. But we have to be careful."

At last, researchers are taking steps in that direction. The LORIS (Low Risk DCIS) Trial, taking place in the United Kingdom, will randomize patients with DCIS detected by screening or incidental DCIS to standard treatment (surgery with standard adjuvant treatment and postoperative annual mammographic follow-up) or active monitoring (mammographic follow-up alone with no surgical treatment) (Francis A, et al. *Clin Oncol.* 2015;27:6–8).

Similarly, the LORD trial, taking place in continental Europe, will also randomize patients with DCIS between active surveillance (annual mammography, and treatment if there is progression to invasive breast cancer or high-grade DCIS) and standard treatment, which will vary according to local policy and could include breast-conserving surgery, radiation therapy, mastectomy, or hormonal therapy.

"These trials are absolutely critical," says Dr. Schnitt. "They're long overdue, and I applaud any woman who is going to enroll."
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