

Laying worries to rest over breast biopsy discord

Karen Titus

May 2015—With the regularity of a pension fiscal crisis they appear: one study or another, in various journals, pointing out discrepancies in pathology findings. Editorials appear, the news jumps to the lay press, and suddenly the conversation feels hijacked.

The latest such study was published in *JAMA* in March (Elmore JG, et al. 2015;313:1122–1132). Participants interpreted 240 cases of breast biopsies (one slide/case); their diagnoses were compared to the reference interpretations from a three-member expert consensus panel. The three experts unanimously and independently agreed on the diagnosis in 75 percent of cases; the overall concordance rate between 115 randomly selected pathologists and the consensus panel was 75.3 percent. An accompanying editorial (Davidson NE, et al. 2015;313:1109–1110) called the findings “disconcerting.”

By now, it’s not news to anyone. “I guess everyone is aware of this article,” says Shi Wei, MD, PhD, head, section of surgical pathology, and associate professor of pathology, University of Alabama at Birmingham. While previous studies (most published in the 1990s) have looked at diagnostic disagreement among pathologists, this is the largest, with randomly selected cases. “It’s well designed,” says Dr. Wei, “but weighted heavily toward the interpretive concordance for the diagnoses of atypia and DCIS.”

Says Kenneth Bloom, MD, chief medical officer, In Vitro Diagnostics, GE Healthcare, Life Sciences: “I think it was a shock for some of my clinical colleagues—‘Oh my God.’ The initial read, without realizing the actual practice of pathology is quite different from the study design, is a shock.”

Dr. Wei uses similar language: “If you give the numbers to somebody who has no idea what we’re doing, I’m not surprised that some people would be shocked.”

Pathologists may not have been shocked, but they weren’t cheering the study, either. “The pathologists I’ve talked to have not viewed the study in a particularly good light,” says Jean Simpson, MD, president, Breast Pathology Consultants Inc., Nashville, Tenn., and adjunct professor of pathology, University of South Alabama, Mobile. “I think it makes them feel defensive.

“I talked to a pathologist yesterday,” she continues, “and he was going to give a talk to his clinical colleagues and assure them that they [his fellow pathologists] were on top of things.”

It’s possible that this study will, after its initial burst, eventually fade, like so many gorillas in the mist. But the study might be worth a closer look. Are there deeper issues to explore? What concerns have clinicians and patients raised, and how should pathologists respond?

“In the end, it’s a communication issue,” Dr. Bloom says.

It’s possible to see the study as a compliment, says Dr. Simpson, who also chairs the CAP Cancer Committee. “The lay public as well as many of our clinical colleagues think that anatomic diagnoses are straightforward and absolute,” she says. They may not always appreciate, for example, the differences between a core biopsy and a final excision, and why information from the former can be more launchpad than landing strip.

Given those lofty expectations, Dr. Simpson wasn’t necessarily surprised that her practice recently experienced an uptick in requests for case reviews, from patients and clinicians. “I suspect it’s as a result of the *JAMA* study.” Pathologists may feel under scrutiny and want confirmation that they’re on the right track, she hypothesizes, though she’s quick to add that their concerns might be groundless. Community pathologists, she says, “do just fine. They’re quite good at breast pathology.”



Dr. Simpson

The issue of trust—between pathologists, surgeons, oncologists, and radiologists—ripples beyond this study. “I’ve seen this go all sorts of ways,” says Dr. Bloom. “I’ve seen institutions where the pathologists lack expertise in breast disease and could actually use some help. And I’ve seen places that will read this [JAMA] study, and even though they’ve got world-class pathologists, they’ll say, ‘Oh, we need to send out everything for a second opinion.’”

Most of the consultations Dr. Simpson receives are from pathologists looking for guidance on cases involving atypical ductal hyperplasia and low-grade ductal carcinoma in situ. These same types of cases showed the least amount of concordance in the study. The participating pathologists agreed with the consensus diagnosis on 48 percent of the atypia cases. Overinterpretation of DCIS as invasive carcinoma occurred in three percent of cases; overinterpretation of atypias was noted in 17 percent; and overinterpretation of benign without atypia was seen in 13 percent. Underinterpretation of invasive breast cancer was noted in four percent of cases; underinterpretation of DCIS was seen in 13 percent; and underinterpretation of atypia was seen in 35 percent.

The study oversampled cases with atypia and DCIS to gain statistical precision for concordance in these categories. The breakdown was benign without atypia, 30 percent (10 percent nonproliferative and 20 percent proliferative without atypia); atypia, 30 percent; DCIS, 30 percent; and invasive carcinoma, 10 percent. “That’s not reality,” Dr. Wei says. “That’s not the percent in the real world.”



Dr. Wei

That’s a key point to consider when talking to clinical colleagues who raise concerns about the study, says Dr. Wei. The distinction between ADH and low-grade DCIS is one of the biggest diagnostic challenges for all, expert or nonexpert, he says, “and borderline cases may be seen at either the low end or high end of the spectrum.” Were similarly challenging cases over-sampled in other specialties, Dr. Wei speculates, results would likely be similar. The authors note that it was unclear how overweighting the test sets with more difficult lesions might have influenced pathologists’ performance.

It doesn’t surprise Dr. Wei that clinical colleagues might be shocked by the results in the *JAMA* study. “If I didn’t know they oversampled ADH and DCIS, I’d be shocked, too.”

Dr. Simpson offers a reality check of her own. The method used in the *JAMA* paper “is not how we practice pathology,” she says. When the study’s findings are placed in the broader context of pathology practice, “It’s less of an issue than the media would have us believe.”

Pathologists typically don’t rely solely on one slide, Dr. Wei says. “In reality, we do stains to confirm our impression or confirm that it’s not correct. We show it to colleagues; we send it out for a second opinion.”

One cut and one view is simply not sufficient to interpret a complex breast case. As with the Establishment Clause, there are reasons why interpretations vary and why even experts look for more information before deciding. “The

idea that you can look at anything and always have the exact same impression is unrealistic,” says Dr. Bloom. Context is essential. “Our radiology colleagues frequently ask for additional studies if something isn’t clear on the first mammogram,” he adds.

Nor do pathologists practice in a Cone of Silence, although that’s how the study was essentially set up, Dr. Simpson says. “Pathologists frequently know when they need help. They know when a case is difficult, when they’re on the fence. And they either informally show it to a colleague or send it for a formal consultation.”

The *JAMA* authors acknowledge that the checks and balances of everyday practice weren’t part of their study. They restricted participants to one slide per case to enhance participation, they said, but that also meant that a possible solution to the discrepancies was, by design, left out of the study.

When Dr. Bloom considers the *JAMA* study, core biopsies come to the fore. For him, it’s a matter of nuance and historical perspective.

The advent of core biopsies, coupled with greater adherence to mammograms (along with ultrasound and breast MRIs), means “now we’re chasing more things,” he says. Calcifications are perhaps today the most common reasons for biopsying. “We have lesions today that didn’t exist when I went through residency,” he says, such as columnar cell change and its spectrum of atypia. “So now studies say that pathologists can’t agree on atypia, but some atypias are new entities that were only described in the last decade. That’s something I think people aren’t quite getting—that context is important. It does make a difference whether we’re assessing a core biopsy or the excisional sample.” In the study, cases included both core (57.5 percent) and excisional (42.5 percent) biopsies.



Dr. Bloom

Sounding a bit like a French deconstructionist, Dr. Bloom expounds on the essence of biopsies. They’re less about tissue specimens than decision points, in his worldview. Faced with deciding between atypical ductal hyperplasia and low-grade ductal carcinoma in situ on a core biopsy, Dr. Bloom gives a mental shrug in many circumstances. “The designation is unimportant if the woman is going to undergo the same surgical excision of the lesion.” Unless the next clinical step hinges on making a clear distinction between ADH and low-grade DCIS, “the name you place on the lesion is more semantic than clinical.”

He also squints at the congratulations being passed around at the study’s high agreement rate for invasive breast cancer. Another shrug. The act of naming something needs to be significant, like Adam labeling the world in Genesis, and not just serve as a medical version of slapping on a “Hello, my name is ____” tag. The reason to name things, says Dr. Bloom, is so physicians can agree on what the next level of therapy should be. More surgery? Chemotherapy? Radiation?

“Even if we all agree that something is invasive breast cancer, questions may still remain. ‘Is my surgery complete? And do I or don’t I need chemotherapy?’” he says.

Patient care doesn’t require a group of pathologists to agree on whether something is DCIS or atypia; rather, it depends on a group of physicians—pathologist, surgeon, oncologist, radiologist—sorting through the complexities of a difficult case, including the tradeoffs of each treatment option. The patient needs to weigh in as well. Can she live with the uncertainty of not pursuing aggressive treatment? How tolerant might she be of treatments with considerable side effects? Or, conversely, how important is it for her to avoid them, especially knowing the treatment might be unnecessary? Even if three pathologists agree on the diagnosis and a reasonable next step,

says Dr. Bloom, the patient is the final umpire. That's the whole point of pathology—classifying disease so clinicians can explain to patients better, and more reproducibly, what their therapy options are and their likelihood of benefiting from them, says Dr. Bloom.

"It's not the name we place on a lesion that's important," he says. "It's what therapeutic options should be considered. Because if we agree on the therapy, who cares what we call it?"

Continuing his swim up the semantic stream, Dr. Bloom takes on the notion of "disagreement" and how the word is used to discuss differences in diagnoses. Surgical pathologists learn their profession in a mentorship setting, and deciding whether to call a borderline lesion (which is easily agreed on) atypia or DCIS (a mushier distinction) can be shaped by who one's mentor was. "They had a school of thought," he explains, adding that the same is true of oncologists. "It's true of all of medicine, actually. I wouldn't call these disagreements. Because they're not really disagreements. They have philosophies on how to care for patients." Differences are inherent in philosophies, which is why one surgeon, for example, might recommend a lumpectomy and another will insist on a mastectomy.

Pathologists can help tip those recommendations in one direction or the other based on the words they use. "If we call something invasive breast cancer, that has to be removed, right? You wouldn't just leave it in the patient unattended," says Dr. Bloom. Likewise, calling something an invasive breast cancer of a certain size, with spread to the lymph nodes, is a strong recommendation, if not guarantee, that a patient will receive chemotherapy. In borderline cases, the various philosophies all mingle. Depending on their training, some clinicians might call for chemotherapy, while others might hesitate; likewise, some will recommend additional surgery, while others will advise against it.

Without understanding these decisions in context, "They're making it look like it's a specific pathology problem," Dr. Bloom says.

But it's not, he says. It's simply the way medicine is practiced. "That's why patients seek out certain physicians depending on their beliefs and needs. One patient may like that a particular oncologist treats as aggressively as possible, while another patient seeks an oncologist who is less aggressive and more homeopathic."

Those differences bring it all back to a basic element: communication. That's why pathologists have pushed to have a strong presence at tumor boards and to tighten communication with treating physicians, Dr. Bloom says. In a blow to binary thinkers everywhere, he adds, "The words aren't enough. You have to understand the nuance of those words." Talking over puzzling cases at a tumor board speaks loud and clear. Without that, however, "It's very easy to misinterpret what's going on."

That should surprise exactly zero pathologists. When a patient seeks a second opinion at another institution, the pathologists at the latter institution invariably request the original slides. "Even pathologists have recognized that reading somebody else's report doesn't always tell you about the nuances of the case. So you need to look," says Dr. Bloom.

When pathologists discuss cases with surgeons, it might help to turn those talks into mini-philology conferences. Pathologists, says Dr. Bloom, sometimes use the word "atypia" to connote that the tissue does not look normal to them. When surgeons hear that word, however, they can see that as a surgical "start" button. "I wouldn't call it the misuse of words, but the miscommunication of wording," says Dr. Bloom.

Everyone agreeing that a lesion is DCIS, he continues, is not the sole solution. Some patients with that diagnosis do well, and some will do poorly. "That just means our categorization is too broad—because that categorization doesn't tell us how to take care of the patient."

Talking to patients appears to be a regular part of Dr. Simpson's practice, and one she relishes. It can be challenging to explain medical complexities to patients, she concedes. Patients often equate an AP diagnosis with a clinical lab result. (Such misunderstandings aren't limited to patients. "There are a lot of clinicians who don't

understand the subtleties” of AP diagnoses, she says.) Similarly, telling a patient that her risk might be doubled might sound high, when in reality it’s barely clinically significant. “But with a little bit of effort on my part, they can come away with a much better understanding of the issues.” It generally takes a couple of conversations. She also can reassure patients who might be alarmed by results of a well-publicized study—such as the *JAMA* paper—that pathologists consider the clinical setting and imaging findings when making a diagnosis from a core biopsy, with the understanding that occasionally excision is necessary for the pathologist to be completely sure of the final diagnosis.

None of these issues are new, of course. For 15 years, Dr. Bloom notes, he led a course on the pathologist’s perspective at American Society of Breast Surgeons conferences. The need for these conversations about the meaning and practice of pathology is, like the hereafter, eternal.

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