Prostate biopsy's role in active surveillance

Anne Paxton

December 2015—As a treatment option, a strategy of active surveillance is becoming more widely accepted for early stage prostate cancer where risk of progression is low. But the new emphasis on active surveillance brings increased anxiety among prostate cancer patients about the information they're getting from their physicians and how to deal with it.

When M. Elizabeth H. Hammond, MD, participated four years ago in an open dialogue with prostate cancer patients at a conference on active surveillance, "I was really rocked by the things I heard," she said. "The patients were angry and frustrated by our telling them active surveillance is a good treatment option. They said, 'Why are you calling it cancer? Why don't you call it something else? Don't you know what you're doing?' Clinicians also wanted to know: 'Why don't pathologists help us deal with patients who are on active protocols? We don't know what the right thing is to do.'"

Dr. Hammond, professor of pathology at the University of Utah School of Medicine, was one of three panelists who addressed those questions at a scientific plenary session at the CAP '15 annual meeting. Acknowledging the trend toward shared decision-making in patient care, the plenary explored measures pathologists should take to improve active surveillance, to clarify the grading system used for biopsies in prostate cancer, and to strengthen pathologists' role in guiding diagnosis and treatment.

Active surveillance used to be known as watchful waiting, said panel member Jonathan I. Epstein, MD, professor of pathology, urology, and oncology at Johns Hopkins School of Medicine. Unfortunately, that term connoted inaction. "Watchful waiting implies passivity, as though you're just basically watching somebody who has cancer."

But active surveillance is anything but passive, he said. "Many patients will get repeat biopsies, and the role of the pathologist is very active and critical in this process of both clarifying who is a candidate for active surveillance and in the follow-up of those patients."

The rationale for active surveillance is that 97 percent of men with prostate cancer will die of competing causes, most commonly cardiovascular disease, said panelist John L. Gore, MD, MS, associate professor of urology at the University of Washington. Despite this fact, in the cohorts he has studied, a large portion of patients drop out of active surveillance for nonclinical reasons.

"In the absence of clinical progression, a substantial proportion of men are choosing primary treatment despite not having any signs that they have a more aggressive cancer than initially diagnosed," Dr. Gore said. The overwhelming majority of the patients who drop out for nonclinical reasons do so, he said, because of anxiety around prostate cancer progression.

Once a patient is on active surveillance, prostate needle biopsies are used to iteratively evaluate the patient's prostate cancer risk. But there are problems with the Gleason score scale used for such biopsies. It's for that reason that the CAP, other pathology organizations, and the Prostate Cancer Foundation united to develop a consensus, published in 2014, for a new five-level grading system to replace traditional Gleason scores (Amin MB, et al. *Arch Pathol Lab Med.* 2014;138:1387–1405).

Dr. Epstein's group at Johns Hopkins was, in 1994, the first to come up with criteria for candidates for active surveillance, he said. "The criteria were no Gleason pattern 4 or 5—meaning a Gleason score of 3+3=6—and in terms of trying to predict who was more likely to have significant cancer, the extent of the cancer on the biopsy was critical. We found you had to have only one or two positive cores in order to be a candidate. We also found that PSA density [PSA divided by the gland volume, which can be estimated on ultrasound] of less than 0.15 was

the optimal cutoff."

Another key criterion was that the maximum involved cancer core be less than 50 percent. But there was a problem with this criterion that has prompted clinicians and patients to be upset at times with pathologists: "There are different ways you can measure how much cancer involves a core."

To improve the Gleason scoring system, the group at Johns Hopkins asked how it could come up with the least number of grades for prostate cancer, each with a different prognosis that would be simple and intuitive for patients and clinicians. "We came up with a five-grade group system and it's very simple," Dr. Epstein said.

"Grade group 1 is a Gleason score of ≤ 6. Grade group 2, which is Gleason score 3+4, is predominantly well-formed glands with a lesser component of either poorly formed, fused, or cribriform glands. Grade group 3, which is equivalent to Gleason score 4+3=7, is predominantly poorly formed, fused, or cribriform glands with a lesser component of well-formed glands."

"Grade group 4 would be equal to Gleason score 4+4=8 or 3+5=8 or 5+3=8, where you have only poorly formed, fused, or cribriform glands or a mix of the well-formed glands and no glands. And grade group 5, which is the worst grade, is equal to a Gleason score of 9–10."

With this system, "Now grade group 1 has an excellent prognosis and you can tell patients you have a grade group 1 out of 5. It's intuitive, it's a very low grade, and they can understand how they could be a candidate for active surveillance," Dr. Epstein said. This allows clinicians to convey to patients that their prognosis is good, instead of telling them they have a Gleason score of 6 out of 10, which does not sound as favorable.

In developing new modified criteria for active surveillance, what Dr. Epstein's group also found was a simpler objective measurement: unilateral or bilateral cancer, which replaces the prior criterion of less than 50 percent of cancer on any core. Many institutions have their own variations on the criteria. "Some people say less than 10 percent of the core; some people use a fraction of the positive cores or less than a third of the positive cores. But, in general, the overall definition involves grade, extent of cancer, and usually a PSA measurement."

The cohorts that have been studied have fairly consistent criteria for progression when a patient is on active surveillance, and those criteria include rules about PSA, Dr. Gore said. "Some of the cohorts look at the PSA velocity [change in the absolute value of the PSA over the course of a year]. Some of them look at the PSA doubling time to account for how rapidly the PSA is growing. In general, a PSA doubling time of less than three years at different stages of prostate cancer care has been associated with an adverse outcome."

But for all the cohorts, the researchers looked at the increase in the Gleason score plus other markers. "The PSA is more a marker that helps to diagnose prostate cancer. But all it really does in patients on active surveillance is potentially direct an earlier need for biopsy," Dr. Gore said. "It's that repeat biopsy that defines progression—not so much the PSA."

Experts in prostate cancer agree, says Dr. Epstein, that “we would prefer to have screening and find the cancers, but then make a rational decision of which ones to treat and which ones not to treat.”

“It turns out,” said Dr. Epstein, “that whether it’s PSA velocity, density, absolute value, or urinary PCA3, these various measurements really are not that helpful in predicting who, while on active surveillance, is failing active surveillance.”

More important, he said, is the biopsy. “It turns out that pathology is the key, and so grade on biopsy ends up being probably the most important thing. If somebody goes from a 6 to a 7 Gleason score on repeat biopsy, that’s typically going to generate somebody going off active surveillance and being recommended for treatment. So it’s a critical breakpoint for pathologists to remember.”

“If you’re struggling to decide whether it’s a 6 versus a 7, recognize that could make the difference between somebody being recommended for radical prostatectomy or radiation versus staying on active surveillance.”

At Johns Hopkins, one-third of the patients basically leave the active surveillance program because of anxiety, he said. “The good candidates for active surveillance have favorable repeat biopsies, but they just basically can’t live with the fact that there’s a cancer inside of them, and they say, ‘Do something. Take out my prostate.’”

Dr. Epstein pointed to several indicators of likelihood as to whether someone will have worse disease on a subsequent biopsy. One is “How many times have you been biopsied without having worse findings?” That’s one of the most powerful questions, he said. Whether they have bilateral versus unilateral cancer is another factor that goes into trying to reassure patients, to say, “Yes, you have a low likelihood of having worse disease on a subsequent biopsy, and you should basically stay the course.”

Whether patients stay on active surveillance will typically depend on their Gleason grade on repeat biopsy, Dr. Epstein added. But Dr. Gore emphasized that under the shared decision-making model of care, patients and providers are equal partners in the transaction. An important part of shared decision-making is knowledge transmission, Dr. Gore said. “Patients cannot be their own personal expert unless they have information about their clinical diagnosis, and the pathology report for many patients with cancer—specifically patients considering active surveillance—is the foundational document.”

In that context, the University of Washington started a program to develop patient-centered versions of pathology reports. “The idea was to use what we call a user-centered design process to develop these new tools. So we worked with local experts in the Seattle area to identify elements of a pathology report that are foundational to decision-making and prognosis. Then we worked with patients through a couple of different focus groups to identify layouts and language that can translate those elements into patient-centered versions.”

To test the effectiveness, the UW randomized patients to get the standard report and the patient-centered pathology report or the standard report alone. The study team used bladder biopsies, since they are simpler and it’s easier to create patient-centered versions. The most important finding, Dr. Gore said, is that “patients exposed to the patient-centered pathology report were significantly better able to represent the stage of their bladder cancer. The ability to report their stage of bladder cancer was pretty atrocious in people who were exposed to just the standard report.”

When he was in medical school, he recalled, a teacher said that medical school students learn in their first year as many new words as someone immersed in a country speaking a foreign language. “So what we’re trying to do is speak German to our patients with cancer. Ideally, if we can create English patient-centered versions of some of these documents, it’s an opportunity to get patients better engaged in their cancer care.”

Dr. Epstein has found that talking to patients is a good way to realize that “what we put in our pathology reports can easily be misunderstood.” Many times an active surveillance candidate, when receiving another biopsy, will get a report of a high-grade prostatic intraepithelial neoplasia, or PIN. “I’ve had many patients who have read their reports and said, ‘OK, I understand the Gleason score. But what’s this high-grade PIN? High-grade I read is bad. I shouldn’t be on active surveillance with this.’ We all know as pathologists that the high-grade PIN means nothing once you have cancer. But from a patient standpoint, you can understand why they would be concerned.”

In response to this and similar comments, he worked with patients to develop a “Frequently Asked Questions” list for the common organs: prostate, bladder, breast, cervix, colon, and so on. “We came up with FAQs to explain all the words in the pathology report and what they mean in patient language.”

This work was done with the Association of Directors of Anatomic and Surgical Pathology, he said. “Now we are partnering with the American Cancer Society, and patients can look on the ACS website and ask, ‘How can I read my pathology report and better understand it?’ And I think it’s important as a bridge between what we write and what patients are reading, to try to help them better understand what we are saying.”

To maintain quality of biopsies, Dr. Epstein recommended having only two cores per cassette, or a maximum of three. “Once you have too many cores in a given cassette, cores fragment and you can’t come up with a simple measurement of how many cores are involved by cancer, which is critical to determine active surveillance. Just that simple thing of keeping the number of cores to two or maybe three is a simple way that you can improve the pathology.”

Urologists should turn a “critical eye” to the quality of biopsy, Dr. Gore added, “which we as a field really haven’t done.

“When most urologists talk about prostate needle biopsy quality and complications, they’re talking about avoidance of infectious complications. But we need to look at how we can ensure there’s consistent quality of the actual biopsy across urologists.”

Dr. Hammond agreed, noting that pathologists can act on this need at their own institutions. “If you see there’s variation in the quality among your urologists, engender a conversation with your urology colleagues about what constitutes a really good biopsy so that you can use it. It will make a big difference.”

Molecular markers are proving helpful in managing patients with prostate cancer, the panelists said. “There is a large emergence of genomic tests that are specifically targeted toward decision-making for active surveillance,”

noted Dr. Gore, citing Myriad's Prolaris and Genomic Health's Genome Prostate Score. The question is, "Can you look at a genomic signature of a patient's prostate cancer based on a core of prostate cancer tissue, based on different markers of the cell cycle, and determine that that patient, within that low-risk category, is also genomically low risk?"

Some of the molecular tests, in Dr. Gore's opinion, are "not ready for prime time."

Dr. Gore

"There are a number of decision-making studies using both of these tests that are currently underway to determine, No. 1, if they actually validly represent future risk of adverse prostate cancer events. But No. 2 is whether these tests actually do help the patient and the provider make confident decisions. We hear a lot from local clinicians that they have a very hard time understanding what Gleason score 6 (grade group 1) cancers are actually at risk for progression."

At the University of Washington, Dr. Gore said, researchers have the PASS cohort, the Prostate Active Surveillance Study, which is looking at active surveillance patients at sites across the U.S. to explore the molecular tests and their role in decision-making. "I would say when the test clearly confirms your suspicion that that patient is an excellent candidate for low risk, or for active surveillance, it is very reassuring."

One problem with the tests is that they have been developed on a different patient population than active surveillance, Dr. Epstein pointed out. "With active surveillance, we often have very little tissue, so a lot of these tests are difficult to do. Most of these tests have been done on radical prostatectomy patients and involve asking how did they predict progression going forward after radical prostatectomy."

From his standpoint, it's not easy to apply those findings to active surveillance patients—until they're tested on those patients and the patients are followed prospectively, and "that will take years.

"I'm less comfortable advocating their use in clinical medicine," he said. "But the tests are there, and I think as pathologists all of you are probably being asked to send out for various types of these tests."

One clinical exam that potentially is useful is multiparametric MRI, a new form of MRI that looks at different parameters, not just the anatomical T2 weighted images. "That's definitely been very useful as a negative predictive value, meaning if their MRI looks totally normal, we don't see a big lesion there, it's been showing that most of these patients don't have a significant tumor. So we've been using it for patients who, for example, have very good pathology but a high PSA, where there's a discordance."

"We'll do a multiparametric MRI if we don't see anything," Dr. Epstein explained. "It reassures us. We use it for patients if we want to lengthen out how often we do the biopsies to maybe every two years instead of every year." Or, when under the program they stop doing active surveillance when a patient reaches age 75, "first we'll do a multiparametric MRI and make sure the patient doesn't have a big tumor that was missed on the prior biopsy."

Dr. Gore hopes that the MRI might help clinicians get a better sampling of likely targets within the prostate. "One thing that's very unique about prostate cancer is we don't do lesion-directed biopsies. It's not like kidney cancer where you have a well-circumscribed, discrete lesion. We do a sampling. We essentially take a dartboard approach and hope that within our mapped-out anatomy of the prostate, we can capture the cancer."

Dr. Hammond

One of the important actions the CAP has taken is to convene guideline-writing groups, Dr. Hammond said. "Certainly this is going to go on in the future as the area develops. There will be new guidelines and new recommendations coming out to give guidance on how best to help clinicians and patients with these issues."

There is no single best way to monitor patients under active surveillance, Dr. Gore said. In studying the different cohorts, all of which consisted of relatively young patients, "we were very nervous at the outset of active surveillance that we were going to miss adverse cancers. And so most of these cohorts employed an annual biopsy." A biostatistician modeler at the Fred Hutchinson Cancer Research Center in Seattle is now combining the larger cohorts that were studied, including Johns Hopkins, the University of California at San Francisco, and the University of Toronto, to try to understand if modeling can produce the best algorithms for conducting active surveillance, he said.

Biopsies remain a foundational information document, Dr. Gore noted, but they are not innocuous. "There's been quoted a one percent urosepsis and hospitalization rate associated with prostate needle biopsy, so avoidance of biopsy would be an important positive outcome if certain parameters were met."

Johns Hopkins employs a nomogram approach to predict who potentially has a good chance of not having adverse findings on a repeat biopsy, so the interval between biopsies can be lengthened. "We've now lengthened the period out to every two years in certain groups, based on their findings on the biopsy and their PSA," Dr. Epstein said.

In making these decisions, patient demographics are critical. "You have to look at patient morbidity, patient age, what's their life expectancy. If somebody has less than a 10-year life expectancy and they have very good pathology on their biopsies and low PSA, the likelihood of their dying of prostate cancer is virtually nil. So you don't in a sense have to follow them as closely."

On the other hand, "For patients who have a discrepancy—they may have good pathology but a high PSA—you would want to follow them more closely," Dr. Epstein said. "I think we're now entering an age of personalized medicine, where you look at each patient individually and all their biopsy and imaging, and you say, what can we do that's best for that individual patient to follow up? And it will be more tailor-made on an individual basis. But again, the pathology is key."

PIN, interobserver variability, computer-aided image analysis, cost

The pathologists who attended the scientific plenary at CAP '15 in October asked several questions of the panel members. Here are their questions and the panelists' answers.

Since high-grade prostatic intraepithelial neoplasia is not used in the management of patients on active surveillance or to establish a diagnosis of prostate cancer, and can be misinterpreted by patients, should pathologists even be making a PIN diagnosis?

Dr. Epstein agreed that if a patient has cancer elsewhere, the finding of high-grade PIN has no meaning. "But high-

grade PIN does have a role in patients who don't have cancer, especially when it's extensive high-grade PIN, so I think it's important as a diagnostic criterion in some cases. Even if high-grade PIN is obvious, I would still mention it because it's there."

Clinically, Dr. Epstein added, "we only use high-grade PIN in decision-making for people at risk for prostate cancer, so it doesn't really weigh into our decision-making for people who have a diagnosis of prostate cancer and are on active surveillance."

"When we queried our expert panelists," Dr. Gore said, "high-grade PIN was definitely subjugated in importance. That's one of those factors on the standard report that has sort of been weeded out of our patient-centered pathology report," though it can be entered in the comments section.

Have there been studies on interobserver variability among pathologists on reading whether a cancer is Gleason pattern 4 or belongs to Gleason pattern 3?

"Basically, the definition of pattern 4 is cribriform glands of any type. Poorly formed and fused glands are also pattern 4," Dr. Epstein said. He believes that the cribriform glands are more objective now, where in the past there was some subjectivity as to what cribriform glands were pattern 3 or 4. The problem comes with the issue of poorly formed glands versus a tangential section of pattern 3.

"The key should be that if you're going to call pattern 3 based on poorly formed glands, there should be a cluster of poorly formed glands that are sufficient in number," Dr. Epstein said. "You don't call pattern 4 on one or two poorly formed glands identified at high magnification." If it's a borderline case, he added, "I would back off to the lower grade as opposed to having somebody be treated for more aggressive cancer that may not be the case."

The best way to make sure all pathologists come up with the same answer if they look at the same slide, Dr. Hammond added, is to have discussions with colleagues. "Remember that you, as a group, hold the responsibility of consistency of interpretation among your colleagues. Have conversations about these kinds of issues with them, so that everyone understands what the terminology you're using really implies about what is going on with that patient."

At UW, Dr. Gore said, "we have rules about second opinions; everyone who comes to see us for a second opinion has to have a re-review of their pathology." But a study of past data at UW found that even within a cohort of dedicated genitourinary pathologists, "there was still interobserver variability in calling something a 7 and calling something a 6." This is an area where he is hoping to see more improvement in the future. "Because it influences such a fundamental and important decision as primary treatment or active surveillance, more clarity would be really helpful."

What kind of progress is occurring in computer-aided image analysis that could more accurately identify and quantify the proportions of Gleason grade 4?

Studies toward a more objective computerized Gleason score have been done, Dr. Epstein said. "The problem I've experienced when I've worked with individuals on this is that they tend to be 'math' types, and they end up coming up with a complicated algorithm that any physician wouldn't understand; it's just a bunch of mathematical formulas. So it's not very intuitive."

"We're working to try to come up with a morphometrics-based process that would look at the special architecture of the glands. It's not something I foresee in the near future, but I think it's a reasonable thing to keep pursuing."

What do you do clinically with a diagnosis of atypical small acinar proliferation?

ASAP is one of those diagnoses that typically prompts consideration of an earlier biopsy, Dr. Gore said. "If someone, in the absence of a formal cancer diagnosis, has a prostate needle biopsy because of an elevated PSA or an abnormal rectal exam, that's a diagnosis that prompts us to counsel that patient that we would consider them to be a higher risk of eventually developing prostate cancer. We would recommend that they have a repeat prostate needle biopsy sometime in the near future." The time frame of the repeat biopsy is variable, but typically

it might be within the next year.

What is the comparative cost of early definitive treatment versus a surveillance program that may include multiple repeated biopsies over many years plus treatment of biopsy complications?

If active surveillance is successful, Dr. Epstein said, it is going to be more expensive than a one-time surgery. “But if you have surgery, there’s a high risk of impotence and incontinence that you can’t put a dollar number on.” Despite the greater expense, “successful active surveillance and keeping somebody on active surveillance who’s a good candidate is the best medicine, without question.”

Attempts to put a number on such factors are being called “health state utilities,” Dr. Gore said. “It’s the idea of what you give up when you opt for a treatment that may cause incontinence and may cause impotence. And in those studies, because of the high rates of adverse effects, because of the nidus of the genitourinary tract location, active surveillance is always going to be better from a health state utility standpoint.”

Since the rate of prostate cancer death has declined with screening, why are recent U.S. Preventive Services Task Force recommendations deemphasizing the benefits of screening? Has the pendulum swung too far the other way?

Dr. Epstein would say the pendulum has swung too far the other way. “I didn’t think the studies looking at screening, and criticizing screening, had a long enough follow-up. They looked at mortality at seven years. But you need much more follow-up to look at prostate cancer than seven years.”

“Prior to screening, a third of the men would walk in with prostate cancer, with metastatic disease,” Dr. Epstein said. “When screening took place with PSA, we virtually never saw that, and now we’re starting to see that again.”

“So it comes down to a philosophy. Do you want to basically put your head in the sand and not overtreat a lot of patients, but allow certain men to present with advanced metastatic disease and die of cancer that you might have been able to save? Or would you like to have the information, but rather than just treat everybody—which is what the standard has been—think about who’s a candidate that we don’t have to treat? And educate patients that they do not necessarily have to be treated, which is the whole idea of active surveillance?” Experts in prostate cancer are now agreeing, he said, that “we would prefer to have screening and find the cancers, but then make a rational decision of which ones to treat and which ones not to treat.”

There’s no advantage to halting screening, Dr. Gore said. “If we did that in the U.S., the rate of men presenting with metastatic prostate cancer… would rebound to 25 or 30 percent of pre-PSA screening levels in about 13 years, which is pretty remarkable.”

PSA screening has been reframed, and how the pathologist’s role in prostate cancer diagnosis fits with it has been reframed as well, Dr. Gore said. “The judgment against PSA screening, starting with the U.S. Preventive Services Task Force report in the 1990s, was essentially a judgment against the overtreatment of prostate cancer in the U.S.” Now, Dr. Gore added, the idea of PSA screening is no longer to screen for prostate cancer, but to screen for high-grade prostate cancer. *—Anne Paxton*

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