CONTROVERSIES IN UROLOGIC CANCER

Is MRI fusion biopsy the new gold standard for PCa diagnosis?

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PROSTATE CANCER

Is MRI fusion biopsy the new gold standard for diagnosis?

Cheryl Guttman Krader, UT Contributing Editor

Advances in magnetic resonance imaging (MRI) technology have led to increased utilization of MRI for prostate cancer evaluation, and results from studies evaluating the performance of MRI fusion biopsy provide clear evidence to support its use as the gold standard for men at risk for prostate cancer diagnosis following an initial negative biopsy, according to Michael S. Cookson, MD, and Kelly L. Stratton, MD.

“In its most recent policy statement relating to MRI use in prostate cancer, the AUA supports fusion biopsy for men with a prior negative biopsy. And for biopsy-naïve men, it suggests that fusion biopsy may benefit those with uncertain clinical indications for biopsy, such as minimal PSA increase, abnormal digital rectal exam with normal PSA, or marginal indications based on age.”

The current NCCN Guidelines for Prostate Cancer Early Detection state that for initial and repeat transrectal ultrasound (TRUS)-guided biopsy, multiparametric MRI (mpMRI) followed by lesion targeting may maximize the detection of higher risk disease and limit the detection of lower risk disease,” said Dr. Cookson, professor and chairman of the department of urology, University of Oklahoma College of Medicine, Oklahoma City.

“Although the NCCN guidelines also note that MRI is not recommended routinely prior to initial prostate biopsy, we believe that studies supporting the utility of multiparametric MRI-ultrasound fusion biopsy (mpMRI fusion biopsy) has multiple limitations, including cost, interobserver variability, and low diagnostic accuracy for clinically significant cancer in the anterior prostate,” says E. David Crawford, MD. Furthermore, according to the AUA Policy Statement on mpMRI in the diagnosis, staging, and management of prostate cancer, which provides a framework for clinical practice, mpMRI itself has a limited role as a diagnostic tool.

“Most centers offering MRI fusion biopsy combine it with 12-core systematic biopsy.”

NELSON STONE, MD

Therefore, mpMRI fusion biopsy cannot be considered as the gold standard for prostate cancer diagnosis, according to Dr. Crawford, professor of surgery, urology, and radiation oncology, and head of the section of urologic oncology, University of Colorado Anschutz Medical Campus, Aurora.

“The coincidental timing of the advent of mpMRI technology with a higher field strength and the growing controversy about overdiagnosis and overtreatment...
prostate MRI will create the basis for its earlier use.”

Dr. Stratton, assistant professor of urology at the University of Oklahoma, said, “There is little debate that repeat biopsy following a prior negative biopsy is improved by using prostate MRI technology, and in the interest of controlling cost, some may argue that MRI fusion biopsy should be limited to this population. It makes more sense, however, to obtain the MRI when the prostate cancer diagnosis is first suspected, prior to any decision for biopsy.

“We believe that studies supporting the utility of prostate MRI will create the basis for its earlier use.”

M I C H A E L S. C O O K S O N , M D

“The fact that many men initially have a negative biopsy means that repeat biopsy is an inevitability for any urologist,” Dr. Stratton added. “Clinicians will have to determine how they want to handle that situation. As more and more urologists become familiar with the technology, the use of prostate MRI and fusion biopsy will continue to grow. Its benefits for improving cancer detection, clarifying anatomical detail, and potentially assisting in staging cancer spread make prostate MRI and fusion biopsy the new gold standard for prostate biopsy.”

Benefits of MRI fusion biopsy

mpMRI is the cornerstone of fusion biopsy. Because this technology utilizes several image series to obtain both anatomical assessments of the prostate and physiologic assessments that represent potential changes arising from tumor cell proliferation, it not only helps identify prostate cancer but also directs the biopsy to areas of clinically significant disease, said Dr. Stratton.

Many reports show that mpMRI fusion biopsy improves biopsy accuracy. For example, in a retrospective study of 135 patients undergoing prostatectomy, Baco et al reported that the index lesion identified on mpMRI fusion biopsy was concordant with findings from prostatectomy pathology in 95% of patients.

Other research shows the benefits of mpMRI fusion biopsy for maximizing detection of higher risk disease and limiting detection of low-risk disease. For example, in the multicenter PROMIS study that included 576 biopsy-naïve men, patients underwent mpMRI followed by mapping biopsy and TRUS biopsy. The study found that including mpMRI would improve the detection of clinically significant prostate cancer by 18% while potentially reducing the detection of clinically insignificant cancer by 5%.

Radtke et al studied 294 consecutive biopsy-naïve men undergoing combined transperineal template saturation biopsy and MRI-guided targeted biopsy, including 186 men who were biopsy-naïve and 108 men who had a prior negative biopsy. Targeted biopsy of PI-RADS 2-5 lesions missed fewer clinically significant (Gleason score ≥7) cancers than the systematic biopsy (11 [12.8%] vs. 18 [20.9%]) and also missed 43.8% of Gleason score 6 tumors. If the targeted biopsy was limited to PI-RADS 3–5 lesions, it would have missed 17 significant cancers (19.8%).

In one study, the index lesion identified on mpMRI fusion biopsy was concordant with findings from prostatectomy pathology in 95% of patients.

“The gold standard to optimize diagnosis of clinically significant prostate cancer should be combined systematic and targeted fusion biopsy.”

K E L L Y L. S T R A T T O N , M D

“These results show that while targeted fusion biopsy can reduce detection of lower grade disease, the gold standard to optimize diagnosis of clinically significant prostate cancer should be combined systematic and targeted fusion biopsy,” said Dr. Stratton.

Similarly, results of a study by Tran et al evaluating the utility of MRI fusion biopsy in men undergoing a confirmatory biopsy as part of an active surveillance regimen support its use for guiding clinical decisions, but also indicate that in this setting as well, MRI fusion biopsy is best used in combination with systematic biopsy and not as a replacement for it. Among 207 men undergoing MRI fusion biopsy with concurrent systematic biopsy, 83 men (40%) were upgraded after biopsy, but the upgrading was based on systematic biopsy alone in 49 men, MRI fusion biopsy alone in 30 men, and both techniques in four men.
Addressing the idea that MRI fusion biopsy should not be considered the gold standard for prostate cancer diagnosis because it is inferior to mapping biopsy, Dr. Cookson and Dr. Stratton did not dispute the fact that mapping biopsy would provide an accurate representation of any pathology present in the prostate.

“Just as with MRI fusion biopsy, however, there are concerns with cost and utilization of resources accompanying the use of mapping biopsies,” Dr. Cookson said.

Ensuring quality

Although published studies support the adoption of MRI fusion biopsy for prostate cancer diagnosis, its value, as noted in a 2016 joint consensus statement from the AUA and the Society for Abdominal Radiology, depends on high-quality prostate MRI and experienced radiologic interpretation.7

“Urologists considering building a fusion biopsy program should work with their radiology colleagues to evaluate the technology that is locally available and should team up with a radiology champion, reviewing cases together and confirming histological diagnosis to quickly build expertise and ensure quality interpretation,” Dr. Stratton said.

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Numerous studies show that the accuracy of mpMRI fusion biopsy is not much better than cognitive fusion biopsy and that MRI fusion biopsy misses a significant number of high-grade cancers that are detected by 12-core systematic biopsy.”

E. DAVID CRAWFORD, MD

Men diagnosed with low-risk disease cannot be monitored with mpMRI alone, and this imaging technology cannot be used to plan focal therapy,” said Dr. Stone. Dr. Crawford said, “Our research shows that 3-dimensional mapping biopsy is currently the most accurate biop-
Studies that show MRI fusion biopsy misses between 5% and 35% of high-grade cancers, including relatively large lesions.

Dr. Crawford further contends that the fusion technique is not needed considering that areas of suspicion identified on mpMRI can be equally well targeted through cognitive co-registration, assuming the urologist has good ultrasound interpretation skills.

“I do both techniques, and when sampling areas with good accessibility, use of an mpMRI fusion system may have a slight accuracy advantage, but that remains to be proven,” Dr. Crawford said.

Defining a more limited role

Dr. Crawford said that use of mpMRI fusion biopsy as an initial diagnostic test should be reserved for research studies conducted by experts.

“We need to consider that the best data for mpMRI fusion biopsy comes from studies done by expert radiologists and urologists at centers of excellence, and the findings do not necessarily translate to what is achievable in the hands of less experienced practitioners. To minimize the rate of missing high-grade cancers, it is important that the radiologist knows how to read and interpret the MRI,” said Dr. Crawford.

“We need a cost-effective, reliable technique that will guide the decision to perform biopsy because there is a high likelihood of finding high-risk disease, and that has been met through developments in genomic testing.”

To improve the accuracy and efficiency of prostate cancer diagnosis and risk stratification, Dr. Crawford and Neal Shore, MD, developed an algorithm based on the use of genomic markers. According to the algorithm, initial prostate biopsy is limited to men with PSA >1.5 ng/mL with at least one genomic test indicating the patient is at risk for high-grade prostate cancer.

“Patients may benefit from mpMRI when initial biopsies are negative and genomic tests identify a methylation abnormality signaling the risk for a significant prostate cancer. The mpMRI can help to identify these lesions and direct a biopsy,” Dr. Crawford said.

Disclosures: Drs. Crawford and Stone are owners of 3DBiopsy, Inc. Dr. Crawford is a consultant/speaker for MDxHealth, Genomic Health, Janssen, Dendreon, Ferring, and Bayer.

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Is HIFU for low-risk prostate Ca ready for prime time?

Cheryl Guttman Krader, UT Contributing Editor

POINT: Evidence shows HIFU can provide cancer control outcomes comparable to those associated with radical prostatectomy or radiation therapy in properly selected patients.

Cary Robertson, MD

COUNTERPOINT: Recommending either whole-gland or focal HIFU cannot be justified when their pros and cons are judged relative to the appropriate comparator.

Erik P. Castle, MD

Addressing the question of whether high-intensity focused ultrasound (HIFU) for localized prostate cancer is ready for prime time requires a multi-part discussion that considers the whole-gland approach separately from hemiablation/focal HIFU, says Erik P. Castle, MD.

He concluded, however, that there is no justification for recommending either modality when its potential pros and cons are judged relative to those of the appropriate comparator.

Dr. Castle is professor of urology at Mayo Clinic, Phoenix. Discussing the role of HIFU for localized prostate cancer, he said that whole-gland HIFU would be considered as a treatment for patients whose cancer is expected to impact their survival and should be compared against radical prostatectomy. On the other hand, hemiablation/focal HIFU aims to address concern about overtreatment of low-risk prostate cancer and should be considered in relation to active surveillance.

Taking into account data on cancer control and complications, Dr. Castle said that whole-gland HIFU has yet to be proven equal to standard therapies as far as intermediate- and long-term outcomes. He foresaw potential growth of hemiablation/focal HIFU, but concluded that active surveillance is the better option for men with low-risk disease seeking to preserve quality of life.

“There is no free lunch with prostate cancer therapy. Patients pay upfront with continence and potency...
“My main message about HIFU’s role for management of localized prostate cancer is that while it can be used to treat men with high-volume, low-risk disease, it is not meant for only that setting,” said Dr. Robertson.

According to Dr. Robertson, optimal candidates for HIFU are men with “low” intermediate-risk prostate cancer who have a small gland (<40 cc) that can be treated without the need for an adjuvant procedure to downsize or debulk the prostate.

“A patient with high-volume Gleason grade 3+3=6 or low-volume Gleason grade 7 (3+4) prostate cancer would be ideal, but HIFU may also be considered for a man with a small focus of higher grade disease,” he said.

One niche for whole-gland HIFU is for a subgroup of men who have comorbidities that make them poor candidates for surgery or radiation therapy. And, when prostate cancer is unilateral, HIFU hemiablation is something that can be considered as an alternative to surgery or radiation therapy by men who are concerned about the functional side effects of those traditional interventions.

“Hemiablation in men with unilateral prostate cancer is probably the future for HIFU because it has a favorable safety profile relative to traditional treatments for prostate cancer. In addition, available data indicate that hemiablation HIFU is associated with acceptable cancer control rates, although follow-up duration in studies of hemiablation HIFU is much shorter,” Dr. Robertson said.

HIFU outcomes

Currently, the largest amount of published data on HIFU outcomes is reported out of centers in France, Germany, and the United Kingdom and pertains to whole-gland treatment. These results show good efficacy using HIFU to treat localized prostate cancer, said Dr. Robertson.

He cited long-term data from a HIFU center of excellence in Munich. Chaussy and Thüroff reported outcomes for 704 patients with a mean follow-up of 5.3 years (range, 1.3 to 14 years); 78.5% of men in the series had intermediate- or high-risk disease.1 Cancer-specific survival was 99%, metastasis-free survival was 95%, and 10-year salvage treatment-free rates were 98% in low-risk, 72% in intermediate-risk, and 68% in high-risk patients. The investigators reported that PSA nadir and Gleason score predicted biochemical failure, side effects were moderate, and the HIFU retreatment rate since 2005 was 15%.

“It is important to realize that after HIFU, there may be a small residual amount of tumor as documented by biopsy or MRI and biopsy. But, HIFU is repeatable, and including patients who had a second treatment, long-term cancer control rates measured by freedom from biochemical recurrence are similar for HIFU as for surgery and radiation therapy across the spectrum from low-risk to high-risk disease,” Dr. Robertson said.

Dr. Robertson noted findings from analyses of data collected in the IDE registration trial for the Ablatherm platform showing that at 2 years post-HIFU, of the 28% of men demonstrating a positive biopsy after a single HIFU treatment, the per core negative biopsy rate was significantly increased compared with baseline.2

Cancer control outcomes for HIFU hemiablation are encouraging, but the data are less mature. French investigators published on a series of 111 patients prospectively followed after HIFU hemiablation and reported a radical treatment-free survival rate of 89% at 2 years.3

“While HIFU can be used to treat men with high-volume, low-risk disease, it is not meant for only that setting.”

CARY ROBERTSON, MD

Data from the French study of hemiablation HIFU support a benefit of the technique for minimizing morbidity with prostate cancer treatment. At 12 months after HIFU, continence was preserved in 97% of men and erectile function in 78%.

Safety data from studies of whole-gland HIFU show that loss of erectile function occurs at a rate of about 50%.4 While erectile function may be temporary, there is a protracted course until recovery, similar to radical prostatectomy, Dr. Robertson said.

The incidence of incontinence after whole-gland HIFU is 2% to 3%, and to avoid post-HIFU bladder outlet obstruction, it is recommended that men undergo a TURP procedure before or at the time of HIFU.4 In addition, urinary obstruction secondary to urethral strictures has been reported in 2% to 5% of men having whole-gland HIFU.4

Disclosure: Dr. Robertson is a consultant for EDAP TMS, Inc.

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issues if they choose radical prostatectomy. If they choose whole-gland HIFU, they pay later in life with the possible need for retreatment and other issues, such as stricture,” Dr. Castle explained.

“Whereas hemiablation/focal HIFU might be considered for a patient who is a candidate for active surveillance because he has low-risk disease, determining when these men should be treated is the real target for their care, and I think we are doing a better job with that now than we were a decade ago.”

“I would argue that there are no treatment-related side effects associated with active surveillance.” ERIK P. CASTLE, MD

Whole-gland HIFU

Dr. Castle said that because whole-gland HIFU is intended to be an extirpative procedure, it should be compared against radical prostatectomy. Therefore, it is inappropriate to evaluate the success of whole-gland HIFU using radiation criteria. More relevant are reports showing that whole-gland HIFU left vital tissue at ventral, lateral, and dorsal aspects of the prostate and residual cancer in a significant proportion of patients. 1-3

Complication rates after whole-gland HIFU were also high. Impotence occurred in up to 70% of men, and prolonged retention, stress urinary incontinence, and urethral/prostate stricture were reported at rates in the range of 22% to 30%.4,5

Dr. Castle acknowledged that those data are from earlier patient series and that results are improved considering more recent studies of whole-gland HIFU. The outcomes, however, are not good enough to support its use over radical prostatectomy, he said.

Dr. Castle cited a study reported by Ganz et al that included more than 500 patients with up to 14 years of follow-up.6 Using Phoenix criteria, the analyses showed biochemical disease-free survival rates of 81% at 5 years and 61% at 10 years. Overall, 75 patients (13.9%) died and 18 patients (3.3%) died of prostate cancer. The salvage treatment rate was 18%, and the rate of bladder outlet obstruction was almost 30%.

Dr. Castle also noted that whole-gland HIFU is restricted to men with a low prostate volume (<40 cc). Because of that limitation, up to 50% of men have had a neoadjuvant procedure (ie, androgen deprivation to shrink the gland or debulking with transurethral resection of the prostate) that introduces additional risks. In addition, because of the risk for urinary retention, it is often recommended that a bladder outlet procedure be performed with whole-gland HIFU.

Hemiablation/focal HIFU

Reported outcomes for hemiablation/focal HIFU show that complication rates are lower than for whole-gland HIFU.6,7 However, problems with potency, incontinence, and urinary retention still exist, and the rate of retreatment is higher compared with whole-gland HIFU.

“Advocates for hemiablution/focal HIFU say that the ability to retreat is one of its advantages, but as a bottom line, I would argue that there are no treatment-related side effects associated with active surveillance,” Dr. Castle said.

He acknowledged that men choosing active surveillance will be having biopsies, which also exposes them to potential side effects. In addition, the knowledge that they have untreated cancer can create a psychological burden for some men on active surveillance.

“In my mind, however, the bottom line is that you either treat cancer or you don’t,” Dr. Castle said. “Hemiablution/ focal HIFU may be positioned as a compromise that hopefully causes fewer side effects than other interventions and provides some reassurance for patients who think they would feel better having some treatment. But I think we need to do a better job giving patients realistic expectations based on our learning that we don’t need to treat everybody.”

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BLADDER CANCER

Is stand-alone white light cystoscopy a thing of the past?

Cheryl Guttman Krader, UT Contributing Editor

Based on recent developments with blue light cystoscopy, the use of white light cystoscopy alone is now considered suboptimal as a diagnostic tool.

Badrinath Konety, MD, MBA

While white light cystoscopy (WLC) has been the standard for initial diagnosis and surveillance of nonmuscle-invasive bladder cancer, its use alone can now be considered suboptimal based on recent developments with blue light cystoscopy (BLC), according to Badrinath Konety, MD, MBA.

“White light cystoscopy misses many tumors, both papillary lesions and carcinoma in situ (CIS), and that can lead to higher rates of recurrence and progression,” said Dr. Konety, professor and chair of the department of urology, University of Minnesota, Minneapolis.

“Those issues are now remediable to some extent with BLC using hexaminolevulinate HCl (HAL [Cysview]) because this technique detects more tumors and allows for more complete resection.”

Benefits of BLC

Fluorescent cystoscopy performed with blue light following intravesical instillation of a photoactive porphyrin provides better diagnostic accuracy by improving tumor visualization. Photoactive porphyrins selectively accumulate in neoplastic cells and lead to the accumulation of protoporphyrin IX that fluoresces with a red appearance when illuminated with blue light.

As initially performed using 5-aminolevulinic acid, fluorescent cystoscopy demonstrated better diagnostic accuracy than WLC, but was associated with aller-

Although blue light cystoscopy (BLC) has demonstrated diagnostic value in bladder cancer, in detecting cancerous lesions, more evidence is needed before it becomes the standard of care for diagnosis and treatment and relegates white light cystoscopy (WLC) obsolete, according to Michael Risk, MD, PhD.

“Our specialty can be proud of the fact that there are at least 17 randomized controlled trials comparing BLC and WLC, and overall the data show that compared with WLC, BLC has greater sensitivity for tumor detection and that its use can reduce the risk of recurrence,” said Dr. Risk, assistant professor of urology, University of Minnesota, Minneapolis.

“However, the studies conducted so far have some concerning limitations, and it would be preferable to have evidence that BLC has a positive impact on more clinically meaningful endpoints. What is needed are more well-constructed randomized trials that ideally assess outcomes of progression, need for cystectomy, and survival.”

Findings from several systematic reviews show that BLC decreases the risk of recurrence compared with WLC. The most recent study included nine trials that used hexaminolevulinate HCl (HAL [Cysview]) and six trials in which BLC was done with 5-aminolevulinic acid (not available in the United States).1

Dr. Risk said that the analyses in this paper by Chou...
White Light Cystoscopy misses many tumors, both papillary lesions and carcinoma in situ, and that can lead to higher rates of recurrence and progression. Those issues are now remediable to some extent with blue light cystoscopy.

Badrinath Konety, MD

Importantly, findings from an unpublished analysis of registry data undertaken by Dr. Konety and colleagues show that detection rates along with false-negative and false-positive rates for rigid BLC procedures performed in the community are consistent with those reported in the clinical trials.

“These findings support the idea that BLC is easy to deploy and that urologists can expect a short learning curve,” Dr. Konety said.

Narrow-band imaging (NBI) also aims to improve detection of bladder cancer and is both easy to perform and widely used. However, results from comparative studies do not show a consistent benefit for achieving improved tumor detection using narrow-band imaging versus white light cystoscopy, Dr. Konety noted.

“When results of a very large randomized trial comparing 12-month recurrence rates following transurethral resection of bladder tumor using NBI or white light indicate that NBI did not lead to a more complete transurethral resection,” he said, referring to a European Urology study published in 2016.\(^5\)

“Hence, it is unclear if NBI truly improves upon WLC,” Dr. Konety added.\(^6\)

Disclosures: Dr. Konety is a clinical trial investigator for Photocure, Genomic Health, Genentech, Bristol-Myers Squibb.
The meta-analysis found no difference between BLC and WLC. Only three trials included in the 2017 analysis analyzed mortality as an endpoint, and systematic review found no difference between BLC and WLC for that outcome measure. BLC also had no overall effect on progression, according to an analysis that included data from nine trials reporting progression data.

Although information demonstrating that BLC has a positive impact on risk of progression or mortality is desirable, Dr. Risk said that recurrence may be considered as a valid outcome measure recognizing that use of postoperative intravesical mitomycin C in the treatment of non-muscle-invasive bladder cancer is supported by its benefit for reducing recurrence. Dr. Risk proposed, however, that it would be beneficial to also have more data to establish that BLC provides a cost benefit.

“The studies conducted so far have some concerning limitations, and it would be preferable to have evidence that BLC has a positive impact on more clinically meaningful endpoints.”

MICHAEL RISK, MD, PhD

“There are published economic data supporting BLC, but those analyses also suffer from weaknesses because many are based on modeling and used effect estimates from individual studies that showed a benefit of BLC, which considering the latest systematic review, might be overestimates,” Dr. Risk said.

“More economic studies are needed, but when interpreting the data, we need to recognize that cost benefit may vary by country and even between institutions within the same country,” he said.

FKD Therapies, and Spectrum Pharmaceuticals and a consultant to NxThera and MDx Health.

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KIDNEY CANCER

Renal mass biopsy: Is it necessary for localized tumors?

Andrew D. Bowser, UT Correspondent

**POINT.** Biopsy decreases overall uncertainty, is safe, fairly accurate, relatively inexpensive, and improves shared decision-making with patients.

E. Jason Abel, MD

**COUNTERPOINT.** Renal mass biopsy provides actionable information, but only under specific circumstances—yet it is an increasingly necessary part of the nuanced patient discussion.

Robert G. Uzzo, MD

The role of renal mass biopsy may be best viewed in the context of modern treatments for cancer, which have moved away from a “one-size-fits-all” model toward precision treatments that are based on patients and their individual tumor characteristics, according to E. Jason Abel, MD.

“The simplest way to implement precision treatment for patients with small renal masses is to use biopsy up front to improve decision-making,” said Dr. Abel, associate professor of urologic oncology at the University of Wisconsin School of Medicine and Public Health, Madison.

Patients diagnosed with small renal masses have multiple options for treatment, including surgery, thermal ablation, and active surveillance. Having more information up front can help patients to make an informed decision, he noted.

Increasingly, members of the urology community believe that choosing the best treatment solely on radiographic information is an “under-informed” approach for many patients, Dr. Abel added.

**Biopsies safe, inexpensive**

Renal mass biopsy is generally safe, relatively inexpensive, and should be discussed with most patients, as it is a tool that can provide information to guide treatment decision-making.

“If you use a biopsy to distinguish between ‘cancer’ and ‘not cancer,’ you’ve still improved your overall

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RENAL BIOPSY **COUNTERPOINT** continues on page S15
outcomes by deferring active treatments in patients with benign tumors,” Dr. Abel said.

At minimum, biopsy allows identification of benign renal tumors, and nephrectomy can be avoided in many patients who will be spared the impact of poor renal function later in life.

However, not all patients need to have a biopsy before treatment, and in fact, approximately 30% to 40% of the renal mass patients in Dr. Abel’s practice are currently treated surgically without a biopsy up front.

Even so, biopsies should be discussed with most patients, according to Dr. Abel, who views biopsy as a safe and relatively inexpensive tool that can provide information to guide treatment choices.

In fact, perhaps the most compelling reason to offer biopsy is not even scientific or medical: Biopsy provides more information and thereby improves the informed consent process. “Regardless of the subsequent treatment, biopsy empowers physicians and patients to make better decisions,” Dr. Abel said.

“Biopsy is safe, it’s relatively inexpensive, and it provides more information, and I think we really need to evolve as a field to consider this as an approach to shared decision-making.”

E. JASON ABEL, MD

What the guidelines say
Expert thinking on renal mass biopsy has evolved considerably in recent years, Dr. Abel acknowledged.

A current recommendation from the AUA states that renal mass biopsy is not required for young or healthy patients unwilling to accept the uncertainties associated with the procedure, and older or frail patients who will be managed conservatively regardless of biopsy findings. That recommendation, based on expert opinion, appears in the AUA's 2017 guideline on renal mass and localized cancer.

In the context of that recommendation, it’s important to consider that, per the American Cancer Society, the mean age of renal cell cancer diagnosis is 64 years, so a typical patient presenting with a small renal mass is not necessarily a healthy young patient, nor an older, sicker patient, Dr. Abel noted.

Instead, that “typical patient” may provide an illustration of the benefits of renal mass biopsy.

Dr. Abel described a hypothetical patient, a 64-year-old obese man who presents to the clinic with a centrally located, 2-cm endophytic renal mass.

“We know from population-based studies that radical nephrectomy is still the most common treatment for small central renal tumors in this situation,” he said. “However, we also know that statistically, a small kidney cancer is very unlikely to cause this gentleman’s death.”

For that patient, based only on radiographic information, the clinician may be limited to discussing data that, depending on tumor size, 20% to 30% of clinically localized renal masses may be benign.

The biopsy would provide extra information to guide decision-making.

If the biopsy yields benign pathologic findings, the patient may be appropriately counseled toward surveillance. Conversely, if the patient is considering active surveillance and a biopsy shows high-grade cancer, that information could help drive the decision for surgery, Dr. Abel said.

“I think we really need to move away from the idea that we know what's best for each individual patient after just looking at imaging,” Dr. Abel said. “Biopsy is safe, it’s relatively inexpensive, and it provides more information, and I think we really need to evolve as a field to consider this as an approach to shared decision-making.”

Risks and benefits
To understand the evolving role of biopsy and treatment of small renal masses, it may be helpful to draw an analogy to low-risk prostate cancer treatment, which has evolved significantly in the last few decades, according to Dr. Abel.

The 10-year estimated cancer-related mortality in low-risk prostate cancer is similar to what has been reported for small renal cell carcinomas, and the median age of diagnosis is 66 years for prostate cancer versus 64 years in renal cell cancer, according to recent American Cancer Society estimates.

“Just like we learned in low-risk prostate cancer, many patients will die from causes other than kidney cancer, especially patients who are older and more comorbid,” Dr. Abel said. “I think we should focus on treating patients who are most likely to benefit from treatment, and for the vast majority of patients, there’s really no reason to rush into treatment.”

Bleeding and tract seeding are two objections to increased use of renal mass biopsy that have been raised. However, despite being the most significant concern, the risk of significant bleeding after biopsy is less than 1% in
“Biopsy up front allows us to focus our surveillance on a targeted population; namely, patients who have cancer,” Dr. Abel concluded. “Biopsy spares one in four patients the anxiety of having a cancer diagnosis. It spares one in four patients the time and cost of many years of radiographic follow-up for a benign tumor.

“Conversely, if you identify a rare, aggressive tumor, the treatment plan is going to be adjusted up front. So there are definitely benefits to identifying cancer before committing to years of active surveillance.”

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physician won’t accept the uncertainty or test performance characteristics), biopsy can be avoided.

AUA guidelines characterize the complication risk of renal mass biopsy as low. Recent data suggest the most common complications are renal hematoma (4.9%), clinically significant pain (1.2%), gross hematuria (1.0%), and pneumothorax and hemorrhage requiring transfusion in less than 1% of cases.²

Although false negatives and false positives are a potential concern, in practice, core renal mass biopsy has excellent sensitivity and specificity (97.5% and 96.2%, respectively) and a positive predictive value that approaches 100%, studies suggest.

“I don’t think that renal mass biopsy is always necessary, but I think it’s increasingly necessary when having a complex and nuanced discussion with a patient.”

ROBERT G. UZZO, MD

Perhaps the greater concern is the relatively high non-diagnostic rate of 14%, which patients should be aware of, according to Dr. Uzzo. A biopsy can be non-diagnostic, for example, when renal parenchyma or connective tissue is sampled or if the tumor is in a challenging location.

“The upper pole, particularly anterior and medial, can be very tricky,” Dr. Uzzo said.

In some cases, tumors can be histologically heterogeneous, which can cause misleading biopsy results. The non-diagnostic rate can be reduced substantially with repeat biopsy; nevertheless, patients who are young and healthy might not accept the potential uncertainty of a non-diagnostic or false-negative result and instead elect for an intervention, Dr. Uzzo said.

That’s one key reason why current guidelines recommend against renal mass biopsy for patients “unwilling to accept the uncertainties” associated with the procedure, particularly young and healthy patients with decades of future life expectancy at risk. Likewise, the guidelines advise against biopsy in older or frail patients who will be managed conservatively regardless of renal mass biopsy findings.

Not suitable for AS, surgical patients
Active surveillance is a related area of controversy. For patients with small renal masses who are placed on an initial course of active surveillance—who are often elderly or frail—the results of biopsy rarely change the management approach, Dr. Uzzo and colleagues said in a recent editorial.³

Thus, patients whose risk calculations lead them and their physician to an initial course of active surveillance may be able to avoid initial renal mass biopsy as “unnecessary,” unless perhaps the patient has significant anxiety regarding surveillance or the tumor exhibits rapid growth kinetics, the authors said.

Whether a biopsy is warranted in surgical patients who are young and fit is likewise questionable, given the inherent limitations and risk of biopsy, the authors added. Thus, they recommended “surgery without histologic confirmation” be maintained as the standard of care in this setting.

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high-grade cancer when in fact the tumor is low grade; in contrast, the concordance between low-grade biopsy and low-grade tumor is only on the order of 60% to 70%, according to Dr. Uzzo.

“That might be a cause of concern because you might say, ‘I got a biopsy and it was cancer, but it was low-risk, low-grade, so I’ll watch it,’ when in fact, the grade is the least reliable of the metrics on the biopsy,” Dr. Uzzo said.

The bottom line is that the risks, benefits, and limitations of renal mass biopsy must be considered on the whole for each patient to determine whether it’s going to yield actionable information.

“Most of the time, renal mass biopsy provides informative and actionable information with which to make a more informed clinical choice. I don’t think that it’s always necessary, but I think it’s increasingly necessary when having a complex and nuanced discussion with a patient,” Dr. Uzzo said. UFT

REFERENCES

“The availability of good evidence on more clinically meaningful endpoints could potentially change whether BLC should become the new standard of care,” Dr. Risk said. UFT

REFERENCES
Xtandi® (enzalutamide) capsules for oral use

**BRIEF SUMMARY OF PRESCRIBING INFORMATION**

The following is a brief summary. Please see the package insert for full prescribing information.

**INDICATIONS AND USAGE**

Xtandi is indicated for the treatment of patients with metastatic castration-resistant prostate cancer (CRPC).

**CONTRAINDICATIONS**

Pregnancy

Xtandi can cause fetal harm and potential loss of pregnancy.

**WARNINGS AND PRECAUTIONS**

Seizure

Seizure occurred in 0.5% of patients receiving Xtandi in clinical studies. In these trials patients with predisposing factors for seizure were generally excluded. Seizure occurred from 31 to 90 days after initiation of Xtandi. Patients experiencing seizures were permanently discontinued from therapy and all seizure events resolved.

In a single-arm trial designed to assess the risk of seizure in patients with predisposing factors for seizure, 8 of 386 (2.2%) XT and bicalutamide-treated patients experienced a seizure. Three of the 8 patients experienced a second seizure during treatment with XT after their first seizure resolved. It is unknown whether anti-epileptic medications will prevent seizures with XT. Patients in the study had one or more of the following pre-disposing factors: the use of medications that may lower the seizure threshold (≤ 50%), history of traumatic brain or head injury (≤ 25%), history of cerebrovascular accident or transient ischemic attack (≤ 24%), and Alzheimer’s disease, meningoencephalitis, or leptomeningeal disease from prostate cancer, unexplained loss of consciousness within the last 12 months, a history of seizure, presence of a space occupying lesion of the brain, history of arteriovenous malformation, or brain injury in adolescence (all ≤ 5%). Approximately 17% of patients had one or more risk factor.

Advise patients of the risk of developing a seizure while receiving XT and of engaging in any activity where sudden loss of consciousness could cause serious harm to themselves or others.

Permanently discontinue XT in patients who develop a seizure while taking XT.

**Posterior Reversible Encephalopathy Syndrome (PRES)**

There have been reports of posterior reversible encephalopathy syndrome (PRES) in patients receiving XT. PRES is a neurological disorder which can present with a triad of symptoms including altered consciousness, headache, lethargy, confusion, blindness, and other visual and neurological disturbances, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI). Discontinue XT in patients who develop PRES.

**ADVERSE REACTIONS**

Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Three randomized clinical trials enrolled patients with metastatic prostate cancer that has progressed on androgen deprivation therapy (GnRH therapy or bilateral orchectomy), a disease setting that is also defined as metastatic CRPC.

**Study 1: XT ANDI versus Placebo in Metastatic CRPC Following Chemotherapy**

Study 1 enrolled 1199 patients with metastatic CRPC who had previously received docetaxel. The median duration of treatment was 8.3 months with XT ANDI and 3.0 months with placebo. During the trial, 48% of patients on the XT ANDI arm and 4% of patients on the placebo arm received glucocorticoids.

Grade 3 and higher adverse reactions were reported among 47% of XT ANDI-treated patients and 53% of placebo-treated patients. Discontinuations due to adverse events were reported for 16% of XT ANDI-treated patients and 18% of placebo-treated patients. The most common adverse reaction leading to treatment discontinuation was seizure, which occurred in 0.9% of the XT ANDI-treated patients compared to none (0%) of the placebo-treated patients. Table 1 shows adverse reactions reported in Study 1 that occurred at ≥ 2% higher frequency in the XT ANDI arm compared to the placebo arm.

**Study 2: XT ANDI versus Placebo in Chemotherapy-Naive Metastatic CRPC**

Study 2 enrolled 1717 patients with metastatic CRPC who had not received prior cytotoxic chemotherapy, of whom 1715 received at least one dose of study drug. The median duration of treatment was 17.5 months with XT ANDI and 4.6 months with placebo. Grade 3-4 adverse reactions were reported in 44% of XT ANDI-treated patients and 37% of placebo-treated patients. Discontinuations due to adverse events were reported for 6% of XT ANDI-treated patients and 6% of placebo-treated patients. The most common adverse reaction leading to treatment discontinuation was fatigue/asthenia, which occurred in 1% of patients on each treatment arm. Table 2 includes adverse reactions reported in Study 2 that occurred at ≥ 2% higher frequency in the XT ANDI arm compared to the placebo arm.

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>XT ANDI (%)</th>
<th>Placebo (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections And Infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper Respiratory Tract Infection</td>
<td>10.9</td>
<td>6.5</td>
</tr>
<tr>
<td>Lower Respiratory Tract And Lung Infection</td>
<td>8.5</td>
<td>4.8</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>8.8</td>
<td>6.0</td>
</tr>
<tr>
<td>Anxiety</td>
<td>6.5</td>
<td>4.0</td>
</tr>
<tr>
<td>Renal And Urinary Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematuria</td>
<td>6.9</td>
<td>4.5</td>
</tr>
<tr>
<td>Polkauria</td>
<td>4.8</td>
<td>2.5</td>
</tr>
<tr>
<td>Injury, Poisoning And Procedural Complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fall</td>
<td>4.8</td>
<td>1.3</td>
</tr>
<tr>
<td>Non-pathologic Fractures</td>
<td>4.0</td>
<td>0.8</td>
</tr>
<tr>
<td>Skin And Subcutaneous Tissue Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>3.8</td>
<td>1.3</td>
</tr>
<tr>
<td>Dry Skin</td>
<td>3.5</td>
<td>1.3</td>
</tr>
<tr>
<td>Respiratory Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>3.3</td>
<td>1.3</td>
</tr>
</tbody>
</table>

**Table 2. Adverse Reactions in Study 2**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>XT ANDI (%)</th>
<th>Placebo (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections And Infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper Respiratory Tract Infection</td>
<td>16.4</td>
<td>10.5</td>
</tr>
<tr>
<td>Lower Respiratory Tract And Lung Infection</td>
<td>7.9</td>
<td>4.7</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>8.2</td>
<td>5.7</td>
</tr>
<tr>
<td>Renal And Urinary Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematuria</td>
<td>8.8</td>
<td>5.8</td>
</tr>
<tr>
<td>Injury, Poisoning And Procedural Complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fall</td>
<td>12.7</td>
<td>5.3</td>
</tr>
<tr>
<td>Non-pathologic Fractures</td>
<td>8.8</td>
<td>1.3</td>
</tr>
<tr>
<td>Metabolism And Nutrition Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unintended Appetite</td>
<td>18.9</td>
<td>16.4</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight Decreased</td>
<td>12.4</td>
<td>8.5</td>
</tr>
</tbody>
</table>

**Table 3. XT ANDI versus Bicalutamide in Chemotherapy-Naive Metastatic CRPC**

Study 3 enrolled 375 patients with metastatic CRPC who had not received prior cytotoxic chemotherapy, of whom 372 received at least one dose of study drug. The median duration of treatment was 11.8 months with XT ANDI.
and 5.8 months with bicalutamide. Discontinuations with an adverse event as the primary reason were reported for 7.6% of XTANDI-treated patients and 8.3% of bicalutamide-treated patients. Common adverse reactions leading to treatment discontinuation were back pain and pathological fracture, which occurred in 2.8% of XTANDI-treated and 3.4% of bicalutamide-treated patients, respectively. Table 3 shows overall and common adverse reactions (≥10%) in XTANDI-treated patients.

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>XTANDI</th>
<th>Bicalutamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1-4 (%)</td>
<td>Grade 3-4 (%)</td>
<td></td>
</tr>
<tr>
<td>Back Pain</td>
<td>19.1</td>
<td>2.7</td>
</tr>
<tr>
<td>Musculoskeletal Pain</td>
<td>16.4</td>
<td>1.1</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>14.8</td>
<td>0.0</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>14.2</td>
<td>7.1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>11.5</td>
<td>0.0</td>
</tr>
<tr>
<td>Infectious And Infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper Respiratory Tract Infection</td>
<td>12.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Overall</td>
<td>94.0</td>
<td>38.8</td>
</tr>
</tbody>
</table>

### Overall General Disorders
- Asthenic Conditions: 31.7 (Grade 1), 1.6 (Grade 2), 22.8 (Grade 3), 1.1 (Grade 4)
- Musculoskeletal And Connective Tissue Disorders:
  - Back Pain: 19.1 (Grade 1), 2.7 (Grade 2), 18.0 (Grade 3), 1.6 (Grade 4)
  - Musculoskeletal Pain: 16.4 (Grade 1), 1.1 (Grade 2), 14.3 (Grade 3), 0.5 (Grade 4)

### General Disorders
- Asthenic Conditions: 31.7 (Grade 1), 1.6 (Grade 2), 22.8 (Grade 3), 1.1 (Grade 4)
- Musculoskeletal And Connective Tissue Disorders:
  - Back Pain: 19.1 (Grade 1), 2.7 (Grade 2), 18.0 (Grade 3), 1.6 (Grade 4)
  - Musculoskeletal Pain: 16.4 (Grade 1), 1.1 (Grade 2), 14.3 (Grade 3), 0.5 (Grade 4)

### Vascular Disorders
- Hypertension: 14.8 (Grade 1), 0.0 (Grade 2), 11.0 (Grade 3), 0.0 (Grade 4)
- Gastrointestinal Disorders
  - Nausea: 14.2 (Grade 1), 0.0 (Grade 2), 17.5 (Grade 3), 0.0 (Grade 4)
  - Constipation: 12.8 (Grade 1), 1.1 (Grade 2), 13.2 (Grade 3), 0.5 (Grade 4)
  - Diarrhea: 11.5 (Grade 1), 0.0 (Grade 2), 9.0 (Grade 3), 1.1 (Grade 4)

### Infections And Infestations
- Upper Respiratory Tract Infection: 12.0 (Grade 1), 0.0 (Grade 2), 6.3 (Grade 3), 0.5 (Grade 4)
- Investigational
  - Weight Loss: 10.9 (Grade 1), 0.5 (Grade 2), 7.9 (Grade 3), 0.5 (Grade 4)

### Laboratory Abnormalities
In the two randomized placebo-controlled clinical trials, Grade 1-4 neutropenia occurred in 15% of patients treated with XTANDI (1% Grade 3-4) and in 6% of patients treated with placebo (0.5% Grade 3-4). The incidence of Grade 1-4 thrombocytopenia was balanced between arms. No patients experienced hypersensitivity (tongue edema, lip edema, and pharyngeal edema).

### Gastrointestinal Disorders
- vomiting
- Neurological Disorders: posterior reversible encephalopathy syndrome (PRES)

### Drugs that Inhibit CYP2C8
- Co-administration of a strong CYP2C8 inhibitor (gemfibrozil) increased the area under the plasma concentration-time curve (AUC) of enzalutamide plus N-desmethyl enzalutamide by 2.2-fold. Co-administration of XTANDI with strong CYP2C8 inhibitors should be avoided if possible. If co-administration of XTANDI with a strong CYP2C8 inhibitor cannot be avoided, reduce the dose of XTANDI.
- Drugs that Induce CYP3A4
- Co-administration of a moderate CYP3A4 inducer (rifampin) decreased the AUC of enzalutamide plus N-desmethyl enzalutamide by 57%. Co-administration of strong CYP3A4 inducers (e.g., carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, and ritonavir) with XTANDI should be avoided if possible. If co-administration of a strong CYP3A4 inducer with XTANDI cannot be avoided, increase the dose of XTANDI.

### Effect of XTANDI on Drug Metabolizing Enzymes
Enzalutamide is a strong CYP3A4 inducer and a moderate CYP2C9 and CYP2C19 inducer in humans. At steady state, XTANDI reduced the plasma exposure to midazolam (CYP3A4 substrate), azathioprine (CYP2C9 substrate), and omeprazole (CYP2C19 substrate). Concomitant use of XTANDI with narrow therapeutic index drugs that are metabolized by CYP3A4, CYP2C9, cyclosporine, diltiazem, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus and tacrolimus, CYP2D6 (e.g., phenytoin, warfarin) and CYP2C19 (e.g., S-mephénytoïn) should be avoided, as enzalutamide may decrease their exposure. If co-administration with warfarin cannot be avoided, conduct additional INR monitoring.

### Use in Specific Populations

#### Pregnancy

Risk Summary
- XTANDI is contraindicated for use in pregnant women because the drug can cause fetal harm and potential loss of pregnancy. XTANDI is not indicated for use in females.
- There are no human data on the use of XTANDI in pregnant women.
- In animal reproduction studies, oral administration of enzalutamide in pregnant mice during organogenesis caused adverse developmental effects at doses lower than the maximum recommended human dose.

Animal Data
- In an embryo-fetal development toxicity study in mice, enzalutamide caused developmental toxicity when administered at oral doses of 10 or 30 mg/kg/day throughout the period of organogenesis (gestational days 6-15). Findings included embryo-fetal lethality (increased post-implantation loss and resorptions) and decreased anogenital distance at ≥ 10 mg/kg/day, and cleft palate and absent palatine bone at 30 mg/kg/day. Doses of 10 or 30 mg/kg/day resulted in systemic exposures (AUC) approximately 0.4, 0.4 and 1.1 times, respectively, the exposures in patients. Enzalutamide did not cause development toxicity in rabbits when administered throughout the period of organogenesis (gestational days 6-18) at dose levels up to 10 mg/kg/day (approximately 0.4 times the exposures in patients based on AUC).

#### Lactation

Risk Summary
- XTANDI is not indicated for use in females. There is no information available on the presence of XTANDI in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production.
- Enzalutamide and/or its metabolites were present in milk of lactating rats.

#### Females and Males of Reproductive Potential
Contraception

Males
Based on findings in animal reproduction studies, advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the final dose of XTANDI.

Infertility
Based on animal studies, XTANDI may impair fertility in males of reproductive potential.

#### Pediatric Use

Safety and effectiveness of XTANDI in pediatric patients have not been established.

### Geriatric Use
Of 1671 patients who received XTANDI in the two randomized placebo-controlled clinical trials, 75% were ≥65 years old, while 31% were ≥75 years old. No overall differences in safety or effectiveness were observed between these patients and younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

### Patients with Renal Impairment
A dedicated renal impairment trial for XTANDI has not been conducted. Based on the population pharmacokinetic analysis using data from clinical trials in patients with mild, moderate, and severe renal impairment, no significant difference in enzalutamide clearance was observed in patients with pre-existing mild to moderate renal impairment (30 mL/min ≤ creatinine clearance [CrCl] ≤ 89 mL/min) compared to patients with baseline normal renal function (CrCl ≥ 90 mL/min). No initial dosage adjustment is necessary for patients with mild to moderate renal impairment. Severe renal impairment (CrCl < 30 mL/min) and end-stage renal disease have not been assessed.

### Patients with Hepatic Impairment
Dedicated hepatic impairment trials compared the composite systemic exposure of enzalutamide plus N-desmethyl enzalutamide in volunteers with baseline mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, or C, respectively) versus healthy controls with normal hepatic function. The composite AUC of enzalutamide plus N-desmethyl enzalutamide was similar in volunteers with mild, moderate, or severe baseline hepatic impairment compared to volunteers with normal hepatic function. No initial dosage adjustment is necessary for patients with baseline mild, moderate, or severe hepatic impairment.

### OVERDOSAGE
In the event of an overdose, stop treatment with XTANDI and initiate general supportive measures taking into consideration the half-life of 5.8 days. In a dose escalation study, no seizures were reported at 360 mg daily, whereas 3 seizures were reported, 1 each at 360 mg, 480 mg, and 600 mg daily. Patients may be at increased risk of seizure following an overdose.

### NONCLINICAL TOXICOLOGY

#### Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term animal studies have not been conducted to evaluate the carcinogenic potential of enzalutamide.

Enzalutamide did not induce mutations in the bacterial reverse mutation (Ames) assay and was not genotoxic in either the in vitro mouse lymphoma thymidine kinase (TK) gene mutation assay or the in vivo mouse micronucleus assay.

Based on nonclinical findings in repeat-dose toxicity studies, which were consistent with the pharmacological activity of enzalutamide, male fertility may be impaired by treatment with XTANDI. In a 26-week study in rats, the atrophy of the prostate and seminal vesicles was observed at ≥ 30 mg/kg/day (equal to the human exposure based on AUC), in 4-, 13-, and 53-week studies in dogs, hypospermatogenesis and atrophy of the prostate and epididymides were observed at ≥ 4 mg/kg/day (0.3 times the human exposure).

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Marketed by: Astellas Pharma US, Inc., Northbrook, IL 60062
Pfizer Inc., New York, NY 10017
Revised: July 2017
16K089-XTA-WPI
Rx Only
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XTANDI® is a registered trademark of Astellas Pharma Inc.
Indication and Important Safety Information

Indication
XTANDI (enzalutamide) capsules is indicated for the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC).

Important Safety Information

Contraindications
XTANDI is not indicated for women. XTANDI can cause fetal harm and potential loss of pregnancy.

Warnings and Precautions

Seizure occurred in 0.5% of patients receiving XTANDI in clinical studies. In a study of patients with predisposing factors, seizures were reported in 2.2% of patients. See section 5.1 of the Prescribing Information for the list of predisposing factors. It is unknown whether anti-epileptic medications will prevent seizures with XTANDI. Permanently discontinue XTANDI in patients who develop a seizure during treatment.

Posterior Reversible Encephalopathy Syndrome (PRES)
In post approval use, there have been reports of PRES in patients receiving XTANDI. PRES is a neurological disorder which can present with rapidly evolving symptoms including seizure, headache, lethargy, confusion, blindness, and other visual and neurological disturbances, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably MRI. Discontinue XTANDI in patients who develop PRES.

Adverse Reactions
The most common adverse reactions (≥ 10%) that occurred more commonly (≥ 2% over placebo) in the XTANDI patients from the two placebo-controlled clinical trials were asthenia/fatigue, back pain, decreased appetite, constipation, arthralgia, diarrhea, hot flush, upper respiratory tract infection, peripheral edema, dyspnea, musculoskeletal pain, weight decreased, headache, hypertension, and dizziness/vertigo. In the bicalutamide-controlled study of chemotherapy-naive patients, the most common adverse reactions (≥ 10%) reported in XTANDI patients were asthenia/fatigue, back pain, musculoskeletal pain, hot flush, hypertension, nausea, constipation, upper respiratory tract infection, diarrhea, and weight loss.

In the placebo-controlled study of patients taking XTANDI who previously received docetaxel, Grade 3 and higher adverse reactions were reported among 47% of XTANDI patients and 53% of placebo patients. Discontinuations due to adverse events were reported for 16% of XTANDI patients and 18% of placebo patients. In the placebo-controlled study of chemotherapy-naive patients, Grade 3-4 adverse reactions were reported in 44% of XTANDI patients and 37% of placebo patients. Discontinuations due to adverse events were reported for 6% of both study groups. In the bicalutamide-controlled study of chemotherapy-naive patients, Grade 3-4 adverse reactions were reported in 38.8% of XTANDI patients and 37.6% of bicalutamide patients. Discontinuations due to adverse events were reported for 7.6% of XTANDI patients and 6.3% of bicalutamide patients.

Lab Abnormalities: In the two placebo-controlled trials, Grade 1-4 neutropenia occurred in 15% of XTANDI patients (1% Grade 3-4) and 6% of placebo patients (0.5% Grade 3-4). Grade 1-4 thrombocytopenia occurred in 6% of XTANDI patients (0.3% Grade 3-4) and 5% of placebo patients (0.5% Grade 3-4). Grade 1-4 elevations in ALT occurred in 10% of XTANDI patients (0.2% Grade 3-4) and 16% of placebo patients (0.2% Grade 3-4). Grade 1-4 elevations in bilirubin occurred in 3% of XTANDI patients (0.1% Grade 3-4) and 2% of placebo patients (no Grade 3-4).

Infections: In the study of patients taking XTANDI who previously received docetaxel, 1% of XTANDI patients compared to 0.3% of placebo patients died from infections or sepsis. In the study of chemotherapy-naive patients, 1 patient in each treatment group (0.1%) had an infection resulting in death.

Falls (including fall-related injuries) occurred in 9% of XTANDI patients and 4% of placebo patients in the two placebo-controlled trials. Falls were not associated with loss of consciousness or seizure. Fall-related injuries were more severe in XTANDI patients, and included non-pathologic fractures, joint injuries, and hematomas.

Hypertension occurred in 11% of XTANDI patients and 4% of placebo patients in the two placebo-controlled trials. No patients experienced hypertensive crisis. Medical history of hypertension was balanced between arms. Hypertension led to study discontinuation in < 1% of patients in each arm.

Drug Interactions

Effect of Other Drugs on XTANDI Avoid strong CYP2C8 inhibitors, as they can increase the plasma exposure to XTANDI. If co-administration is necessary, reduce the dose of XTANDI.

Avoid strong CYP3A4 inducers as they can decrease the plasma exposure to XTANDI. If co-administration is necessary, increase the dose of XTANDI.

Effect of XTANDI on Other Drugs Avoid CYP3A4, CYP2C9, and CYP2C19 substrates with a narrow therapeutic index, as XTANDI may decrease the plasma exposures of these drugs. If XTANDI is co-administered with warfarin (CYP2C9 substrate), conduct additional INR monitoring.

Please see adjacent pages for Brief Summary of Full Prescribing Information.

References:
FDA approved for metastatic CRPC since 2012

Supported by 3 randomized, controlled trials

**AFFIRM TRIAL**
1199 patients with metastatic CRPC who were previously on docetaxel therapy were randomized to XTANDI + GnRH therapy* (n = 800) or placebo + GnRH therapy* (n = 399).1

**PREVAIL TRIAL**
1717 patients with metastatic CRPC who were asymptomatic or mildly symptomatic were randomized to XTANDI + GnRH therapy* (n = 872) or placebo + GnRH therapy* (n = 845).1,2

**TERRAIN TRIAL**
375 patients with metastatic CRPC who were asymptomatic or mildly symptomatic were randomized to XTANDI + GnRH therapy* (n = 184) or bicalutamide + GnRH therapy* (n = 191).1,3

In the US alone, 106,000 patients have been prescribed XTANDI—and counting†4


Visit [XtandiHCP.com](http://XtandiHCP.com) to learn more about XTANDI in metastatic CRPC patients

**Indication**
XTANDI (enzalutamide) capsules is indicated for the treatment of patients with metastatic castration-resistant prostate cancer (CRPC).

**Select Safety Information**
XTANDI is not indicated for use in women. XTANDI can cause fetal harm and potential loss of pregnancy.

Seizure occurred in 0.5% of patients receiving XTANDI in clinical studies. In a study of patients with predisposing factors, seizures were reported in 2.2% of patients. See section 5.1 of the Prescribing Information for the list of predisposing factors. It is unknown whether anti-epileptic medications will prevent seizures with XTANDI. Permanently discontinue XTANDI in patients who develop a seizure during treatment.

There have been post approval reports of posterior reversible encephalopathy syndrome (PRES), a neurological disorder that can present with rapidly evolving symptoms and requires confirmation by brain imaging. Discontinue XTANDI in patients who develop PRES.

Please see reverse for Important Safety Information and adjacent pages for Brief Summary of Full Prescribing Information.