Adding Multiparametric MRI to Prostate Cancer Screening Will Save Lives and Money

Robert Princenthal, MD  Rolling Oaks Radiology, Ventura County, California  805-778-1513

In recent years, recommendations for prostate cancer screening have been caught amidst growing controversy. The utility of prostate-specific antigen (PSA) blood testing, the most prominent front-line screening exam for prostate cancer, has been heavily critiqued. Meanwhile, numerous men present with incurable late-stage prostate cancer while men with low-risk, indolent disease receive treatment that offers little benefit in terms of health outcomes. Prostate cancer patients and their physicians have long sought an alternative to the current standard of care in prostate cancer detection and diagnosis. Multiparametric MRI is an emerging technology that could be added to PSA-based prostate cancer screening to improve diagnosis and management.

CONTROVERSY SURROUNDING PROSTATE CANCER SCREENING

PSA is a protein produced by the prostate gland. PSA is present in the blood of most healthy men, although normally at low levels. However, PSA levels can become elevated in men with prostate cancer and other prostate conditions.
Researchers identified PSA as a potential biomarker for prostate cancer in the 1970s. PSA tests were initially used to monitor the progress of disease in men already diagnosed with prostate cancer. In the early 1990s, additional research showed that PSA tests could be used as a first-line screening exam for prostate cancer. The standard of care in prostate cancer detection and diagnosis remained largely unchanged in the following two decades.

**PROS & CONS OF PSA TESTING**

PSA blood tests provide useful information about prostate health and have helped to save many lives from prostate cancer. With PSA-based screening available, prostate cancer mortality rates dropped by more than 40 percent from 1991 to 2009. However, the conventional process for detecting and diagnosing prostate cancer can be improved.

Despite the benefits of PSA-based screening, the standard of care in prostate cancer diagnosis has been somewhat crude over the past two decades. PSA levels are a volatile biomarker. They can fluctuate for numerous reasons besides the presence of cancer. Prostate enlargement, infection and age can all affect PSA levels.

In the past, a PSA level of 4 was commonly used to determine which men should be biopsied. This benchmark is somewhat arbitrary and others suggest an even lower benchmark of 2.5.

- **15%** of men with PSA levels less than 4 will have prostate cancer.
- **25%** of men with PSA levels between 4 and 10 will have prostate cancer.
- More than **50%** of men with PSA levels of 10 or more will have prostate cancer.
While PSA testing is imperfect, it can be useful. Rather than using a PSA level of 4 to triage men for biopsy, doctors could consider PSA levels along with other factors. These include rate of PSA level increase and size of prostate at initial screening.

**TRUS BIOPSY**

The second step in the conventional process for diagnosing prostate cancer has required transrectal ultrasound (TRUS) biopsy. TRUS biopsy is far from perfect as a diagnostic exam. During this procedure, around 12 or more biopsy needles are fired into the prostate in relatively blind fashion to draw tissue samples for testing. The grey scale ultrasound used in the TRUS biopsy is not effective at detecting cancer cells or specific nodules within the prostate, so there is no real attempt to biopsy suspicious areas in a targeted approach.

More than 1 million TRUS biopsies are performed each year. Up to two-thirds provide no useful clinical data. Many men without prostate cancer are indeterminately biopsied based on PSA levels alone or clinically insignificant cancers are identified by chance. In other instances, important cancers are missed due to the inadequacy of TRUS biopsy. Additionally, roughly one-half of cancers diagnosed by TRUS are inappropriately sampled and under-graded. For instance, a higher-grade, Gleason 7 cancer could be misrepresented as a low-grade, Gleason 6 cancer.

If an initial TRUS biopsy does not detect cancer and PSA levels remain elevated, men are often asked to return for repeat transrectal biopsies once per year or less. Each repeat biopsy puts men at additional risk for complications, such as bleeding or infection – even erectile dysfunction. In addition to causing unnecessary harm, repeat biopsies can become costly. This process repeats itself year after year until
cancer is finally detected or until a man becomes too frustrated to continue.

ACTIVE SURVEILLANCE OR TREATMENT?

To complicate prostate cancer screening, many prostate cancers can be safely monitored rather than treated. Most prostate cancers are low-grade (Gleason 6), slow-growing cancers that will not cause harm for many years. However, the early detection and treatment of high-grade, aggressive cancers is critical to achieving the best possible outcomes.

Incomplete information provided by a combination of PSA tests and TRUS biopsy often leads to inappropriate treatment recommendations. Men with cancers that can be safely monitored often receive radical treatment. They may suffer undesirable side effects of treatment, such as incontinence and impotence, when they didn’t require treatment at all.

USPSTF RECOMMENDATIONS FOR SCREENING

By using incomplete data provided by PSA testing to indeterminately recommend men for biopsy, doctors are doing their patients a disservice. This unnecessarily places men at risk for complications from biopsy and has subjected many men to the side effects of unnecessary treatment. It also led the U.S. Preventive Services Task Force (USPSTF) to recommend against PSA-based prostate cancer screening in a 2012 decision.

“Prostate cancer is a serious health problem that affects thousands of men and their families,” read a statement from USPSTF co-chair Michael LeFevre, MD, issued at the same time as prostate cancer screening guidelines. “But before getting a PSA test, all men deserve to know what science tells us about
PSA screening: there is a very small potential benefit and significant potential harms.”

To the USPSTF, saving lives is a “very small potential benefit” of screening men with the PSA. While there are significant potential harms, it is irresponsible to recommend against screening when lives can be saved. Rather than denying access to screening, the medical community should adopt a strategy to recommend screening while communicating both the potential harms and the potential benefits to patients. Patients with high-grade, aggressive cancers should not be denied the chance for treatment or a cure.

Fortunately, advocates for prostate cancer screening can point to advancements in prostate cancer treatment and in new diagnostic tools to make their case. Over the past several years, multiparametric MRI has emerged as an effective way to detect prostate cancer, triage men for biopsy and guide treatment recommendations.

WHAT IS MULTIPARAMETRIC MRI & HOW DOES IT WORK?

Researchers have experimented with MRI of the prostate since the 1980s. However, recent technological advancements and the development of specific imaging techniques have allowed MRI to emerge as an effective way to visualize the prostate gland that can aid in prostate cancer detection. Multiparametric MRI provides detailed anatomical and functional information unavailable from grey scale ultrasound.

MULTIPARAMETRIC MRI SEQUENCES

Radiologists can use multiparametric MRI to measure the extent of a tumor, identify the location or locations of a tumor,
estimate the Gleason score of a tumor and determine whether a
tumor has spread beyond the prostate gland. A multiparametric
MRI exam consists of three separate imaging techniques
(‘parameters’): T2-weighted imaging, diffusion-weighted
imaging and dynamic contrast-enhanced imaging.

- T2-WEIGHTED IMAGING

A T2-weighted imaging sequence provides anatomic information
about the prostate gland. It offers detailed visualizations of
the prostate gland and its distinct zones. T2-weighted imaging
has applications in the detection, localization and staging of prostate cancers.

On T2-weighted images, cancers in the peripheral zone of the
prostate typically appear as areas of enhancement or bright
spots against a dark background. Cancers in the transition
zone are more difficult to detect. They appear as smudged
charcoal against a grey background.

T2-weighted imaging also provides opportunity to evaluate
seminal vesicles and the bladder wall to determine if a tumor
has spread beyond the prostate. Other prostate conditions can
be mistaken for cancer on T2-weighted images.

- DIFFUSION-WEIGHTED IMAGING

Diffusion-weighted imaging (DWI) measures the motion of water
molecules within the prostate to provide useful functional
data about cancers. This sequence produces an ADC value for
different areas of the prostate gland. ADC values measure the
degree of motion through different tissues. Lower ADC values
appear in cancerous tissue than healthy tissue. ADC values
also correlate with Gleason scores, with lower ADC values
indicating a higher Gleason score.

- DYNAMIC CONTRAST-ENHANCED IMAGING

During dynamic contrast-enhanced (DCE) imaging, a contrast
agent (gandolinium) is used to evaluate blood flow through the
prostate. Cancerous tissue absorbs the contrast agent more quickly than healthy tissue, which is apparent on DCE images. The role of DCE imaging is secondary to T2-Weighted Imaging and DWI, but it can help to detect small, yet significant cancers missed by the other two sequences.

MULTIPARAMETRIC MRI INTERPRETATION

Multiparametric MRI exams are interpreted according to the Prostate Imaging Reporting and Data System (PI-RADS). This is a classification system that uses a 5-point scale to standardize assessment of exams. A PI-RADS assessment indicates the likelihood of intermediate- and high-risk cancers based on findings from the three multiparametric MRI sequences.

**PI-RADS 1** – Highly unlikely that clinically significant cancer is present.
**PI-RADS 2** – Unlikely that clinically significant cancer is present.
**PI-RADS 3** – Uncertain whether clinically significant cancer is present.
**PI-RADS 4** – Likely that clinically significant cancer is present.
**PI-RADS 5** – Highly likely that clinically significant cancer is present.

For results of PI-RADS 4 or 5, patients should be recommended for biopsy. For results of PI-RADS 1 or 2, a recommendation for biopsy is likely inappropriate, but other factors should be considered. For results of PI-RADS 3, biopsy may be appropriate depending on patient history, local preferences and preferred standard of care.
TARGETED BIOPSY

Another benefit of multiparametric MRI is that it enables targeted biopsy. Biopsy needles can be guided using real-time MRI images or multiparametric MRI images can be fused with real-time ultrasound images to guide biopsy needles. These procedures are respectively referred to as MRI-guided biopsy and MRI-TRUS fusion biopsy.

When PI-RADS results are used to triage men for biopsy, both MRI-guided and MRI-TRUS fusion biopsy offer improved higher diagnostic yields with fewer needles over TRUS biopsy. However, MRI-TRUS fusion biopsy is less costly.

* Editor’s note – Dr Peter Choyke of NIH stated at AUA 2016 that PI-RAD Scores of 3, 4 and 5 all warrant a biopsy. It is common for experts to disagree on developing issues such as this, but Dr Choyke’s comment is noteworthy as he is one of the leaders in prostate MRI in the US & PI-RAD development.

PATIENT CONSIDERATIONS

Physicians referring patients for multiparametric MRI and patients thinking about multiparametric MRI should consider the technology used by different radiology facilities. They should also consider the experience of radiologists interpreting exams. Evidence suggests that
Multiparametric MRI is ideally performed with 3T MRI and results interpreted by radiologists with significant experience reading multiparametric MRI exams.

**Magnet Field Strength**

Different MRI machines utilize magnets of different field strengths, with a 3T magnet offering higher field strength than a 1.5T magnet. Multiparametric MRI can be adequately performed with either 1.5T or 3T MRI. However, multiparametric MRI with a 3T magnet benefits from higher signal-to-noise ratio, which produces images of higher quality than those produced by 1.5T MRI.

**Endorectal Coil**

An endorectal coil may be inserted into the rectum during multiparametric MRI to improve image quality, essentially acting as an antenna. Multiparametric MRI can often produce quality results without the use of an endorectal coil. An endorectal coil is more likely to be used during multiparametric MRI performed with a 1.5T magnet.

**Multiparametric MRI as an Aid to Prostate Cancer Screening & Management?**

Dr. LeFevre of the USPSTF was correct to call prostate cancer a ‘serious health problem.’ According to American Cancer Society estimates, more than 220,000 new cases will be diagnosed in 2015 and more than 27,500 will die from prostate cancer. Around 1 man in 7 will be diagnosed in his lifetime. However, many men have been led to fear prostate cancer screening more than they fear the disease.
This assertion and these statistics do not suggest that prostate cancer screening is unimportant. The European Randomized Study of Screening for Prostate Cancer shows that a screening program can decrease prostate cancer mortality by 20 percent or more. Additional research shows that men who forego screening often present with late-stage, often incurable, prostate cancer. While harms of screening should be taken seriously, they should not outweigh the potential to save lives. These numbers show that men deserve a more effective screening program that reduces harms and still saves lives.

A PSA-based prostate cancer screening program that incorporates multiparametric MRI could improve screening for and management of prostate cancer in several ways.

- Reduce total number of biopsies and total number of biopsy needles used, limiting complications associated with biopsy.
- Improve diagnostic accuracy for intermediate- and high-risk prostate cancers.
- Reduce detection of low-risk, indolent prostate cancers.
- More confidently recommend active surveillance when appropriate rather than radical treatment.

**MRI-GUIDED BIOPSY VS TRUS BIOPSY**

Researchers led by Morgan Pokorny, MD, published results July 2014 in European Urology that show how multiparametric MRI could improve the process for triaging patients for biopsy. Their study investigated multiparametric MRI in 233 men with elevated PSA and no prior prostate biopsy. Each patient received multiparametric MRI that was subsequently interpreted according to PI-RADS.

If MRI results showed no suspicious findings, patients received conventional TRUS biopsy. If results returned PI-RADS
score of 4 or 5, patient received targeted, MRI-guided biopsy. Patients who received targeted biopsy also received subsequent TRUS biopsy. A strategy that referred men with PI-RADS 4 or 5 results for targeted biopsy produced desirable results.

- **36%** reduction in number of biopsies compared with TRUS.
- **84%** reduction in number of needles used.
- **87%** reduction in detection of low-risk, indolent cancer.
- **18%** increase in detection of intermediate- and high-risk cancer.

By using multiparametric MRI in asymptomatic men with elevated PSA to selectively guide biopsy decisions, rather than indiscriminately ordering TRUS biopsy, researchers showed an ability to reduce the need for biopsy while improving overall detection of intermediate- and high-risk cancers.

One of the greatest benefits of multiparametric MRI is its ability to help men more confidently choose active surveillance as a management strategy rather than radical therapy.

**MRI-TRUS FUSION BIOPSY VS TRUS BIOPSY**

Researchers led by Mohummad Minhaj Siddiqui, MD, performed a similar study, except they compared MRI-TRUS fusion biopsy rather than MRI-guided biopsy with TRUS biopsy. MRI-TRUS fusion offers several benefits over MRI-guided biopsy. While both offer high accuracy, MRI-TRUS fusion biopsy is more cost-effective and keeps biopsies in the realm of urologists rather than radiologists.
Siddiqui and his colleagues studied more than 1,000 men with elevated PSA or suspicious digital rectal exam results. Each patient received multiparametric MRI followed by concurrent MRI-TRUS fusion biopsy and conventional TRUS biopsy. Targeted MRI-TRUS fusion biopsy was able to detect 30 percent more high-risk cancers than conventional TRUS biopsy. Additionally, MRI-TRUS fusion biopsy detected 17 percent fewer low-risk cancers.

Researchers concluded that MRI-TRUS fusion biopsy was associated with increased detection of high-risk prostate cancers and decreased detection of low-risk prostate cancers.

**APPLICATIONS FOR MULTIPARAMETRIC MRI BEYOND BIOPSY**

Researchers have produced convincing evidence that multiparametric MRI could aid prostate cancer screening and diagnosis, with the most prominent benefit being higher diagnostic yields with fewer needles. This reduces harms associated with biopsy, decreased chance of identifying low-risk and increased detection of intermediate- and high-risk cancers. Once a diagnosis of prostate cancer has been confirmed, multiparametric MRI can continue to play a role in patient management.

Detailed anatomic and functional information provided by multiparametric MRI can help to guide treatment decisions. For instance, multiparametric MRI can effectively identify seminal vesicle invasion, extracapsular extension and pelvic lymph node involvement. For patients requiring surgery, this can help to determine surgical approach and whether a nerve-sparing procedure is possible.

In addition to predicting the likelihood that a lesion is cancerous, multiparametric MRI provides details about lesion location, volume and relation to the urethra, neurovascular bundle and rectum. This can help patients
and physicians to determine whether focal therapy would be a safe and appropriate treatment option. Guidelines for focal therapy treatments are beginning to call for the use of multiparametric MRI to guide these decisions. MRI is also increasingly used during focal therapy. For instance, real-time MRI is often used to guide high-intensity focused ultrasound and laser induced thermal therapy. Innovative MRI-TRUS fusion platforms are also emerging as effective tools for the guidance of focal therapy.

One of the greatest benefits of multiparametric MRI is its ability to help men more confidently choose active surveillance as a management strategy rather than radical therapy. Monitoring men in active surveillance was previously accomplished using a combination of PSA tests and blind biopsy. With multiparametric MRI and targeted biopsy, doctors are able to better differentiate patients with low-risk, indolent disease from those with intermediate- and high-risk disease. This approach allows men with low-risk disease to delay therapy and their side effects, potentially indefinitely, until there is evidence of disease progression.

**MULTIPARAMETRIC MRI WILL IMPROVE PROSTATE CANCER CARE**

For many years, prostate cancer patients and their doctors have sought diagnostic tools that provide accurate information about the disease. The conventional model for prostate cancer screening requires men to receive routine PSA testing and, if PSA levels are elevated, subsequent TRUS biopsy. There are problems with this model. PSA levels are a useful biomarker, but they provide incomplete information about prostate health. Additionally, the diagnostic accuracy of TRUS biopsy does not allow us to differentiate men with low-risk, indolent disease from those with intermediate- and high-risk disease.
TRUS biopsy does not detect cancer in approximately two-thirds of men with elevated PSA levels. PSA levels can fluctuate due to numerous factors and a group of men with normal PSA levels still develop prostate cancer. The inability of grey-scale ultrasound to identify suspicious lesions means many cancers are missed and many more are under-graded. This often results in inappropriate disease management strategy and this process, as well as the potential for harms, has led the USPSTF to recommend against prostate cancer screening.

Prostate cancer is a tale of two diseases. Many men with prostate cancer have low-risk, indolent tumors that are unlikely to grow or cause harm for many years, if ever. Other men have high-risk tumors that can quickly become lethal if they are not detected and treated as early as possible. Because the combination of PSA testing and TRUS biopsy provides incomplete assessment of the prostate gland, many men with low-risk, indolent disease elect to receive radical treatment that could be more harmful than it is beneficial. Numerous men unnecessarily suffer from complications like impotence and incontinence, even with the introduction of robotic prostatectomy.

USPSTF recommendations against screening and uncertainty surrounding prostate cancer diagnoses have led many men to fear screening more than they fear the disease itself. Prostate cancer kills more men than any other cancer besides lung cancer. With more than one million biopsies performed each year, men deserve a screening model that can better identify those who would benefit from biopsy and offer high diagnostic accuracy. The emergence of multiparametric MRI as an adjunct to PSA allows us to better identify candidates for biopsy, as well as differentiate those who require treatment from those who can be safely monitored.

High-quality anatomic and functional data provided by multiparametric MRI can identify suspicious prostate nodules and enables targeted biopsy. A screening model that adds
multiparametric MRI to PSA testing would require fewer biopsies while improving detection of intermediate- and high-risk cancers. This model would allow men to avoid complications associated with biopsy and to more confidently adopt a disease management strategy appropriate for their disease.

Discouraging men from screening is a misguided approach to a serious health problem like prostate cancer. Prostate cancer screening has been proven to save lives. By working together and implementing a screening model that utilizes multiparametric MRI, we can achieve higher diagnostic yields with fewer biopsy needles.