“When prostate cancer returns, how soon can we find it?”

-- by Michael F Kipper MD, Genesis HealthCare

Risk factors for recurrence: a PSA measuring greater than or equal to 15 nanograms per milliliter, a Gleason score greater than or equal to 8, and the most recent “stage” of the cancer.

Definitions of biochemical failure:

1. Follow-up PSA greater than 0.2 ng/ml.

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lowing prostatectomy -- Failure of the PSA to fall to undetectable levels is considered PSA persistence. If there is an undetectable PSA after radical prostatectomy and then PSA increases on two or more determinations, this is referred to as PSA recurrence, and is considered biochemical failure. 2. Following radiation therapy: A PSA increase by 2 nanograms per milliliter or more above the lowest PSA after the radiation treatment, with or without use of hormone therapy. Or, in younger patients, any confirmed PSA rise.

The role of imaging in prostate cancer recurrence. Imaging is used to detect and characterize the disease and to aid in treatment planning and management changes. Imaging can evaluate anatomic features as well as “functional” parameters. Techniques used to obtain anatomic information include plain X-rays, ultrasound, CT, and MRI. Bone scans, PET/CT and advanced MRI techniques measure functional (biological activity) parameters.

The efficacy of imaging early on in biochemical recurrence depends upon the man's risk group prior to treatment, his Gleason score, his tumor stage, his PSA and his PSA doubling time. How often imaging is advisable depends upon various individual risk factors and does not have a simple answer.

Early localization is important because there are certain cut off points which correlate with response to treatment; for example, determining if salvage radiation is appropriate. We want to know the location of the site, whether in the prostate region, in the lymph nodes, in the bone or in organs. Is there a single identifiable site or multiple? Are additional studies necessary and is tissue sampling a consideration?


Common signs and symptoms of local recurrence: 1. Burning or pain during urination. 2. Difficulty urinating or trouble starting and stopping while urinating. 3. More frequent urges to urinate at night. 4. Loss of bladder control. 5. Decreased flow or velocity of urine stream. 6. Blood in the urine (which is called hematuria).

Signs and symptoms of metastatic prostate cancer: 1. Erectile dysfunction or painful ejaculation. 2. Swelling in the legs or pelvic area. 3. Numbness or pain in the hips, legs or feet. 4. Bone pain which does not go away or which results in fractures.

Blood tests can include PSA, along with PSA doubling time calculations; Testosterone level; Alkaline phosphatase activity; Complete blood count; Liver function test; and Renal function tests.

The PSA test measures for a “prostate specific antigen,” which is an enzyme produced in the prostate and mostly found in the semen, but also in the blood. It is an enzyme which liquefies semen to allow sperm to swim freely and to dissolve cervical mucus. Free PSA is unbound to protein. The ratio of free to bound is important; the lower the ratio, the greater the risk of prostate cancer.

Testosterone facts: In men, testosterone is produced by the testes and the adrenal glands. Production begins in the fetus at about week 8. As men age, levels may fall -- which is called andropause or male menopause. Women also have a little testosterone. Prior to a competition, a man's testosterone level rises. After the game, both the winners’ and their fans’ testosterone levels rise even more. In men and boys, the right pointer finger is shorter in relation to the right ring finger than it is in girls. It is a marker for (evidence of) fetal exposure to testosterone.

Plain radiographs (x-ray images), may be used to evaluate symptomatic regions in the skeleton. But standard radiographs will not detect a lesion until about 50% of the mineral content of the bone is lost. Therefore plain radiographs have little value in assessing possible recurrence of prostate cancer.

A whole body bone scan refers to a nuclear medicine study performed on a gamma camera, usually using a technetium radioisotope. Metastatic disease to the bone may be diagnosed based on the pattern...
of abnormalities on the bone scan or the combination of the findings seen on this bone scan along with an anatomical imaging study such as plain x-ray, CT or MRI.

Another type of whole body bone scan uses radioactive sodium fluoride as the tracer with a PET/CT scanner. However, it is no longer paid for by Medicare, so is based on cash purchase. Sodium fluoride is more sensitive, more specific, and more accurate than standard technetium bone scans.

**The timing for doing bone scanning** is dependent on many patient-specific factors. Has the patient had surgery or radiation? Is it needed to monitor metastatic prostate cancer, to assess the clinical benefit of systemic (i.e., hormone) therapy? Is the patient symptomatic? And, should it be done on a routine basis for patients who have castrate resistant prostate cancer?

Standard technetium bone scans are rarely positive (useful) in men who are asymptomatic and who have PSA values less than 10 nanograms per milliliter, unless the doubling time is less than 8 months. It is a highly sensitive test, but it is not very specific. Many other conditions will show as hot areas. It should not be done during the "flare" phenomenon which can occur after initiation of hormone therapy. Unfortunately, oftentimes there are no prior studies for direct comparison. If a technetium scan shows more than a hundred metastases, this is called a Superscan. It is very bad news!

**CT scans** can provide excellent anatomic detail and can detect disease in lymph nodes and in the visceral organs, as well as in the bones. CT may be useful in patients after a radical prostatectomy if the PSA fails to fall to undetectable levels, or if after becoming undetectable it rises on two or more subsequent determinations. It may be used after radiation therapy if there is a rising PSA or a positive digital rectal exam -- if the patient is a candidate for additional radiation or systemic therapy.

**MRI (sometimes referred to as multiparametric MRI or mpMRI)** is superb for soft tissue characterization. It utilizes no ionizing radiation. It can be done with or without a contrast agent. It provides both anatomic as well as functional imaging. It can be used for initial evaluation of high-risk patients and it provides good risk stratification for men considering active surveillance.

MRI is extremely valuable as a correlative study when combined with technetium bone scanning, PET or other examinations that have given equivocal results. MRI is particularly helpful in detecting higher-grade cancers, those with Gleason score greater than or equal to 7. As with CT scanning, it is very useful for patients with biochemical recurrence.

**PET/CT.** Essentially all PET studies are now performed with a hybrid scanner, which combines PET with CT Imaging. PET/CT studies for other cancers are typically performed with FDG, which is an analog of glucose. However, this agent is not usually effective for prostate cancer imaging, as it is not well taken up by the prostate cancer cells. A new agent, F-18 fluciclovine (Axumin), has been approved for prostate cancer and is covered by Medicare. Axumin is a synthetic amino acid which does show enhanced uptake by prostate cancer cells vs. other cells. This allows recurrent prostate cancer to be located in lymph nodes, bone and visceral organs with high accuracy even when PSA values are still below 1 nanogram per milliliter during recurrence.

**Axumin** has been approved by the FDA for use in suspected prostate cancer recurrence based on elevated PSA levels after prior treatment. If pelvic metastases are identified, this could lead to a change in the radiation field to include those nodes, and if extra-pelvic disease is found then therapy is likely to change from salvage radiation therapy to systemic hormonal therapy.

Both the PSA and its doubling time are relevant in whether the Axumin study will find positive sites of disease. For extra-prostatic disease, the specificity is in the range of 95%. That is, if a site is hot in this study, it is a tumor! Currently available methods allow us to identify subcentimeter sites of disease by CT, MRI and PET/CT. We can find lesions with PSA values of 0.1 nanograms per milliliter or less using
PET/CT and we can deliver precise treatment to the small sites using CyberKnife, proton therapy or systemic agents. What we do not know is the lower limit of size and number of metastasis we will ultimately be able to identify, and more importantly, we do not yet know whether subsequent earlier treatment will change ultimate outcomes.

Questions:

Can scans differentiate fast vs. slow growing bone metastases? How are they handled?
Osteoblastic lesions are slow growing and can be “seen” as hot spots by technetium scans, but osteolytic (“eating away”) lesions, which are fast growing (but only occur 5-10% of the time) cannot. Both types of lesions can be seen by Axumin or sodium fluoride scans. PSA and Alkaline Phosphatase help determine which type of lesion predominates, but they are not typically treated differently. Note that bone scans will typically stay positive for life, as the body will continue to repair the site even if the cancer is eliminated or inactive there. It’s uncommon for the lesion to disappear entirely. Progression is defined as more lesions, or lesions in different areas of the body. Otherwise, the cancer is considered to be “stable.”

When to get a scan, say, if PSA rises from 2 to 10 in 3 months (then goes back down on cycles of hormone therapy)? If you have a doubling time of less than 8 months, or if you have symptoms, get a scan. Start with a bone scan. If negative, go to Axumin to look at the whole body. Axumin is almost 100% accurate at any PSA above 2.

What about any ongoing concerns five years after a prostatectomy, when all seems fine?
Prostate cancer can come back many years later, so PSA tests should be run periodically, for life.

Are there reasons an Axumin study could be falsely negative? It’s a rarity, but if the prostate cancer changes to a neuroendocrine type, or if the tumor is not actually prostate cancer, the Axumin could miss it.

If PSA doubles fairly quickly, but is still only about 0.1, is it time for scans and treatment?
No, usually no action is taken below a PSA of about 0.3 or 0.5.

Sodium fluoride scan costs? PET scans, whether sodium fluoride for prostate cancer, or FDG for other cancers, cost in the range of $1000 to $1500.

If a man has had low PSA on ADT (hormone therapy), but it starts to eventually rise after ADT is stopped, should he go back on ADT, or get scans? It depends on the patient’s history, and needs discussion with the urologist. It could go either way.

Is there a scan that would point the patient to HIFU (high intensity focused ultrasound) treatment? Best for planning would be mp-MRI, but the choice of HIFU vs other treatments depends on many factors, including the individual’s preferences.

How do you figure out if your symptoms are meaningful or not? The urologist looks for change. New symptoms or changes in old symptoms or re-scans would indicate action should be taken. See the list of symptoms in the summary above.

Many images from various scans are shown in the video of this presentation, which, including the PowerPoint slides, will be available via the website shortly before the next meeting, or at the August meeting on the 18th.
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Yu Shares Insight on Recent Advances in Castration-Sensitive Prostate Cancer

Angelica Welch
Evan Ya-Wen Yu, MD

The prognosis for patients with castration-sensitive prostate cancer continues to improve, with the recent FDA approval of abiraterone acetate (Zytiga), an agent that has shown promising survival signals. Results from the LATITUDE and STAMPEDE trials have contributed to this dramatic shift, said Evan Ya-Wen Yu, MD.

Abiraterone was approved in February 2018 for use in combination with prednisone for patients with metastatic high-risk castration-sensitive prostate cancer. This approval was based on findings from the phase III LATITUDE trial, in which the addition of abiraterone and prednisone to androgen deprivation therapy (ADT) demonstrated a 38% reduction in the risk of death compared with ADT alone.1

The STAMPEDE trial also investigated abiraterone, showing that it lowered the relative risk of death by 37% when added to standard ADT. Additionally, abiraterone improved progression-free survival by 71% in metastatic and nonmetastatic patients with high-risk hormone-naïve prostate cancer.2

In an interview during the 2018 OncLive® State of the Science Summit™ on Genitourinary Cancers, Yu, a professor in the Division of Oncology at the University of Washington, and member of the Clinical Research Division at Fred Hutchinson Cancer Research Center, discussed the evolution of treatment for patients with castration-sensitive prostate cancer and how he decides between treatment with abiraterone and docetaxel for this population.

OncLive: Please discuss how treatment has changed for patients with castration-sensitive prostate cancer.

Yu: The field has recently changed dramatically after the [results of the] CHAARTED and STAMPEDE trials showed that 6 cycles of docetaxel, when added to standard ADT, led to a dramatic survival benefit for men with newly diagnosed metastatic prostate cancer. There were some patients in the STAMPEDE trial who did not have metastatic disease, but in regard to subsets, we still have to see the long-term benefit. For metastatic disease, it is very cut and dry; there is benefit with docetaxel, especially for those with high-volume disease.

More recently, the LATITUDE and STAMPEDE trials showed that adding abiraterone to ADT also leads to...
a dramatic survival benefit. This increases the number of choices that one has. We certainly do not know whether abiraterone or docetaxel is better. Personally, I am using abiraterone for my low-volume disease patients. For high-volume disease, I offer both. I recognize that there are many considerations in regard to the number of doses of docetaxel, duration of therapy of abiraterone, and financial toxicity. All of these things need to come to light.

The other thing regarding treatment intensification is the future of these diseases. There are many clinical trials with combination therapy as well. Additionally, there are many trials that are now thinking about doing metastases-directed therapy, removing oligometastatic disease surgically or with radiation, and also studies looking at removing the primary lesion of the prostate or providing radiation to the prostate. Those trials are underway, and we look forward to seeing the results of that.

Finally, I spoke about identifying metastases early for patients with biochemical recurrence using next-generation imaging such as prostate-specific membrane antigen-PET to identify early metastases to then do metastases-directed therapy. This is early ongoing research, but it is generating a lot of excitement in the field.

What else would you like to highlight from LATITUDE, CHAARTED, and/or STAMPEDE? If you look across cancer studies, regardless of the malignancy or agents, it is not uncommon to see a 2-, 3-, 4-, or 5-month median survival benefit. With these agents, we are seeing survival benefits in terms of 1 to 2 years in certain subsets. These are incredibly dramatic and convincing data. There is really no doubt about it.

What other agents are promising other than abiraterone and docetaxel? There are a lot of studies going on right now that take the same theories—adding chemotherapy earlier. There will be a study coming out looking at cabazitaxel chemotheraphy in this setting. There are studies looking at enzalutamide (Xtandi) and apalutamide (Erleada) in this setting, and there are studies that allow combinations of chemotherapy with a second-generation androgen-targeted agent.

Now that we have seen the survival benefit with docetaxel and abiraterone, the question is, “Should we be sequencing them or possibly combining them?” There will be some studies with other related types of agents out there that will sequence and combine these agents. That will teach us the best thing to do in the future.

What are the factors that you take into consideration when treating a patient with low-volume disease? Certainly, comorbidities are always important. Duration of therapy, financial toxicity, and patient comorbidities are all important. Patient side effect profiles are important; certainly, docetaxel has its unique side effect profile with neuropathy, hepatic issues, and some patients needing to take high doses of steroids prior to dosing.

One nice thing is that they don’t have to take chronic steroid dosing. For instance, in metastatic castration-resistant prostate cancer trials, [the regimens] are all accompanied with 5 mg of prednisone twice daily. In the CHAARTED trial, they did not use prednisone. Whereas when you give abiraterone, that might be a consideration for someone who is a brittle diabetic. There are multiple comorbidity associations that may push you one way or another.

What would you say is the prognosis for castration-sensitive prostate cancer? The prognosis has improved over time. Traditionally, [findings from] older studies in this setting have shown a prognosis ranging from 3.5 years to 5 years. We have not had long-term outcomes, because a lot of these patients from these studies that we are talking about are still alive. A lot of the data that have come out are from interim analyses. Plus, with all of the new drugs available for metastatic castration-resistant prostate cancer (mCRPC), I would be shocked if the prognosis overall wasn’t better.

Is there anything coming up on the horizon that you would like to mention? There is a lot of excitement in this area. When it comes to treating patients with castration-sensitive disease, the challenge is trial development. This is actually a good challenge, because the prognosis is good—these patients live for years. But, it takes a long time for the data to mature.

I would say that the more immediate things occurring in the field that will garner a lot of press are the use of immunooncology agents such as PD-1/PD-L1 antibodies and selecting patient populations for that. Also, the introduction of PARP inhibitors for homologous recombination deficient patients. Should we be combining immunooncology agents with PARP inhibitors? These are the things that are the most immediate because they are already being tested in patients with mCRPC. We will get to an answer soon.
The focus of the ASCO expert panel was appropriately centered on the optimal application of the two tested therapeutics: abiraterone (Yonsa, Zytiga) and docetaxel. The authors correctly noted that the significant improvement in all outcomes justifies their use for the treatment of the majority of men with hormone-naive metastatic cancers as initial therapy in combination with luteinizing hormone-releasing hormone (LHRH) agonists. Physicians should now discuss and offer both options to patients with newly diagnosed hormone-naive metastatic prostate cancer who are not frail.

Subject of Much Speculation

There is strong evidence favoring the addition of abiraterone in men irrespective of the volume or number of metastases. In the course of developing the guidelines, the authors exposed two issues that have been the subject of much speculation: the first is the discordance in the findings of CHAARTED and STAMPEDE, which demonstrated benefit for docetaxel, relative to GETUG, which detected no benefit. The strength of data is, according to their interpretation, greatest for men with higher volumes of metastatic cancers. However, citing potential differences in the studies and meta-analyses across data sets, they concluded that observations favor meaningful benefit for docetaxel in all.

A remaining clinical question is, should ADT alone be abandoned altogether, or is there a role for it in selected patients?

Meta-analyses have been recently reported with controversial conclusions. Although post hoc analyses have limitations and must be interpreted with caution, they are “hypothesis-generating” and contextualize observations across studies.7,8 The meta-analysis of outcomes in contemporaneously accrued STAMPEDE treatment with abiraterone and docetaxel suggested equivalence between the two arms with regard to overall survival. Based on this finding, both docetaxel and abiraterone are acceptable treatment options for men with metastatic hormone-naive prostate cancer. The benefits of intervention in the hormone-naive state relative to waiting for the emergence of castrate resistance is also clear in patients able to tolerate such therapies. The findings are supported and further extended to the “nonmetastatic castrate-resistant state” by the SPARTAN study.9

The second issue not addressed by the studies is how best to select between docetaxel and abiraterone in individual patients. This issue was likely untouched due to the absence of direct comparative data. The lack of robust data on the clinical interaction between docetaxel and abiraterone may have critical effects on the overall impact of treatment choice on outcomes. Although speculative, it is reasonable to assume there is an optimal sequence that is patient-specific. These and other limitations of the proposed guidelines must generate sufficient con-
cern to take the steps to urgently address the knowledge gaps.

**Remedy for Prostate Cancer Research**

The weaknesses of our current research approach are obvious. Although treatment algorithms in many adult common solid tumors are transitioning from prognosis-based to those informed by predictive markers linking driver biology to treatment, this is not yet the case for prostate cancer. The improved understanding of androgen signaling in prostate cancer and its dominant role in progression have yet to result in the development of widely used predictive markers. Several reasons may account for this: a significant majority of patients will derive benefit, serial sampling of metastases is challenging, and patients are often elderly or frail. These often-cited reasons require a remedy if the promise of prostate cancer research will efficiently lead to improved outcomes.

The limitations of the guidelines point to the urgent need to prioritize the development of predictive markers, which will be the foundation of future guidelines.

— Christopher Logothetis, MD and Eleni Efstathiou, MD, PhD

The priority to be addressed is the development of a categorization of prostate cancer by probability of benefit from androgen-signaling inhibition. Such a classification is the first and necessary step to replace the prevailing “one-size-fits-all” approach. Given the therapeutically relevant heterogeneity over time, informative tissues will need to be harvested contemporaneous to the planned intervention. To achieve this, broadly applicable methods must be developed to obtain tissues from bone-forming metastases or liquid biopsies that reflect the underlying biology with fidelity. New imaging techniques will provide us the opportunity to detect the emergence of cancer and guide specific therapy if developed as biomarkers with the purpose of linking biology to anatomy. The more precise imaging approaches may be a particularly useful tool to enable the integration of surgery or radiation with systemic therapies.

**Foundation of Future Guidelines**

Taken together, the limitations of the guidelines point to the urgent need to prioritize the development of predictive markers, which will be the foundation of future guidelines. Longitudinal characterization of patients and their cancer will, most likely, improve outcomes by informing course corrections in anticipation of overt clinical disease progression. This is particularly relevant given that patients receiving active treatment in the STAMPEDE and LATITUDE trials were more often offered alternative therapies than those treated with ADT alone. We can only speculate what the cause of this perplexing finding was and how it impacted outcomes. However, it is clear that an understanding of why this difference occurred, and what its impact on outcomes may be, will assist in establishing future research directions.

Bridging the gap between the benefits in patient populations and the challenge faced by physicians tasked with recommending therapy for individuals has been measurably improved with the newly revised guidelines. Although improved, the challenge of individualizing therapy looms large. In our view, the gap will be minimized by the development of a biologically based, therapeutically relevant classification, and methods to monitor patients throughout the course of their illness. We add our voice to the chorus that champions the importance of such a classification and the predictive markers necessary for its clinical application. Failure to do so condemns us to continue the prevailing approach of conducting research in unselected populations and using empiricism to guide the care of individual patients.

**DISCLOSURE:** Drs. Logothetis and Efstathiou reported no conflicts of interest.

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**REFERENCES**


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Directions to Sanford-Burnham-Prebys Auditorium
10905 Road to the Cure, San Diego, CA 92121
Take I-5 (north or south) to the Genesee exit (west).
Follow Genesee up the hill, staying right.
Genesee rounds right onto North Torrey Pines Road.
Do not turn into the Sanford-Burnham-Prebys Medical Discovery Institute or Fishman Auditorium.
Turn right on Science Park Road. Watch for our sign here.
Turn Left on Torreyana Road. Watch for our sign here.
Turn Right on Road to the Cure (formerly Altman Row). Watch for our sign here.

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