PET-Based Imaging Improves Metastases Detection in Biochemically Recurrent Prostate Cancer

Gallium-68 prostate-specific membrane antigen positron emission tomography ($^{68}$Ga-PSMA PET) accurately detects metastases in biochemically recurrent prostate cancer (PCa), particularly at low PSA blood levels, researchers say.

“Historically, conventional imaging modalities have included computerized tomography and whole body radionuclide bone scans,” Dr. Marlon Perera of the University of Melbourne in Victoria, Australia told Reuters Health by email. “While cost-effective and readily available, these conventional imaging modalities are fraught with limited accuracy.”

$^{68}$Ga-PSMA PET is a novel imaging technique,“ he said. “PSMA is a transmembrane ligand that is expressed on prostatic cells. Excitingly, the expression of PSMA increases with increasing cellular dysplasia (i.e., more malignant). Accordingly, this represents an ideal target for imaging in PCa.”

In a 2016 paper in European Urology, Perera’s team reported a meta-analysis of 18 studies involving 1,306 men that showed “significantly superior accuracy, sensitivity and specificity” for $^{68}$Ga-PSMA PET vs. conventional imaging. For the current study, the researchers expanded the meta-analysis, including 37 articles involving 4,790 men.

As reported online February 14, also in European Urology, in men with biochemical recurrence (BCR), positive $^{68}$Ga-PSMA PET scans increased with higher pre-PET PSA levels. Specifically, for PSA categories 0.0-0.19, 0.2-0.49, 0.5-0.99, 1.0-1.99, and (Continued on page 3)

Long-Term Androgen Deprivation Therapy (ADT) Underused for Prostate Cancer

Long-duration androgen deprivation therapy (ADT) is widely underused in men, especially African-Americans (A-A), who are undergoing definitive external beam radiotherapy (EBRT) for high-grade prostate cancer (PCa), a new U.S. study has found.

Nearly a quarter of men in the population-based retrospective trial received no long-term ADT, and fewer than 20% received the recommended 24 to 36 months.

“Oh, that underutilization is concerning, as multiple randomized controlled trials have confirmed a survival benefit to longer durations of concomitant ADT, and thus long-term ADT constitutes the current standard of care,” Dr. Amar Kishan of the University of California, Los Angeles, and colleagues wrote online in European Urology Oncology, Feb. 1st.

“I think a lot of individuals would be surprised to know that ADT is so commonly being underutilized,” Dr. Kishan added. “That is troubling, and the racial aspect, even more so.”

The study examined records from the Surveillance, Epidemiology, and End Results (SEER) Medicare-linked database of non-Hispanic white (NHW) and A-A men with Gleason grade group 4-5 (Gleason score 8-10), and PCa treated definitively with EBRT from 2008 to 2011.

In all, 961 men (852 white and 109 A-A) were included in the study. Significant differences at baseline in all covariates between A-A and NHW men were largely reduced after adjustment via (Continued on page 4)
Intervention Helps Prostate Cancer Patients Make Better Choices
Patient Preference Assessment Tool Aligns with Pros and Cons of Prostate Cancer Therapies

A tool that aligned patient preferences with the advantages and disadvantages of prostate cancer (PCa) treatments improved patient satisfaction with care, researchers reported.

“From January 2014 through March 2015, 743 patients with localized PCa were recruited and randomly assigned to receive Patient Preferences for Prostate Cancer Care (PreProCare) or usual care,” according to Ravishankar Jayadevappa, PhD, of the University of Pennsylvania in Philadelphia, and colleagues.

For the general satisfaction subscale, improvement at 24 months from baseline was significantly different between groups (P<0.001), they reported in the Journal of Clinical Oncology.

For the intervention group, mean scores at 24 months improved by 0.44 (SE, 0.06, P<0.001) from baseline, noting that the use of PreProCare improved patient satisfaction with treatment decisions, and reduced regrets about those decisions.

“The results speak for themselves,” commented Otis Brawley, MD, of Johns Hopkins University in Baltimore, to MedPage Today.

“Structured approaches make sure that things are actually covered in a conversation, and it doesn’t surprise me that men are happier with their decisions when there is a regimented discussion that has gone on,” said Brawley, who was not involved in the study.

“And this is especially important in PCa because there are so many different treatment options or observation options that are currently available,” he added. Jayadevappa and colleagues pointed out that in patient-centered care — now one of the key goals in the U.S. healthcare system — “concordance between patient preferences and treatment attributes may help optimize outcomes.”

However, they also noted that there is little data supporting that conclusion when it comes to PCa, adding that there “is a need for a comprehensive analysis of the effects of preference assessment on longitudinal changes in satisfaction with care, satisfaction with decision, decision regret, and treatment choice.”

For the multicenter, randomized controlled trial, the authors recruited 743 men with localized PCa, half of whom were assigned to receive PreProCare and the other half usual care.

Men in the PreProCare cohort completed a 30-minute, web-based assessment tool briefly introducing PreProCare, and completing a questionnaire ranking the attributes of PCa treatments (from not important to extremely important). Based on those rankings, choice scenarios were provided (combinations of attributes), and they selected the preferred combination. Patients were encouraged to share the results of the PreProCare intervention with their provider.

Men in the usual care group received standard educational material about PCa treatments.

The primary outcome of the trial was satisfaction with care, while secondary outcomes included satisfaction with decision, decision regret, and treatment choice, with assessments performed at baseline, three, six, 12, and 24 months.

Patient satisfaction was assessed via an 18-item patient satisfaction questionnaire in which those items were consolidated into seven subscales — general satisfaction with care and six different aspects of care.

The authors reported that the improvement in the general satisfaction subscale at 24 months from baseline was equal to 0.5 standard deviation, and considered clinically significant.

Treatment satisfaction decision scores improved in both groups, with the improvement more significant in the PreProCare group. And treatment decision regret scores declined in both groups, but the decline was greater in the PreProCare group.

Among low-risk men, a higher proportion of the PreProCare men selected active surveillance (66%) vs. the usual-care group (54%). Treatment choice was similar for intermediate- and high-risk patients.

“Our study demonstrates that in localized [PCa], helping patients identify their own preferences using a structured, standardized, computer-based preference assessment tool may be a mechanism for enhancing patient-centered decision making and outcomes,” the authors concluded.

Study limitations included no data on cancer recurrence and complications among participants, and the authors did not measure the quality of patient-physician interactions post-intervention.

MedPage Today
19 March 2019
Ah, another week goes by in my wonderful life and I am reminded of why I love to give the following phrase in lectures such as “take or want nothing until you need something.” What the heck am I taking about? It is still shocking how many folks are surprised when they ask me what pills I currently take and I say “nothing” but then I always add the following: “but when I NEED a pill then I will definitely take a pill.”

Many pills are utilized by folks that are not sure why they are taking them, and yet they WANT to still take them despite not truly needing them. For example, a large prospective study just released received a good deal of attention by concluding that the use of over-the-counter pills (aka supplements), in general, did not appear to reduce the risk of dying.¹ Wait, when did we accept the fact that taking a bunch of pills that we were not sure we even qualified for would actually reduce the risk of dying younger or improve longevity? Great supplements, when they work, are like great drugs, except we just give them a different name and they are less regulated. However, this does not make prescription or other pills labeled as “drugs” harmless either.

Recent research suggests countless inactive ingredients in drugs (including ones you buy over the counter) might not be that inactive after all.² An average of 8.8 inactive ingredients, to be exact, in these pills (aka drugs) They may contain many allergy exacerbating ingredients, such as lactose, or all kinds of fun compounds and chemical stuff (dyes). Most of the drugs studied contained at least one potential allergen.

My point is that we have accepted pills for everything when, in reality, they should be taken for nothing unless there is a damn good reason to take a pill. Why don’t we have the same stringent criteria for NOT taking pills that we do for taking pills? Why are you taking that cancer drug? Is it because it could save my life? Okay that is a good reason. However, why are you so quick to take that sleeping pill or that acid reflux pill or even strong pain pill? Have you tried the plethora of non-pill solutions or lifestyle changes first to see if it would mitigate or solve the problem? No?

No one really needs a pill until they really and truly need a pill. Whether it is the exposure to inactive ingredients, heavy metals, problems with self-medication and quick fixes, purity or other contamination issues, allergens, tremendous financial costs long-term... why take a pill unless you need it? I love supplements and drugs as much as anyone when they are needed, but never when they are just wanted. People love to freak out if they find out their fish, or juice, or another food product contains some kind of contaminant and yet taking handfuls of pills that your poor liver has to sift through with all the potential inactive ingredients and contaminants is no big deal? Say what?

The word “pill” should be considered a four-letter word up until the very moment you truly need it and then, and only then, can be considered your buddy or pal.

References:

²⁶⁸Ga-PSMA PET Imaging Improves Metastases Detection in Men with BCR

(Continued from page 1)

2.0 ng/mL or greater, the percentages of positive scans were 33%, 45%, 59%, 75%, and 95%, respectively. No significant differences in ²⁶⁸Ga-PSMA PET positivity and Gleason score were noted. Men with a Gleason sum of 7 or less had positivity of 72% vs. 80% in men with a Gleason sum of 8 or more.

“In the BCR setting, local recurrence was identified in 22% post prostatectomy and 52% post radiotherapy,” Dr. Perera noted. “Radiotherapy cohorts also had higher rates of positivity in extrapelvic lymphadenopathy and bone metastases.

“A further novel finding of our meta-analysis identified interesting patterns of disease based on ²⁶⁸Ga-PSMA PET,” he said. “In the primary setting, ²⁶⁸Ga-PSMA PET identified intraprostatic (local) PCAs in 90%.”

He acknowledged that the study did not take potential selection bias into account. Dr. Ash Tewari, Chair of urology at the Icahn School of Medicine at Mount Sinai in New York City, said “²⁶⁸Ga-PSMA PET “is still not FDA approved in the U.S., but many of us have access to it because of research collaboration, research activity.

“But in Europe, it is available very easily and I have sent many patients to European institutions that have the largest experience in doing PSMA scans,” he told Reuters Health by phone.

“The bottom line is that above a certain PSA level, a gallium PSMA scan is of use because it tells us exactly where the recurrence is happening,” he said. “It has a reasonable sensitivity and accuracy and I don’t think there is any other test available right now which does as well as this.

“Also, this meta-analysis is very clear in stating that it is not being recommended, at least based on this data, for pretreatment staging,” he added. “It has not yet been proven for that.”

Reuters Health Information
28 March 2019

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Men scoring high for the personality trait of neuroticism tend to have worse recovery and suffer from more adverse events after radical prostatectomy (RP) than men with a more serene outlook on life, investigators reported at the European Association of Urology (EAU) 2019 Congress.

“Neuroticism was identified by using the validated Eysenck Personality Questionnaire at a mean of three years after surgery. Approximately one fifth (22%) of the 761 who answered scored high for neuroticism, and these men had 21% higher severity scores for symptoms such as erectile dysfunction, urinary leakage, and bowel problems than men with low neuroticism scores,” said Karol Axcrona, MD, from Akershus University Hospital in Lørenskog, Norway.

“This is significant in our opinion, and it’s very, very interesting since many men are offered radical treatment for their prostate cancer (PCAs). In this instance, we analyzed patients operated on with RP; it would be very interesting to also analyze patients treated with radical radiation therapy,” he told Medscape Medical News.

Axcrona emphasized that men were asked to fill out the questionnaire only after undergoing RP, and that the investigators did not have baseline data on the degree of neuroticism for each man in the study. At the poster session where he presented his data, however, Axcrona noted that a psychiatrist at his institution informed him that “the personality trait is constant during life.”

Neuroticism Defined

In an entry in the International Encyclopedia of the Social & Behavioral Sciences, David Watson, PhD, from the University of Iowa, described neuroticism as “a broad personality trait that reflects the extent to which a person experiences the world as stressful, threatening, and problematic. Neurotic individuals experience frequent and intense negative emotions; they report a wide variety of problems and are dissatisfied with themselves and the world around them.”

The self-absorbed, nebbish character Alvy Singer, played by Woody Allen in his Academy Award-winning comedy Annie Hall — and in fact nearly every character he played in his early films — are among the best known avatars of neuroticism. For contemporary audiences, think of the persona of Larry David, creator and star of the TV show Curb Your Enthusiasm, or the entire cast of uber-nerds in The Big Bang Theory.

Axcrona and colleagues note as examples six of the 12 questions in the Eysenck Personality Questionnaire neuroticism domain:

- “Are your feelings easily hurt?”
- “Do you worry too long after an embarrassing experience?”
- “Do you often feel ‘fed up?’”
- “Are you a worrier?”
- “Do you worry about awful things that might happen?”
- “Have you often felt listless and tired for no reason?”

Axcrona told Medscape Medical News that while the effects of surgical technique and age on post-RP outcomes are well known, the effects of personality on the ability to recover urinary function have been less well

Long-Term ADT Underused (Continued from page 1)

propensity score.
Men were excluded if they had more than one primary malignancy, positive lymph node involvement, or metastasis at diagnosis; underwent orchiectomy or ADT not coded as a gonadotropin-releasing hormone agonist; started ADT more than six months before start of RT, or received consecutive ADT for more than 36 months.

Of the participants, 23.4% received no ADT, 30.9% received one to six months of treatment, 32.6% seven to 23 months, and 13.1% received 24 to 36 months.

Use of ADT differed between A-A and NHW men, with 33.9% vs. 22.1% receiving no ADT, respectively. This difference was significant even after adjusting for covariates.

“This racial disparity is consistent with recent reports of disparities in the delivery of definitive treatments in A-A men vs. NHW men and could, in part, explain the inferior PCAs-specific mortality outcomes reported for A-A men,” the authors write.

While it is certainly possible that a fair number of men had cardiac or other comorbidities that led to a medical decision to decrease the duration of ADT, the degree of underutilization is quite significant and unlikely to be wholly explained by this limitation,” they add.

“More training on the clear survival benefit of longer-term ADT, and training on minimizing the side effects, may be helpful,” Dr. Kishan said. “An alternative approach, which is also ongoing, is trying to learn how to decrease ADT duration without compromising survival.”

Dr. Ronald C. Chen, associate professor and associate chair for education with the department of radiation oncology at the University of North Carolina at Chapel Hill, told Reuters Health that “there are now multiple studies consistently showing underutilization of ADT in men with high-risk PCAs treated with EBRT. This is very concerning.

“While ADT does have side effects, as all cancer treatments do, patients need to be informed that long-duration ADT improves cure rates and prolongs life, as demonstrated by multiple clinical trials,” he continued.

“Therefore, skipping ADT or giving short-duration instead of long-duration ADT for these patients with the most aggressive form of localized PCAs, has significant potential negative consequences.

“Further research is needed to better understand if men are deciding not to receive ADT, or physicians are recommending against ADT,” said Dr. Chen, who was not involved in the study. “I suspect there is some of both.”

In an email to Reuters Health, Dr. Quoc-Dien Trinh, co-director of the prostate-cancer program at Dana-Farber/Brigham and Women’s Hospital in Boston and assistant professor of surgery at Harvard Medical School, called the racial disparity “a notable finding.”

“Many investigators (including myself) feel that the racial differences in PCAs outcomes have more to do with access to quality care rather than biological differences,” he explained. “To demonstrate that A-A men are under-treated for potentially lethal PCAs supports that hypothesis.”

Reuters Health Information 12 March 2019
Carbon-Ion Radiotherapy for Prostate Cancer May Cut Risk for Subsequent Tumors

Hypothesis-Generating Study Needs More Validation

Patients with localized prostate cancer (PCA) seemed to have a lower risk of developing subsequent primary cancers when treated with carbon-ion radiotherapy (CIRT) vs. photon beam radiotherapy (RT) or surgery, according to researchers from Japan.

“Based on a propensity score-weighted analysis, CIRT was associated with a hazard ratio (HR) of 0.81 (95% confidence interval [CI] 0.66-0.99, P=0.38, not a statistically significant difference) compared with photon beam RT, and an HR of 0.81 compared with surgery (95% CI 0.68-0.95, P=0.0088),” reported Hirokazu Makishima, MD, of the National Institute of Radiological Sciences (NIRS) in Chiba, and colleagues online ahead of print in Lancet Oncology.

The findings could have safety implications for PCA patients in an era of younger age diagnosis and expanding life expectancy. In addition, charged-particle therapy is thought to achieve better dose distribution and higher biological effectiveness than photon RT. “The heavy ion and larger mass of carbon has the potential to lead to deeper tissue penetration and efficacy in hypoxic tumors,” the authors explained.

The study observed a cumulative incidence of subsequent primary cancers at 9.9 years’ follow-up of 16.1% (95% CI 13.9-18.4) in the CIRT group, 24.0% (95% CI 20.5-27.6) in the photon beam RT group, and 18.7% (95% CI 17.4-20.1) in the surgery group.

“Although prospective evaluation with longer follow-up is warranted to support these results, our data supports a wider adoption of CIRT for men with expected long-term overall survival or those with poor outcomes after receiving conventional treatments,” the authors stated.

The retrospective study drew on the records of men receiving CIRT for PCAs from 1995 to 2012 at the NIRS, and from control cohorts of PCA patients receiving photon RT or surgery in the Osaka Cancer registry from 1994 to 2012. It excluded those with metastasis, node-positivity, locally invasive PCAs, prior synchronous malignancies, and previous RT or chemotherapy.

In the NIRS cohort, 1,455 eligible men received CIRT. In the Osaka Registry, 1,983 men received photon beam RT, and 5,948 had surgery. The median follow-up in the three groups was 7.9, 5.7 and 6.0 years, respectively.

In the CIRT group, 218 (15%) men developed 234 subsequent primary tumors. The most common malignancies were stomach (19%), lung (17%), colon (12%), and bladder (9%), with a median time to first subsequent cancer of 5.7 years. Risk factors for these later tumors were increased age and smoking.

“This hypothesis-generating study requires further validation in prospective studies, or from additional multinational datasets, in disease sites other than PCAs, especially in the setting of similar proton RT data,” Makishima’s group wrote.

The study is limited by its observational design, the uncontrolled use of external beam and brachytherapy in the photon RT group, and the lack of details on dose fractionation and field design.

In addition, the maximum follow-up was only 10 years; the results could not reflect an increase in cancers in all cohorts over time.

Howard M. Sandler, MD, of Cedars-Sinai Medical Center in Los Angeles, said that the findings were “encouraging.” He added that CIRT facilities would be more expensive because of high start-up costs and much larger facilities required for the heavy cyclotron-charged particles.

He also pointed out that widespread adoption of CIRT will only happen if studies show it is more effective. And in an era when we try to keep healthcare costs down, it will have to be, not only more effective, but also cost-effective.

Worry Postprostatectomy a Self-fulfilling Prophecy (Continued from page 4)

People with neuroticism are more susceptible to stressors, and might be susceptible to developing somatic diseases and mental disorders such as depression in response to these stresses,” he said. For example, neuroticism is known to exacerbate conditions such as inflammatory bowel disease and ulcerative colitis in some patients, and to influence urinary symptoms and sexual function.

Study Details

Axcrona and colleagues sent surveys to 982 men who had RPs at the Oslo University Hospital from 2005 through 2010, and based their study on responses from 761 men who reported adverse events and who responded to the neuroticism questionnaire. Quality of life was measured by the self-reported EPIC-26 (Expanded Prostate Cancer Index Composite – Short Form) instrument.

At a mean of three years after surgery, 21% of the men reported treatment failure, defined as salvage radiation treatment, hormonal treatment, or significant PSA elevation, and 22% reported high neurotic tendencies. Compared with men who reported low neuroticism, the men with high neurotic scores reported significantly more overall comorbidities (P=0.006) and significantly worse scores in the EPIC-26 urinary domain (P <0.001), including incontinence and irritation subscales (P <0.001) for each.

Men who scored high on neuroticism also fared less well in bowel problems (rectal urgency, loose/liquid stools, fecal incontinence, bloody stools, rectal pain; P <0.001 for overall bowel problems). Similar results were seen in the sexual problems domain: such men had more erectile dysfunction and had difficulty achieving orgasm (P <0.001 for overall sexual problems). In the hormonal domain, men with high neurotic scores had significantly more hot flashes, breast problems, depression, lack of energy, and weight change (P <0.001 for all).

Christopher Porter, MD, a urologic oncologist at the Virginia Mason Medical Center in Seattle, Washington, who was not involved in the study, said “it’s interesting in their study that one in five men had some form of neuroticism. I think that’s worth looking at. It’s something that’s unknown and maybe
(N=282) or standard of care (N=281). The mean age of the men was 66 years.

Patients had either a Gleason score of 9-10; a score of 7-8 and a PSA level ≥20 ng/mL, with disease of any tumor stage; or a score >8 and a PSA level <20 ng/mL, with stage T2 disease. The maximum allowed PSA level was 150 ng/mL. Men with nodal or distant metastasis at study entry were excluded.

“This trial demonstrated an improvement in disease-free survival, overall survival (OS), and a reduction in distant metastases,” Rosenthal stated. Median follow-up was 5.7 years. However, the impact on OS, which was the primary endpoint, fell short of the trial’s goal.

The reported four-year OS rate was 89% for standard of care and 93% for standard of care plus docetaxel (hazard ratio [HR], 0.69; one-sided P=0.034), or a significant 31% relative risk reduction. However, the OS goal was to detect an improvement from a rate of 86% (standard of care) to 93% (standard of care plus docetaxel), or a 51% relative risk reduction.

For that reason, when these results were first presented last year at the annual meeting of the American Society of Clinical Oncology, meeting discussant Ian Tannock, MD, PhD, from Princess Margaret Cancer Center, University of Toronto, Canada, did not endorse the approach in early-stage disease.

“If there is no effect on overall survival, then chemotherapy is toxicity delayed, and is the preferred strategy,” said Tannock at the time. He added that his opinion might change with longer follow-up. Rosenthal said he anticipated an update in about two years. “Longer-term follow-up may help to clarify the significance of these results,” he agreed.

Comparing the arms (standard of care vs. standard of care plus docetaxel), there were 59 vs. 43 deaths, including fewer deaths from PCa (23 vs. 16). Likewise, the six-year rate of distant metastasis (DM) was lower with standard of care plus docetaxel: 14% vs. 9.1% (HR, 0.60; two-sided P=.044, a statistically significant difference). The six-year disease-free survival (DFS) rate was improved with the addition of chemotherapy: 55% vs. 65% (HR, 0.76; 95% Confidence Interval [CI], 0.58-0.99; two-sided P=.043, a statistically significant difference).

The investigators reported that treatment was “well tolerated” in both arms. However, there were two patient deaths due to adverse events (AEs) in the standard of care plus docetaxel arm. As expected, the difference between arms was primarily related to greater hematologic AEs in the standard of care plus docetaxel arm. “Rates of gastrointestinal and genitourinary AEs were not significantly different between arms,” researchers said.

“Chemotherapy consisted of six 21-day cycles of docetaxel plus prednisone starting 28 days after RT. The RT doses (72-75.6 Gy) were standard at the time of study but are ‘modestly’ lower than contemporary doses (e.g., 79.2 Gy),” say the authors.

RTOG 0521 is one of four major studies evaluating docetaxel in untreated, high-risk, early-stage PCa. The others had negative findings. The Groupe d’Étude des Tumeurs Uro-Génitales (GETUG) 12 demonstrated no statistically significant improvement among men with high-risk disease for the pre-specified endpoint of metastasis-free survival, and the Scandinavian trial SPCG-13 (Scandinavian Prostate Cancer Group) demonstrated no benefit in biochemical DFS in intermediate- or high-risk disease. Similarly, the SPCG-12 study showed no benefit in biochemical DFS for patients with high-risk disease who were randomly assigned to undergo radical prostatectomy (RP) plus adjuvant docetaxel vs. RP alone.

“The discordance in results between RTOG 0521, which showed benefits in OS, DM, and DFS, and the three European studies may stem from differences in the studies’ patient populations,” suggest Rosenthal and colleagues.

“The RTOG 0521 cohort included men with more aggressive disease,” they say. “Notably, 84% of men in RTOG 0521 had Gleason score 8-10, whereas for a majority of men in GETUG-12, SPCG-13, and SPCG-12, Gleason score was ≤7.”

Omar Mian, MD, PhD, a radiation oncologist at the Taussig Cancer Center, Cleveland Clinic, said “The results of this randomized phase 3 study, taken in the context of prior negative studies administering chemotherapy to men with treatment-naïve localized PCa, illustrate the importance of appropriate patient selection,” said Mian, who was not involved in the trial.

“Noting the survival benefit and acceptable risks in the NRG Oncology/RTOG 0521 study, one may reasonably consider adjuvant chemotherapy for the highest-risk patients (e.g., Gleason 9-10 disease),” he concluded.

Worrying (Continued from page 5)

it’s part of a whole host of other factors that need further investigation.

“The center takes a multidisciplinary approach to the care of men with PCa, including a psychologist and social workers who can intervene when there are potential health effects of a patient’s personality,” he said.

Anne Sofie Friberg, MD, from the Rigshospitalet in Copenhagen, Denmark, is lead author of another study showing that men who undergo RP have a significantly increased risk for depression. She commented, “The neuroticism trait could be a vulnerability factor for depression, of course, so this would be a way to find some of those patients who are at most at risk,” she said.

Presented at the 2019 EAU Congress, Abstract 1172
Medscape Medical News 23 March 2019

Resources Address Anxiety, Depression and Prostate Cancer

Many men who are diagnosed with prostate cancer, or are managing the disease, experience some level of anxiety and/or depression. Caregivers may also be affected. The psychosocial challenges surrounding treatment choices and side effect management can have a negative impact on the prostate cancer journey. Anxiety and depression aren’t always effectively treated, in part because the symptoms may not be recognized.

We encourage you to visit the Us TOO web page for important information on recognizing and managing anxiety, depression and prostate cancer.

www.ustoo.org/anxiety-and-depression
P1, “Chemo for Early...” Can men with high-risk non-metastatic disease treated with external radiation benefit from the addition of docetaxel chemotherapy? That question was addressed in a prospective randomized study reported by Rosenthal and co-workers. The primary end point was overall survival, which was not significantly different at four years. However, the chemotherapy group did show an improvement in disease-free survival, overall survival, and a reduction in distant metastases. Given that the follow-up is relatively short, it is too early to make definitive recommendations. However, based on the results thus far, one might anticipate an eventual improvement in survival. Importantly, three other randomized studies did not show a survival benefit, which is why longer follow-up is needed.

The Bottom Line: A randomized study has found improvement in secondary outcomes for men with high-risk disease receiving external radiation plus chemotherapy, but more time is needed before we know the impact on overall survival.

P1, “PET-Based Imaging...” A growing number of studies are showing that Gallium PET scans are better at finding metastases in men with rising PSA after local therapy than conventional CT and bone scans. That finding is demonstrated from a meta-analysis of non-randomized studies reported by Perera, et al that expands on a previous meta-analysis. One would think that with all the non-randomized studies available, someone would be undertaking a randomized study by now. Until one is done, we are unlikely to see this test available for men in the U.S. This is critical because many men with a rising PSA after radical prostatectomy will be advised to receive radiation when, in fact, they actually have metastatic disease. Hopefully, the necessary studies will be done soon.

The Bottom Line: Gallium PET scans appear to be able to pick up more metastatic disease in men with a rising PSA than CT and bone scans but randomized data are needed before it will become available to most patients.

P1, “Long-Term Androgen...” Over and over again, academic physicians talk about the need and value of randomized studies for determining the optimal management for each disease. In the case of high-risk prostate cancer, numerous studies have proven that ADT significantly improves survival of men with high-risk disease when combined with external radiation. The optimal duration continues to be studied but it is now known that 18-36 months is better than 6-12 months, but no study has shown that omitting ADT is beneficial.

So the study by Kishan and co-workers raises several questions. They found that in men with Gleason grade 4-5 cancers, nearly 55% received either no or up to six months of ADT and African-American men were significantly less likely to receive any ADT. Why is this happening? The studies demonstrating improved survival are not new and existing guidelines clearly recommend ADT for these men. Are doctors not reading these guidelines or studies? Is there any financial reason to withhold therapy? Most importantly, what can be done to insure that the recommended guidelines are followed for more patients? Clearly something must be done for all patients, but in particular African-American men, or they will continue to have worse outcomes by receiving suboptimal care.

The Bottom Line: ADT is not being used properly for men with high-risk disease when they are treated with external beam radiation and something must be done so they receive optimal care.

P2, “Intervention Helps...” On so many occasions I have commented on the need for improved patient education about their treatment options for managing localized prostate cancer. A recent randomized study provides support for the impact of that approach. The authors used a validated survey to assess patient satisfaction and regret and found that the education tool they used improved patient satisfaction with treatment decisions, and reduced regrets about those decisions. As pointed out, it is unclear how complications or the likelihood of cure impacted on the answers to the questionnaire. Interestingly, the intervention group had a higher percentage of men choosing active surveillance. Perhaps one day, a formal education program will be used on all men with localized disease.

The Bottom Line: Using a formal education program appears to offer patients a benefit in terms of their satisfaction with their treatment choice.

P5, “Carbon-Ion RT...” A seldom-discussed side effect of photon radiation is the increased incidence of secondary pelvic cancers. That risk is brought to light in the retrospective study comparing results with carbon-ion radiation, photon radiation or radical prostatectomy. The authors reported the cumulative incidence of abdominal and/or pelvic cancers at almost ten years after treatment. The incidence was one-third lower with carbon-ion radiation compared to photon therapy and was similar to the incidence in the surgery group.

(Continued on page 8)
Prospective Multicenter Validation of Androgen Receptor Splice Variant 7 and Hormone Therapy Resistance in High-Risk Castration Resistant Prostate Cancer: The PROPHECY Study
J Clin Oncol 13 March 2019; Epub ahead of print

Purpose: Androgen receptor splice variant 7 (AR-V7) results in a truncated receptor, which leads to ligand-independent constitutive activation that is not inhibited by anti-androgen therapies, including abiraterone or enzalutamide. Given that previous reports suggested that circulating tumor cell (CTC) AR-V7 detection is a poor prognostic indicator for the clinical efficacy of secondary hormone therapies, we conducted a prospective multicenter validation study.

Patients and Methods: PROPHECY (ClinicalTrials.gov identifier: NCT02269982) is a multicenter, prospective-blinded study of men with high-risk mCRPC starting abiraterone acetate or enzalutamide treatment. The primary objective was to validate the prognostic significance of baseline CTC AR-V7 on the basis of radiographic or clinical progression free-survival (PFS) by using the Johns Hopkins University modified-AdnaTest CTC AR-V7 mRNA assay and the Epic Sciences CTC nuclear-specific AR-V7 protein assay. Overall survival (OS) and prostate-specific antigen responses were secondary end points.

Results: We enrolled 118 men with mCRPC who were starting abiraterone or enzalutamide treatment. AR-V7 detection by both the Johns Hopkins and Epic AR-V7 assays was independently associated with shorter PFS (hazard ratio, 4.2 [95% CI, 2.1 to 8.5], respectively) and OS (hazard ratio, 4.2 [95% CI, 2.1 to 8.5] and 3.5 [95% CI, 1.6 to 8.1], respectively) after adjusting for CTC number and clinical prognostic factors. Men with AR-V7–positive mCRPC had fewer confirmed prostate-specific antigen responses (0% to 11%) or soft tissue responses (0% to 6%). The observed percentage agreement between the two AR-V7 assays was 82%.

Conclusion: Detection of AR-V7 in CTCs by two blood-based assays is independently associated with shorter PFS and OS with abiraterone or enzalutamide, and such men with mCRPC should be offered alternative treatments.
This column provides the platform for experts in the field to help men and women by providing answers to questions about sexual health and intimacy challenges that can result from prostate cancer treatment.

This column was compiled with the help of Dr. Anne Katz, Certified Sexuality Counselor and Clinical Nurse Specialist at CancerCare Manitoba. She has educated thousands of healthcare providers and cancer survivors about cancer, sexuality and survivorship. She is the editor of the Oncology Nursing Forum, an avid blogger for ASCO Connections, and the author of 13 books on the topics of illness, sexuality and cancer survivorship. (www.drannekatz.com)

QUESTION FROM PROSTATE CANCER SURVIVOR:
Should my partner wear a condom while he is on Zytiga?

RESPONSE FROM DR. ANNE KATZ:
Zytiga (abiraterone) is an anti-androgen (it blocks testosterone). The only caution related to sexual activity is that a man on this medication should use a condom if he is having sex with a pregnant woman or a woman who wants to become pregnant, as the medication can harm the fetus.

We do not know if the medication or breakdown products of the medication are found in the semen of men taking this medication. This means that we don’t know if the sexual partner of a man taking abiraterone can be exposed to the medication during oral or penetrative sex. If you are concerned, then a condom should be used for all sexual activity where you may be exposed to the medication.

Remember that this is a testosterone blocker so, in theory, there should be no adverse effects on a female partner. A male partner may, however, experience some side effects, but this is not discussed in any of the material posted by the drug manufacturer.

QUESTION FROM PROSTATE CANCER SURVIVOR:
I had my prostate removed almost a year ago and am happy to say that I am cancer free! I am able to have the occasional erection but they are not reliable and, of course, this is making me frustrated. But what I did not realize is that I don’t have orgasms – nothing comes out! They didn’t tell me about this before the surgery!

RESPONSE FROM DR. ANNE KATZ:
First, I want to clear up any confusion about orgasms vs. ejaculation. These are two separate processes. However, for most men, they have always occurred together. So many men don’t know there is a difference. Orgasms are the pleasurable sensations that men feel during intercourse, oral sex and/or masturbation; these are a spinal cord reflex. Ejaculation is the usually simultaneous emission of semen and needs both the prostate and seminal vesicles to occur. The surgery for prostate cancer removes both the prostate and seminal vesicles, resulting in no ejaculation. BUT you can still experience the sensations of orgasm without ejaculation. Some men report that their orgasms are more intense after the surgery than before. Of course, there are also men who report that their orgasms are less intense than before and this bothers them.

A lot of the sensation of orgasm comes from contraction of the muscles of the pelvic floor. So if you experience orgasms that are so intense that they are painful OR orgasms that are very weak, you should see a specialized pelvic floor physiotherapist who will assess those muscles and suggest exercises that may help to correct this.

Watch Dr. Katz’ presentation on sexual health and intimacy from the Prostate Cancer Pathways for Patients and Caregivers event recorded at Englewood Health in Englewood, NJ on September 29, 2018. https://www.youtube.com/watch?v=A2zdDHw2WGY&t=8542s

Do you have a question about sexual health or intimacy? If so, we invite you to send it to Us TOO. We’ll select questions to feature in future Between the Sheets columns.

Please email your question to: ustooBTS@ustoo.org

Or mail your letter to:
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Between the Sheets
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Natural Killer Cells for Prostate Cancer Immunotherapy

Achoo! Caught a nasty cold from that co-worker who insisted on bringing her hacking cough to the office? No problem ... your immune system will fight the invading virus and you’ll be feeling better in a few days.

We’re used to thinking of the immune system as the body’s defense against colds, the flu, or a troublesome stomach bug. But it does much more, including detecting and destroying errant cells almost anywhere in our body that have become cancerous. Scientists can harness the power of the immune system to treat cancer, including prostate cancer. (For background, go to https://www.pcf.org/news/immunotherapy-a-vaccine-for-prostate-cancer/ for a three-part primer on the immune system and prostate cancer. These articles provide a clear introduction to what can seem like a complex topic).

Now, PCF-funded investigator Dr. Aaron LeBeau of the University of Minnesota and his team are developing an interesting and provocative new type of immunotherapy using a specific type of immune cell called natural killer cells, or NK cells for short. These cells are like beat cops on patrol, traveling around the body to look for and kill cells infected with a virus, bacteria, and cancer cells.

NK cells have several potential advantages vs. other types of immunotherapy.

A single patient requires an infusion of ten billion NK cells. Where do these cells come from? NK cells can easily be isolated from blood and grown in the lab. They do not require donor matching, a process similar to that used for blood transfusions, so a single donor could, in theory, provide NK cells for many patients. Thus, NK cell treatments can be significantly cheaper than other immunotherapies that must be made from a patient’s own cells. NK cells live for about a week in the body, so they won’t “hang around” too long, possibly causing adverse effects.

What’s the catch? NK cell therapies still face some hurdles, such as a lack of “targeted” action – they don’t necessarily go to where they are needed. Tumors can also influence the environment immediately around them and suppress the immune system locally.

One way to overcome the problem of tumors hiding from the immune system is to create and attach a “targeting device” to the NK cell, such that it would recognize prostate cancer cells and not normal tissue. Dr. LeBeau and his team are creating a specialized “chimeric antigen receptor,” or CAR for short, to accomplish tumor targeting. The CAR is a genetically engineered protein that recognizes a particular protein on the surface of prostate cancer cells and activates the NK cell to kill the tumor cell. Supported by a PCF Challenge Award, the project will move to testing in animal models this fall. It may be possible to start clinical trials in four years.

That may sound like a long time for a patient considering his options for treatment today. However, it is a reminder that clinician-scientists like Dr. LeBeau are working today to ensure that we have safe and effective new treatments in the future. PCF is proud to support promising early-stage research that has the potential to significantly advance the field of prostate cancer therapeutics.

For more information visit www.pcf.org, email info@pcf.org, or call 1-800-757-2873.