Treat Older Prostate Cancer Patients According to Fitness, Not Age

Although many prostate cancer patients are elderly, new guidelines from the International Society of Geriatric Oncology (ISGO) say that the men’s treatment should be based on their individual health status, not on age.

Elderly men who are frail or who have multiple health conditions may not be able to handle aggressive cancer treatment, but aggressive treatment may be the best course for healthier older men, the guideline authors write in *European Urology*.

“If the health status of the patient is okay, the treatment of elderly men is basically the same as their younger counterparts,” said lead author Dr. Jean-Pierre Droz of Claude-Bernard Lyon 1 University in France. “There is no real difference in the approach, however, there are adaptations of treatment based on the man’s health status,” Dr. Droz told Reuters Health.

To update ISGO’s 2014 guidelines for treating elderly prostate cancer patients, the task force reviewed articles published between 2013 and 2016 on treatment of prostate cancer patients over age 70 and each member proposed guideline changes. The results represent their consensus.

The first recommendation is that doctors should decide the treatment of an older patient based on the man’s individual health status and not according to his age. Elderly men should be treated like younger men if they meet certain standards of health, including considerations of physical fitness, nutrition and other health conditions, they write.

The authors recommend assessing each patient with what’s known as the G8 screening tool, which covers...

(Continued on page 4)

Study Uncovers Why BRCA2-Mutant Prostate Tumors are So Aggressive

Men who carry mutations of the tumor-suppressor gene BRCA2 are at higher risk of developing prostate cancer, and chances are they will have a more aggressive form of the disease, but researchers have only now understood why this happens. A recent study has shown that BRCA2 mutations trigger genetic changes in prostate tumors that resemble those seen in metastasis— or cancer spreading to other organs. The mutations lead to more aggressive disease and poorer prognosis.

The research emphasizes the importance of genetic testing in prostate cancer, which can improve personalized treatment and lead to better outcomes. The study, “Germline BRCA2 mutations drive prostate cancers with distinct evolutionary trajectories,” was published in *Nature Communications*.

Prostate tumors in men with BRCA2 mutations are very aggressive, associated with younger age of onset, affect the lymph nodes more often than non-BRCA2-mutant tumors, and lead to higher patient mortality rates. In these patients, localized prostate cancer rapidly progresses to metastatic castrate-resistant prostate cancer. This form of the disease no longer responds to standard hormone therapy, and one result is a five-year survival rate of only 50-60 percent.

(Continued on page 4)
5-Alpha Reductase Inhibitors and the Risk of Prostate Cancer Mortality in Men Treated for Benign Prostatic Hyperplasia

Wallner LP, DiBello JR, Li BH, et al.
Mayo Clinic Proc 27 October 2016; Epub

To compare the risk of prostate cancer-specific mortality (PCSM) among men treated with 5-alpha reductase inhibitors (5-ARIs) vs. those treated with alpha-adrenergic blockers (ABS) in community practice, a retrospective matched cohort (N=174,895) and nested case-control (N=18,311) study were conducted in four regions of an integrated healthcare system. Men 50 years and older who initiated pharmaceutical treatment for benign prostatic hyperplasia (BPH) between January 1, 1992, and December 31, 2007, and had at least three consecutive prescriptions, were followed through December 31, 2010. Adjusted subdistribution hazard ratios (HRs), accounting for competing risks of death, and matched odds ratios (ORs) were used to estimate PCSM associated with 5-ARI use (with or without concomitant ABS) vs. AB use.

In the cohort study, 1,053 men died of prostate cancer (mean follow-up, three years), 15% among 5-ARI users (N=25,388) and 85% among AB users (N=149,507) (unadjusted mortality rate ratio, 0.8). After accounting for competing risks, it was found that 5-ARI use was not associated with PCSM when compared with AB use (adjusted subdistribution HR, 0.85; 95% confidence interval [CI], 0.7-1.0). Similar results were observed in the case-control study (adjusted matched OR, 0.95; 95% CI, 0.8-1.2).

Among men being pharmacologically treated for BPH, 5-ARI use was not associated with an increased risk of PCSM when compared with AB use. The increased prevalence of high-grade lesions at the time of diagnosis noted in our study and the chemoprevention trials may not result in increased PCSM.

Duration of Treatment in Prostate Cancer Patients Treated with Abiraterone Acetate or Enzalutamide

Pilon D, Behl AS, Ellis LA, et al.
JMCP 7 December 2016; Epub

Abiraterone acetate (AA) and enzalutamide (ENZ) are oral therapies offering survival benefit to metastatic castration-resistant prostate cancer (mCRPC) patients. Despite the availability of multiple treatment options for mCRPC, there is a lack of information on the effect that being initiated on AA or ENZ has on the combined prostate cancer treatment duration.

To compare the combined duration of prostate cancer treatments of men initiated on AA with that of men initiated on ENZ, Truven Health MarketScan Research Databases from March 2012 to December 2014 were used to identify males with prostate cancer initiated on AA or ENZ (index therapy). Baseline characteristics were assessed during the six months pre-index. Inverse probability of treatment weights (IPTWs) were used to reduce baseline confounding. Treatment duration spanned from the index date to the earliest of treatment discontinuation (defined as a >60-day gap in treatment), 24 months post-index, health plan disenrollment, or end of data. Weighted Kaplan-Meier and Cox proportional hazard models were used to compare the combined duration of mCRPC treatments (AA, ENZ, chemotherapy, sipuleucel-T, and radium 223) and any prostate cancer treatments (mCRPC, hormonal, and corticosteroid treatments) between men initiated on either AA or ENZ.

A total of 2,591 men initiated on AA with that of men initiated on ENZ were selected for the study. Patient characteristics were generally well balanced after IPTW. At three months, men initiated on AA were associated with fewer discontinuations of mCRPC treatments (hazard ratio [HR]=0.73, P=0.004) or of any prostate cancer treatments (HR=0.61, P=0.002), compared with men initiated on ENZ. This result was maintained at six, nine, 12, 18, and 24 months for mCRPC treatments (HR=0.75, P<0.001) and for any prostate cancer treatments (HR=0.69, P<0.001). Median duration of mCRPC treatments was 4.1 months longer for men initiated on AA compared with those initiated on ENZ (18.3 vs. 14.2 months, P<0.001) and similarly, the median duration of any prostate cancer treatment was longer for men initiated on AA compared with those initiated on ENZ (not reached vs. 22.2 months, P<0.001).

In this study, men with mCRPC initiated on AA, compared with those initiated on ENZ, had a longer combined duration of prostate cancer treatments.
Doc Moyad’s What Works & What is Worthless Column, Also Known As “No Bogus Science” Column

“Eat Fat To Lose Fat and Fight Cancer = End Justifies the Means?!”

Mark A. Moyad, MD, MPH, University of Michigan Medical Center, Department of Urology

Editor’s Note: Us TOO invites certain physicians and others to provide information and commentary for the Hot SHEET to enrich its content to empower the reader. This column contains the opinions and thoughts of its author and are not necessarily those of Us TOO International.

One of the hottest diets now in clinical trials in cancer is the high-fat diet or ketogenic diet. It is very interesting and at least short-term clinical trials in the area of heart health are beginning to show it is an option, and a potentially safe one for some individuals. So, if heart-healthy = prostate-healthy (Moyad Circa 1999), then why not make a high-fat diet an option for some cancer patients?

Does the end justify the means when it comes to diet and weight loss? I think so! For example, bariatric or weight loss surgery itself is not pretty (it is a life-long irreversible change for most) but it can have pretty impressive results! So, along comes this high-fat diet with the idea that you force the body to use an alternative fuel source for energy that some cancers cannot survive on (theoretically speaking). And, if you lose weight during the process and you needed to lose weight, then awesome! This recently published randomized trial from Norway is one that I wish would have received more attention. It consisted of barely obese male individuals assigned to a high-fat or low-fat diet consisting of roughly the same calories for 12 weeks. It took about 8 weeks for the high-fat group to start seeing more healthy changes but, basically, the amount of body fat they lost including the dangerous “visceral” fat (or deep-belly type) was the same as the other group! Insulin changes and other markers (except the bad cholesterol change) were better on the low-fat diet and the good cholesterol increase was better on the high-fat diet! How cool is that! And, now brace yourselves for a second: the average weight loss was 11-12 POUNDS in three months! What the Heck! And, this is without the help of some celebrity-endorsed weight loss program?

Systolic blood pressure dropped by 10-15 points! What is going on here?! Diet should fit personality and I bet you that, many years from now, a high-fat diet will have a stronger role in some cancer patients than other types of diets, which is similar to what we are beginning to see in cardiovascular medicine. There is some suggestion that, for some of the more aggressive cancer types, a high-fat diet could be a good fit for some to try to get an added potential advantage, especially if weight loss is needed.

So, eat fat to lose fat and fight cancer? Maybe, but it does appear to be heart-healthy right now for some people that need to lose weight ASAP but have been frustrated by the pills, powders and other diets thrown at them in the past few years. It is not the only option, of course (don’t freak out, vegetarians or paleo people), but one of many that should be considered in any discussion of how to potentially fight cancer even further, beyond regular treatment with dietary or lifestyle changes.

MAN I LOVE THIS STUFF (I know, I have got to cut back on the caffeine and Coach Harbaugh tweets just a little)! Oh and, by the way, where did Tom Brady go to college?! Go Blue Baby!

References


USPSTF Names Urologist to Review Panel for Updated Prostate Cancer Screening Recommendations

The U.S. Preventive Services Task Force (USPSTF) has selected an AUA-nominated urologist to independently review the evidence report that will inform updated recommendations on prostate cancer screening. The AUA nominated three urologists in response to a formal request from the USPSTF.

The AUA is a long-standing advocate for USPSTF reform, and has worked actively with U.S. Representatives Marsha Blackburn (R-TN-07), Bobby Rush (D-IL-01) and other lawmakers to advance legislation on this important issue. In November, the AUA provided testimony supporting USPSTF reform to the House Energy & Commerce Subcommittee on Health and, most recently, announced support for H.R. 539, the USPSTF Transparency & Accountability Act of 2017, introduced on January 13 by Reps. Blackburn and Rush.

“We truly appreciate the USPSTF’s inclusion of urologists on this important panel and its willingness to consider the AUA’s nominations,” said AUA President Dr. Richard Babayan. “This is an important first step toward the transparency we seek in our efforts to reform the Task Force.”

“We believe that input from a urologist will be meaningful and impactful relative to developing recommendations that the prostate cancer community as a whole can support.”

Ensuring appropriate access to prostate-specific antigen screening and reforming the USPSTF remain top priorities for the AUA. If you have any questions or would like additional information, please contact GovernmentRelations@AUAnet.org.

AUA news release, 1 February 2017
food intake, weight loss, body mass, mobility, neurological issues, medications, health status and age. If the G8 produces an abnormal result, this should be evaluated taking into account whether patients have other health conditions, can perform basic daily activities and if they have had any recent unintentional weight loss.

Healthy men should tolerate any standard treatment, while men considered frail must receive treatment to try to reverse impairments before receiving standard treatments, according to the authors. Men with untreatable health problems should receive symptomatic treatment and may be able to handle adapted treatments. Initially, doctors should also screen men for mental impairments to determine if they are able to make their own treatment decisions. The patient’s decision is important and sometimes there are choices which must be made because there are two equivalent treatments available,” Dr. Droz noted.

Lastly, doctors deciding a treatment method must consider how severe or advanced the prostate cancer is.

“Initially treating a frail patient for reversible health problems can be effective in helping them withstand the standard treatment given to younger men,” said Dr. Joaquim Bellmunt, a researcher at the Dana-Farber Cancer Center at Harvard University in Boston who was not involved in the study.

“There are a variety of factors doctors may want to consider in treatment,” he added.

“Assessment of social situation, financial resources, access to services, and patient preference (in terms of goals of therapy) are all relevant.”

Reuters Health
25 January 2017

Phase 1 Trial Begins for Immunotherapy Vaccine

An open-label, multicenter Phase 1 clinical trial has begun to evaluate the safety and immunogenicity of Panacea Pharmaceuticals’ PANC-301-1, a nanoparticle immunotherapy vaccine that targets HAAH-positive cancer cells in patients with persistent prostate cancer.

The first patient has been dosed, and participants are being enrolled in Alabama, California, Nebraska, and South Carolina.

HAAH, which stands for human aspartyl (asparaginyl) β-hydroxylase, is a protein required for fetal development, but its expression is silenced at birth. Studies have reported, however, that some cancers are able to express HAAH, and it participates in cancer cell growth, motility, and invasiveness. The protein is found in more than 20 types of cancer, and its expression is associated with poor prognosis. Its specificity to cancer cells has made it a target for therapies.

“HAAH provides a new potential treatment pathway for men living with persistent prostate cancer, and with the enrollment of the first patient at our center, we are eager to understand the safety and immunogenicity for PANC-301-1 to address this unmet medical need in cancer diagnosis and treatment,” said lead investigator Luke Nordquist, MD, of GU Research Network in Omaha, NE.

(Continued on page 8)

Mutant BRCA2-Prostate Cancers are Aggressive

To understand why BRCA2-mutant prostate cancers are so aggressive, an international team of scientists, led by Australia’s Monash University Biomedicine Discovery Institute (BDI), sought to characterize the genomic alterations seen in men with localized prostate cancers who inherited BRCA2 mutations. After analysis of localized prostate tumor specimens from 14 men with BRCA2 mutations – collected during surgical removal of tumors – the team compared their data with that in a companion study. The other study, led by Monash-led study collaborators, looked at prostate cancer samples from more than 320 men without BRCA2 mutations. The research was published simultaneously in Nature with the Monash study.

Surprisingly, the team found that localized prostate tumors with faulty BRCA2 were genetically similar to metastasis in metastatic prostate cancer. This was associated with activation of signaling pathways that rendered the cancer more aggressive, which was rarely observed in localized prostate cancer of men lacking BRCA2 mutations.

“As the tumors in men with the BRCA2 gene fault are so different from the ‘get-go,’ our findings raise the question about whether these patients should be managed differently at diagnosis,” Dr. Renea Taylor, a fellow at Monash who led the study, said in a press release.

“These new findings detailing the genomic instability of BRCA2 prostate cancer are important as we may be able to target this with new therapies,” said Declan Murphy, Director of Genitourinary Oncology at the Peter MacCallum Cancer Center and study author.

Prostate Cancer News Today
18 January 2017

Benefits of Multiparametric Magnetic Resonance Imaging in Clinically Significant Prostate Cancer

In the UK PROMIS study reported in The Lancet, Ahmed et al. found that use of multiparametric magnetic resonance imaging (MP-MRI) might reduce the need for transrectal ultrasound (TRUS)-guided prostate biopsy and improve detection of clinically significant prostate cancer.

In the study, 576 men enrolled from 11 UK sites between May 2012 and November 2015 and had PSA levels ≤15 ng/mL and no prior biopsy. They underwent 1.5 Tesla MP-MRI followed by both TRUS biopsy and template prostate mapping (TPM) biopsy, used as the reference test. Clinically significant cancer was defined as a Gleason score 2+3 or a maximum cancer core length ≥6 mm.

On TPM biopsy, 408 men (71%) had prostate cancer, with cancer being clinically significant in 230 of them (40%). Sensitivity for clinically significant cancer was 93% for MP-MRI vs. 48% for TRUS biopsy (P <0.0001), whereas specificity was 41% vs. 96% (P <0.0001). Serious adverse events occurred in 44 men (5.9%), including sepsis in eight men.

It was calculated that use of MP-MRI as triage might allow avoidance of primary biopsy in 27% of patients and reduce diagnosis of clinically insignificant cancers by 5%. Furthermore, it was calculated that using MP-MRI find-
Prostate Cancer Mortality Risk & Where You Live
(Continued from page 1)

South Carolina, and Virginia. Specifically, the highest death rate from prostate cancer in 2014 was in Madison County, MS with 64 deaths per 100,000 residents, followed by Macon County, AL with 57 deaths per 100,000, Wilcox County, AL with 55 deaths per 100,000, Phillips County, AR and Perry County, AL, both with 54 deaths per 100,000. The lowest death rate from prostate cancer was in Summit County, CO with 10 deaths per 100,000 people, followed by Aleutians East Borough, Aleutians West Census Area, AK with 11 deaths per 100,000 and Putkin County, CO with 13 deaths per 100,000.

“Such significant disparities among US counties is unacceptable,” said Mokdad, lead author on the study and Professor of Global Health at the Institute for Health Metrics and Evaluation (IHME) at the University of Washington in Seattle. “Every person should have access to early screenings for cancer, as well as adequate treatment,” he said. Researchers reported the national mortality rate from all cancers combined dropped by 20% from 1980 to 2014. However, 160 of the 3,000 counties studied showed increases in all-cancer death rates during the same period, raising questions about access to care, prevention efforts, treatment, and other issues.

“As the US enters a new debate about access to healthcare, these findings on the wide differences in cancer mortality should inform the discussion,” said Laura Dwyer-Lindgren, co-author of the study. “What’s causing cancer to be so much more fatal in one part of the country than in other parts demands further investigation,” she said. Researchers pointed to some potential explanations for high cancer mortality rates in certain regions. Cancer incidence could be high due to a combination of risk factor profile and poor prevention and screening programs. Also, these high rates could be due to a lack of early detection for some cancers, and lack of specialized treatment, which could be deadly.

PSA Nadir May Guide High-Risk Prostate Care

A retrospective analysis reported online in JAMA Oncology showed that a PSA nadir value >0.5 ng/mL after radiation therapy (RT) for localized prostate cancer identified a subgroup of men who had an increased risk of dying before treatment failure. Post-treatment PSA nadir was one of three PSA-based measures satisfying criteria to qualify as surrogates for all-cause mortality – the other two being PSA doubling time and a shorter interval to PSA failure (PSAF) or recurrence – but had better predictive value. PSAF itself did not have a significant association with all-cause mortality. The findings suggested that post-RT PSA nadir could be used to select men for clinical trials or salvage androgen-deprivation therapy (ADT).

“An additional point of clinical importance is that PSAF was not a surrogate, even among men with no or minimal comorbidity,” Trevor J. Royce, MD, of Brigham and Women’s Hospital in Boston, and co-authors said of their findings. “While this requires external validation, it suggests the need for further investigation.”

Risk of Prostate Cancer Diagnosis and Mortality in Men with a Benign Initial Transrectal Ultrasound-Guided Biopsy Set: A Population-Based Study

Lancet Oncology 13 January 2017; Epub

Background: The risk of missing prostate cancer in the transrectal ultrasound (TRUS)-guided systematic biopsies of the prostate in men with suspected prostate cancer is a key problem in urological oncology. Repeat biopsies or MRI-guided biopsies have been suggested to increase sensitivity for diagnosis of prostate cancer, but the risk of disease-specific mortality in men who present with raised PSA concentration and a benign initial biopsy result remains unknown. We investigated the risk of overall and prostate cancer-specific mortality (PCSM) in men with a benign initial biopsy set.

Methods: Data were extracted from the Danish Prostate Cancer Registry – a population-based registry including all men undergoing histopathological assessment of prostate tissue. All men who were referred for TRUS-guided biopsy for assessment of suspected prostate cancer between Jan 1, 1995, and Dec 31, 2011, in Denmark were eligible for inclusion. Follow-up data were obtained on April 28, 2015. The primary endpoint was the cumulative incidence of PCSM, analysed in a competing risk setting, with death from other causes as the competing event.

Findings: Between Jan 1, 1995, and Dec 31, 2011, 64,430 men were referred for TRUS-guided biopsy, of whom 63,454 were eligible for inclusion. Median follow-up was 5.9 years (interquartile range [IQR] 3.8-8.5) and the total follow-up time, from the enrollment of the first patient on Jan 1, 1995, until the extraction of causes of death on April 28, 2015, was 20 years. 10,407 (30%) of 35,159 men with malignant initial biopsy sets died from prostate cancer, compared with 541 (2%) of 27,181 men with benign initial biopsy sets. Estimated overall 20-year mortality was 76.1% (95% confidence interval [CI] 73.0-79.2). In all men referred for TRUS-guided biopsy, the cumulative incidence of PCSM after 20 years was 25.6% (24.7-26.5) vs. 50.5% (47.5-53.5) for mortality from other causes. In men with benign initial biopsy sets, the cumulative incidence of PCSM was 5.2% (3.9-6.5) vs. 59.9% (55.2-64.6) for mortality from other causes. In men with PSA concentrations 10 ng/mL or lower and benign initial biopsy sets (2,779 men), the cumulative incidence of PCSM was 0.7% (0.2-1.3). Cumulative incidence of PCSM in men with benign initial biopsy sets was 3.6% (95% CI 0.1-7.2) for men with a PSA higher than 10 ng/mL but 20 ng/mL or less (855 men) and 17.6% (12.7-22.4) for men with a PSA higher than 20 ng/mL (454 men).

Interpretation: The first systematic TRUS-guided biopsy set holds important prognostic information. The 20-year risk of PCSM in men with benign initial results is low. Our findings question whether men with low PSA concentration and a benign initial biopsy set should undergo further diagnostic assessment in view of the high risk of mortality from other causes.

(Continued on page 6)
gests that, in men with moderate-to-severe comorbidity, PSAF is unlikely to translate into a surrogate for all-cause mortality and therefore has potential implications on how such men should be managed at the time of PSAF.

“Specifically, some men with moderate-to-severe comorbidity may be optimal candidates for active surveillance (AS).”

The findings “seem intuitive,” except for the lack of association between PSAF and all-cause mortality, “which is in some respects the same as a PSA nadir >0.5 ng/mL,” said William Catalona, MD, of Northwestern University Medical Center in Chicago. He congratulated the authors for a good study of an unmet need in prostate cancer.

“There is a genuine need for surrogate endpoints for all-cause mortality in men with localized, unfavorable-risk prostate cancer, because it often takes 10 to 20 years for men to die after unsuccessful treatment,” Catalona told MedPage Today via email.

“The study had a number of limitations, which the authors acknowledged,” Catalona said. “Those include reliance on data from a single clinical trial and a relatively small sample size and use of a lower dose of RT than current practice.”

“Additionally, some men received ADT, which is a strong driver of PSA expression, sometimes independent of its effects on tumor growth ... Their argument would be more compelling if the adjuvant treatment were a different form of therapy, such as chemotherapy, that does not directly affect the expression of the PSA gene.”

The study added to mounting evidence that poor PSA response to treatment correlated with poor outcome, “possibly due to genetic variants conferring insensitivity to androgen-directed therapy,” said Omar Mian, MD, PhD, of the Cleveland Clinic. Mian said, “the challenge is to operationalize these findings by integrating our understanding of PSA response with emerging molecular and genetic biomarkers to offer men better therapies tailored to their disease.”

Several surrogates for prostate cancer-specific mortality have been identified: PSA nadir >0.5 ng/mL; PSA doubling time (PSADT) <3, 12, or 15 months; and time to PSAF (<1.5, 2.0, or 2.5 years). All of the parameters satisfied the Prentice criteria for surrogacy. Whether or not the parameters satisfy surrogacy criteria for all-cause mortality remained unclear.

To examine the validity of candidate surrogates for all-cause mortality in prostate cancer, Royce and co-authors retrospectively analyzed data on 206 men with newly diagnosed, high-risk prostate cancer (defined as PSA >10 but <40 ng/mL, Gleason score ≤7, or imaging evidence of extracapsular extension or seminal vesicle invasion). The men participated in a randomized clinical trial conducted from 1995 to 2001, receiving RT alone or with six months of postirradiation ADT.

The entire cohort had a median follow-up of 16.6 years. Researchers focused on a subgroup of 157 men who had minimal or no comorbidities and who had a median follow-up of 16.5 years.

Investigators analyzed four surrogate endpoints for all-cause mortality: PSAF (rise to >10 ng/mL), post-treatment PSA nadir >0.5 ng/mL, PSADT (Continued on page 8)

Effect of Long-Term Hormonal Therapy (vs. Short-Term Hormonal Therapy): A Secondary Analysis of Intermediate-Risk Prostate Cancer Patients Treated on NRG Oncology RTOG 9202


Int J Radiat Oncol Biol Phys 8 November 2016; Epub

NRG Oncology RTOG 9202 was a randomized trial testing long-term adjuvant androgen deprivation (LTAD) vs. initial AD only (STAD) with external beam radiation therapy (RT) in mostly high-risk and some intermediate-risk prostate cancer patients.

RTOG 9408 found an overall survival (OS) advantage in men with cT1b-T2b disease and PSA <20 ng/mL, with benefit observed mostly among intermediate-risk patients. It was still unknown whether intermediate-risk patients would experience an additional survival benefit with LTAD; thus, we performed a secondary analysis to explore whether LTAD had any incremental benefit beyond STAD among the intermediate-risk subset of RTOG 9202. Study endpoints were OS, disease-specific survival (DSS), and PSA failure (PSAF).

Analysis was performed for all men enrolled in RTOG 9202 defined as intermediate-risk (cT2 disease, PSA <10 ng/mL, and Gleason score = 7 or cT2 disease, PSA 10-20 ng/mL, and Gleason score <7). This review yielded 133 men: 74 (STAD) and 59 (LTAD). The Kaplan-Meier method was used to estimate OS; the cumulative incidence approach was used to estimate DSS and PSAF. A two-sided test was used, with significance level defined as <0.05.

With over 11 years of median follow-up, 39 STAD patients were alive and 33 LTAD patients were alive. There was no difference in OS (10-year estimates, 61% STAD vs. 65% LTAD; P=0.53), DSS (10-year DSS, 96% vs. 97%; P=0.72), or PSAF (10-year PSAF, 53% vs. 55%; P=0.99) between groups (difference is not statistically significant).

LTAD did not confer a benefit in terms of OS, DSS, or PSAF rates in the intermediate-risk subset in this study. Whereas the subset was relatively small, treatment assignment was randomly applied, and a trend in favor of LTAD would have been of interest. Given the small number of disease-specific deaths and lack of benefit observed regarding our endpoints, this secondary analysis does not suggest that exploration of longer hormonal therapy is worth testing in the intermediate-risk prostate cancer subset.

MP-MRI

(Continued from page 4)

ings to determine the need for subsequent TRUS biopsy could result in detection of 18% more cases of clinically significant prostate cancer compared with use of TRUS biopsy in all men.

Investigators concluded: “MP-MRI, used as a triage test before first prostate biopsy, could reduce unnecessary biopsies by a quarter. MP-MRI can also reduce overdiagnosis of clinically insignificant prostate cancer and improve detection of clinically significant cancer.”

The ASCO Post 1 February 2017
Doctor Chodak’s Bottom Line


Editor’s Note: Us TOO has invited certain physicians and others to provide information and commentary for the Hot SHEET to enrich its content to empower the reader. This column contains the opinions and thoughts of its author and are not necessarily those of Us TOO International.

P1, “Treat Older Prostate...”
The best option for treating prostate cancer depends on many factors. Given the frequent slow progression of the disease, one of the more critical factors is a patient’s life expectancy. Many articles have discussed using a man’s age when considering treatment. However, the article by Droz and co-workers points out that age is less reliable than a man’s health status. This does seem intuitively obvious, and completely logical because some older men have a long life expectancy while many younger men do not. The authors recommend using a G8 screening tool. Another helpful tool is the updated Charlson comorbidity index. However, these tools only provide some estimate of a man’s health status and ultimately each individual will have to weigh the odds the cancer will progress against the odds they will live long enough to be harmed by the disease.

The Bottom Line: Health status and life expectancy are far more important than biological age when considering prostate cancer treatment.

P1, “Study Uncovers Why...”
One of the challenges of managing prostate cancer is its diverse behavior. Some cases will never progress and others will rapidly cause a man’s death. One factor that may help identify those with aggressive disease is the presence or absence of the BRCA2 mutation. Those having it appear to be at greater risk from the disease. One question is whether all men should be tested for this mutation following their diagnosis? Another option might be to consider doing it only for those men considering active surveillance (AS). The reason not to test everyone is that only 2% of men have this mutation so routine testing would be very expensive.

The Bottom Line: A BRCA2 mutation means a prostate tumor is more aggressive and a patient may not be a good candidate for AS; however, more information is needed before such a recommendation can be made.

P2, “5-Alpha Reductase...”
Years ago a randomized trial was conducted to determine if a 5-alpha reductase inhibitor (5-ARI) could prevent prostate cancer. Although the incidence of cancer declined, the FDA did not approve it for that indication because there was a greater incidence of high-grade lesions in the men receiving the drug vs. controls. A subsequent publication found no difference in overall survival at 18 years, but a number of factors prevented a valid analysis of prostate cancer mortality. Nevertheless, the failure to lower mortality needs to be an important outcome beyond simply taking the drug to reduce the detection rate. Now we have a retrospective and case-controlled report by Wallner, et al., which looks at prostate cancer mortality in men taking a 5-ARI compared to those taking an alpha blocker. They found that there was no increased risk of dying from prostate cancer in the men on a 5-ARI. So, should the FDA review this data and approve the drug as a preventive agent? Unfortunately, the data is unlikely to change FDA’s decision because non-random studies are at risk for many potential biases. If the drug does lower detection without reducing mortality, is it worth taking?

The Bottom Line: Long-term use of a 5-ARI may not increase the risk of dying of prostate cancer, but it also does not appear to affect survival. So, there isn’t a good enough case to support taking it to prevent the disease at this time.

P4, “Benefits of...”
Multi-parametric MRI (MP-MRI) is being increasingly studied when men are referred for a prostate biopsy. It appears to lower the incidence of finding non-life-threatening cancer while helping to identify those cancers with a greater malignant potential. The study by Ahmed et al. provides supporting evidence. Using this method lowered the detection of clinically insignificant cancer by 5% while sparing 27% from undergoing a biopsy, but 7% of dangerous cancers were missed. Whether they would be detected at a later time without resulting in higher mortality is unclear at this time. One problem with the study is that they defined dangerous cancers as a Gleason score >4+3 OR a maximum core length ≥6 mm. This latter criterion is less robust as a predictor of a life-threatening cancer. Should all men referred for their first biopsy undergo MP-MRI first? Is the potential gain enough to justify the added cost?

The Bottom Line: MP-MRI does appear to reduce the need for prostate biopsy but it will miss some life-threatening cancers. More data are needed to determine its role in evaluating men needing a prostate biopsy.

P5, “Risk of Prostate...”
If a man has a negative prostate biopsy, follow-up is likely to include a second biopsy. The interesting study by Klemann, et al. provides potentially useful information about whether repeat biopsies are worthwhile. They assessed nearly 65,000 men in Denmark who underwent a prostate biopsy. They found that if a man’s first biopsy set was negative, the risk of dying from prostate cancer at 20 years was only 5.2% vs. nearly 60% of dying from some other cause. If the initial PSA was 10 ng/mL or less, the risk of dying at 20 years was only 0.7%. Based on these results, strong consideration should be given to avoiding a second biopsy if the first one is negative and the PSA remains under 10 ng/mL.

The Bottom Line: Men with a negative biopsy and a PSA ≤10 ng/mL have an extremely low risk of dying from prostate cancer at 20 years and may only warrant observation rather than doing another biopsy, as long as the PSA remains in this range.

P6, “Effect of Long-Term...”
A number of randomized studies have shown the benefit of adjuvant androgen deprivation therapy (ADT) combined with external beam radiation. Following the initial trials, additional testing has been aimed at determining the optimal duration of the ADT. One of these studies, RTOG 9202, tested four months vs. 28 months in men with intermediate- or high-risk disease. Now a separate updated analysis was performed on the intermediate-risk group involving 133 patients to

(Continued on page 8)
Phase 1 Immunotherapy Trial (Continued from page 4)

PAN-301-1 consists of a nanoparticle with hundreds of copies of an HAAH fragment. It induces a specific antibody response and stimulates immune cells to target HAAH.

In preclinical studies, the vaccine significantly inhibited tumor growth and metastasis, and it improved survival in mice and rats. There were also fewer side effects than with current cancer therapies, the release said.

The Phase 1 trial, designed to assess the vaccine’s safety, will enroll up to 18 men with biochemically relapsed prostate cancer (their PSA levels increased after their last hormone therapy). Patients will receive PAN-301-1 injections every 21 days using an escalation-dose scheme to determine the optimal dosage for a Phase 2 trial.

“At Panacea, we have created a promising new vaccine therapy drug candidate that targets a specific and novel cancer-relevant marker, overcoming self-tolerance, yet avoiding autoimmune-like side effects of check-point inhibitors throughout our pre-clinical studies,” said Hossein A. Ghanbari, PhD, president, chief executive officer, and chief science officer at Panacea Pharmaceuticals. “The initiation of the Phase I PAN-301-1 serves as a starting point for utilizing HAAH treatment to prevent the recurrence of cancer. We are excited to explore this new targeted biological pathway in cancer.”

Prostate Cancer News Today 19 January 2017

The Bottom Line (Continued from page 7)

determine if longer therapy was better. The results showed no significant difference in this relatively small cohort of men. Based on this finding, a decision is being made not to design a new prospective study aimed at answering this question.

The Bottom Line: For now, shorter therapy (four months of ADT) seems sufficient for treating men with intermediate-risk prostate cancer.

Post-RT PSA Nadir (Continued from page 6)

<9 months, and interval to PSAF <30 months.

Data analysis showed that three of the four candidate surrogates satisfied Prentice criteria, including the requirement that the surrogate remained significant in adjusted analyses. Only PSAF did not make the cut, as an adjusted analysis yielded an all-cause mortality hazard ratio (HR) of 1.5 (95% confidence interval [CI] 0.9-2.3, P=0.10). The other three remained significant after adjustment:

- PSA nadir >0.5 ng/mL: HR 1.7, 95% CI 1.2-2.5, P=0.01
- PSADT <9 months: HR 2.1, 95% CI 1.3-3.3, P=0.003
- Interval to PSAF <30 months: HR 1.8, 95% CI 1.1-2.9, P=0.03

An analysis of treatment assignment also did not significantly affect all-cause mortality in an adjusted analysis. To identify the best surrogate among the three successful candidates, the authors performed an analysis to determine the proportion of treatment effect (PTE) explained by the surrogate. Perfect alignment with Prentice criteria for surrogacy would produce a PTE of 100%. The analysis produced a PTE value of 103.86% for PSA nadir >0.5 ng/mL, 43.09% for PSA doubling time <9 months, and 41.26% for PSA failure interval <30 months.

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