New Research Finds Low Bone Health Testing Rates After Prostate Cancer Treatment

Quebec study finds bone mineral density (BMD) testing for men with prostate cancer undergoing ADT are not meeting guideline recommendations

New research in the October 2020 issue of INJCCN – *Journal of the National Comprehensive Cancer Network* finds the rate of bone mineral density (BMD) testing in men with prostate cancer (PCa) undergoing androgen deprivation therapy (ADT) has improved in recent years, but remains low. ADT is considered a cornerstone of treatment for high-risk or advanced PCa and is used in nearly half of all PCa patients. However, it can result in preventable side effects like osteoporosis and bone fractures. Despite clinical recommendations that call for BMD testing in ADT recipients, only 23.4% of the men studied received testing in 2015. That is up from just 4.1% in 2000.

“Although we expected BMD testing rates to be fairly low given the prior literature, we were somewhat surprised that they didn’t go up more in recent years,” said senior author Alice Dragomir, MSc, PhD, McGill University in Montreal, Quebec who worked with Armen G. Aprikian, MD, Marie Vanhuyse, MD, MSc, and Jason Hu, MSc, also from McGill. “Bone density testing helps doctors evaluate fracture risk and identify which patients would benefit from additional monitoring and interventions like lifestyle changes and/or medications. Perhaps the low rate of testing will change in the coming years thanks to renewed attention on bone health issues in the clinical oncology community. It may be interesting to re-examine BMD testing rates in a few years.”

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A New AKT Inhibitor for Prostate Cancer

Ipatasertib, an investigational kinase inhibitor targeting a key cancer metabolic pathway showed promise when used in combination with abiraterone for untreated men with asymptomatic or mildly symptomatic metastatic castration-resistant prostate cancer (mCRPC). Results with the combination were presented online during the European Society of Medical Oncology (ESMO) Virtual Congress 2020.

“The combination is promising but isn’t quite ready for the clinic,” commented invited discussant Henrik Grönberg MD, PhD, from the Karolinska Institute in Stockholm, Sweden.

The new results come from the phase 3 IPATential 150 trial, which met only 1 of its 2 primary endpoints as reported by the investigators. Ipatasertib combined with abiraterone improved radiographic progression-free survival (rPFS) for men with mCRPC with PTEN loss (gene deletion), as assessed with immunohistochemistry (IHC, dye-stained tissue analyzed with a microscope), vs. abiraterone treatment alone. The study was presented at the European Society of Medical Oncology in September 2020.

“But the trial failed to meet its other primary endpoint of rPFS in the intention-to-treat (ITT) population, which included men without IHC evidence of PTEN loss,” reported Johann De Bono, MD, PhD, from the Institute of Cancer Research at the Royal Marsden Hospital in London, UK. “In this primary analysis, the combination of ipatasertib plus abiraterone as a
Reserve PARP Inhibitors for mCRPC with BRCA Mutations

For men with metastatic castration-resistant prostate cancer (mCRPC), any new therapy that offers the chance of a higher response rate or longer survival vs. with the standard of care would be welcome. The FDA recently approved 2 such drugs for use in men with mCRPC: the poly(ADP-ribose) polymerase (PARP) inhibitors rucaparib and olaparib.

Both were approved for treating men with advanced prostate cancer (PCa) with deleterious germline and/or somatic BRCA [genetic] mutations following androgen receptor-directed therapy and taxane-based chemotherapy.

But there was difference in the wording of the indication that was approved, as noted by Michael T. Schweizer, MD, and colleagues from the Fred Hutchinson Cancer Research Center and the University of Washington in a recent commentary published in the *Journal of Clinical Oncology*. Olaparib received wider approval for treatment of “deleterious or suspected deleterious germline or somatic homologous recombination repair gene (HRR)-mutated mCRPC” with disease progression following therapy with either enzalutamide or abiraterone.

It’s the “deleterious or suspected deleterious” part of that indication that concerns these experts that this may lead to injudicious treatment of men who may best be treated by other approaches.

“Using standard-of-care PARP inhibitors in those with uncertain or little chance of benefit could mean missing a window of opportunity for more effective therapy. This may result in decreased survival and hamper clinical trial enrollment to the very studies that could define the predictive utility of individual genes,” they write.

Elaborating in an interview with *Medscape Medical News*, Schweizer said: “The issue is that olaparib has a long list of genes that would make you eligible to receive it, but it’s not clear that many of these genes are good biomarkers for response to that drug.”

For men who have “one of the less common HRR genes, maybe without high level of evidence that they are really predictive of response, I would still give careful consideration to some of the other drugs that have been around for a while and that we know have a track record of working well for PCa, such as taxane-based chemotherapy,” Schweizer commented. Mark Pomerantz, MD, a geneticist and specialist in gastrointestinal oncology at the Dana-Farber Cancer Institute in Boston, who was not involved in the study, stated Schweizer and colleagues are “exactly right.”

“The landmark studies leading to the approval of the two PARP inhibitors for PCa were critical studies,” Pomerantz said in an interview. “However, they do not address, the full expanse or limitation of men who benefit most from these drugs.”

“The editorial is a call to action for additional studies of specific mutations to see which may be sensitive to PARP inhibitors,” he said.

In their commentary, Schweizer and colleagues note that the approval of olaparib includes several genes that have not been shown in clinical studies to be predictive of response to PARP inhibitors.

“The unintended consequence of using this permissive biomarker strategy for selecting men for PARP inhibitor treatment may be that men having an unclear chance of benefit are exposed to toxicities and delays in utilizing more effective therapies,” they write.

In the pivotal phase 2 TRITON2 trial, which led to rucaparib’s accelerated approval for mCRPC, a preliminary analysis showed that the objective radiographic response rate among men with BRCA-mutated mCRPC and measurable disease was 44%; for slightly more than half of the men responding, the duration of response was at least six months.

But as the TRITON2 investigators also reported in a separate analysis, “we found limited radiographic/PSA responses to PARP inhibition in men with alterations in ATM, CDK12, or CHEK2. However, patients with alterations in other DDR-associated genes (e.g., PALB2) may benefit from PARP inhibition.”

Olaparib was approved for mCRPC on the basis of the phase 3 randomized PROfound study. The trial had two cohorts: one for men with at least one alteration in BRCA1, BRCA2, and/or ATM, and one for men with alterations in any of 12 other pre-specified genes.

The investigators reported in *The New England Journal of Medicine* in May 2020 that the trial met its primary progression-free survival (PFS) endpoint for the BRCA/ATM mutation population, with a median of 7.4 vs. 3.6 months for control patients (men assigned to receive the physician’s choice of abiraterone or enzalutamide).

(Continued on page 7)
I love Jicama! Yeah, I said it, and I will say it once again — “I LOVE JICAMA!” I am not kidding, but more on this in a moment. I thought that all of us have been so inundated and saturated by election ads/commercials that we needed a break. So, by the time you read this column, which I am writing right before the election, we will either have the same President or a new President, or they will still be counting ballots.

Regardless, who did I vote for? I voted and continued to vote for JICAMA! What the heck? Yes, I am going to give all of you a desperately needed break from not only all the politics, but the medical news, and just talk about one of my favorite subjects, which are the unsung healthy foods on our planet. So, the actual reference for this column will be my memory and what was on my lunch plate yesterday.1

Jicama (pronounced “HEE-kah-ma”) is a wonderful ROOT VEGETABLE native to Mexico, Central and South America, and it is getting more attention... thank goodness. Jicama, also known as “Pachyrhizus erosus” (and other species), is also nutrient-packed, but light in calories and has a simple but wonderful taste, especially as a snack with anything. It is a nice source of fiber – actually a prebiotic, so do not overindulge, but ease into it like with any good fiber source. It also has magnesium, and it is a pretty darn good source of vitamin C and potassium with minimal-to-no sodium. I really like it on salads or when I am late typing this column and I need a small snack to take my mind off the fact that the column is really late. Jicama is also crunchy or even crispy when you bite into it, which is also kind of groovy. I have heard people tell me it tastes like apple, or potato, or pear, but again it is very mild. Personally, I think it is also tofu-like, but only in the sense that it adapts well or blends in with the flavors that are more pronounced in any dish (stir-fry, sautéing ...) with which it is served but, of course, it does not taste like tofu at all. Food is an amazing gift, but it is the diversity of accessible healthy and, at times, not so healthy foods, which also makes life fun and interesting and wonderful. It is easy to get obsessed in our business with one type of food based on some studies or data, but there are a diversity of foods that, if they had the financial backing or resources for more studies, would arguably be on your plate as much as the ones you read about in the scientific journals. In other words, trying something new and wonderful and healthy every month or so only adds to your knowledge and excitement for life and eating and living healthier.

JICAMA is one of those things I learned to like, on occasion, long ago, but now I love the fact that my local grocery store or market is carrying it on a regular basis. I do love Jicama! Vote for Jicama to land on your plate at your next meal, and if you like it or love it then good for you, and if you do not like it then that is okay too. Hey, I am poet and I did not know it!

References:
1. Moyad memory from 20+ years ago and from his lunch table yesterday.

Black Men with Prostate Cancer Found to Be Reluctant to Participate in Trials

A new survey found that, although a majority of Black men with prostate cancer (PCa) were willing to discuss participation in clinical trials, they were significantly less willing to enroll in them than their White counterparts.1

“Black men were more likely than White men to believe that members of their racial group should be suspicious of the health care system, and this suspicion was associated with lower willingness to discuss clinical trials,” researchers wrote.

The cross-sectional study included survey information from 205 participants from Partnering Around Cancer Clinical Trial collected from 2016 to 2019 at two National Cancer Institute-designated comprehensive cancer centers. The primary outcome was response to the question: “If you were offered a cancer clinical trial, would you be willing to hear more information about it?”

In response, 88.3% of said they would be willing to participate. However, 82% of White men indicated willingness compared with 64% of Black men (P=0.01, a statistically significant difference).

Black respondents were significantly more likely to be younger, less educated, have lower income, a greater perceived economic burden, lower health literacy, and greater group-based medical suspicion.

“This finding is consistent with work highlighting medical suspicion as a barrier to minority accrual in clinical trials,” the researchers wrote. “One possibility is that clinicians are less likely to discuss trials with Black patients they perceive as more suspicious. Important-ly, most Black individuals in this sample reported being willing to discuss trials, suggesting that clinicians may find higher acceptance than they expect.”

Reference

Renal & Urology News
11 October 2020

Check Out the Us TOO Advanced Prostate Cancer Brochure at:
www.ustoo.org/AdvancedBrochure
Hold Off Radiotherapy After Prostate Cancer Surgery  (Continued from page 1)

use of early salvage RT for many men following RP,” write experts in an accompanying comment. The editorialists are Derya Tilki, MD, University Hospital Hamburg-Eppendorf, Hamburg, DE, and Anthony D’Amico, MD, Brigham and Women’s Hospital and Dana Farber Cancer Institute, Boston, MA. The editorialists question whether results apply to all men who have undergone a RP.

One possible exception are men at high risk for progression, such as those with a Gleason score of 8 to 10 or whose tumor is of grade pT3b or higher. Such patients made up fewer than 20% of participants in the three clinical trials. For high-risk men, the editorialists think it would be “prudent” to consider adjuvant RT (ART) rather than early salvage RT (SRT).

Results from RADICALS-RT
The RADICALS-RT trial involved 1,396 men who were followed for a median of 4.9 years. Participants had to have at least one risk factor for biochemical progression. These factors included disease of pathologic T-stage 3 or 4, a Gleason score of 7-10, positive margins, or a pre-RP PSA level ≥10 ng/mL.

“Half the men were randomly assigned to receive ART (within six months of study enrollment for 90% of men). One quarter of this group also received neoadjuvant or adjuvant hormone therapy (HT),” the investigators note. The other half was followed with observation and received SRT only if they showed biochemical progression within eight years post-randomization.

Between the ART and SRT groups, Parker and colleagues report, there was no evidence of a difference in biochemical progression-free survival (bPFS). “At five years, bPFS rates for men in the ART vs. SRT groups were 88 and 85%, respectively. At the same time, 92 and 93% of men in the ART and SRT groups, had not received HT,” the investigators report.

On the other hand, at one year, reports of urinary incontinence were worse for those in the ART vs. SRT groups, at mean scores of 4.8 vs. 4.0, respectively (P=0.0023, a statistically significant difference). At two years, grade 3 to 4 urethral stricture was also more commonly reported by men in the ART vs. SRT groups, at 6 and 4%, respectively, (P=0.020, a statistically significant difference).

There was also a small, but significant, worsening of urinary and bowel function with ART one year after study enrollment, although there was no difference at later points of assessment.

When trial data is mature, the primary outcome measure will be freedom from distant metastases. The authors caution that longer follow-up is needed to assess long-term outcomes of the two approaches. Investigators will also assess the effect of HT after RP along with RT, which could delay disease progression.

Given the fact that ART increased the risk for both urinary and bowel morbidity and, in the absence of any evidence that the ART approach does more good than harm, “observation with SRT for PSA biochemical progression should be the current standard of care after RP,” the study authors conclude.

Safe for All Men?
Editorialists Tilki and D’Amico question whether this conclusion is generalizable to all men with localized or locally advanced prostate cancer (PCa) post-RP. They note that “the patient eligibility criteria for RADICALS-RT included men who would not receive ART in clinical practice due to the low risk of recurrence.” For example, a man with pT2 disease, a Gleason score of 3+4=7, a PSA of 4.0 ng/mL, and negative margins would have been eligible to participate in RADICALS-RT. But the editorialists maintain that “most urological, medical, and radiation oncologists would not recommend ART for such a patient.” They also point out that any potential ART benefit would likely have been diluted by including so many men with a favorable risk profile.

On the other hand, with regard to men who are at high risk for progression, Tilki and D’Amico note that the trial might be underpowered to assess potential differences between the RT approaches, even with further follow-up.

GETUG-AFU 17 Trial
This study was published at the same time and included 424 men diagnosed with localized PCa after pathological review. Men were randomly assigned to undergo immediate ART or delayed SRT delivered at the time of biochemical relapse (BCR). Men in both treatment groups were given short-term HT.

“For slightly more than half (54%) of the men in the SRT group, RT was initiated after biochemical relapse (BCR). At five years, the event-free survival rate was similar in the ART and SRT groups, at 92 and 90%, respectively,” as reported by Paul Sargos, MD, Institut Bergonié, Bordeaux, France, and colleagues.

In contrast, acute toxic effects were much more prevalent in the ART vs. SRT groups, at 87 and 44%, respectively. However, rates of grade 3 or worse toxic effects were low in both groups, at 3 and 2%, respectively. Similarly, late grade 2 or worse genitourinary (GU) toxicities were documented in 27 vs. 7%, respectively, of men in the ART and SRT groups (P <0.0001, a statistically significant difference).

The most frequent acute toxicities were urinary incontinence, urinary frequency, and hematuria (blood in the urine). Late gastrointestinal (GI) adverse events and late erectile dysfunction were also reported by significantly more men in the ART group.

“SRT could spare men from overtreatment and RT-induced toxic effects,” Sargos and colleagues observe. “This delayed approach would be preferred unless ART was superior to SRT according to long-term oncological outcomes,” the French investigators conclude.

Results from RAVES Trial
The third study was the Phase 3 RTOG 0803/ANZUP RAVES trial, which was a non-inferiority trial that involved 333 patients. Men were randomly assigned 1:1 to receive ART or SRT. For both groups, RT was dosed at 64 Gy in 32 fractions, but in this trial, it was not administered simultaneously with ADT.

At five years, freedom from biochemical progression (the primary endpoint) was similar in ART and SRT groups at 86 and 89%, respectively. Rates of grade 2 or worse GU toxicity were lower in the SRT group. Rates of grade 2 or worse GI toxicity were similar in both groups. The authors point out that these results from the RAVES trial were released at the
first-line mCRPC treatment resulted in significantly superior rPFS and antitumor activity vs. placebo plus abiraterone in men with PTEN loss,” he stated.

PTEN loss occurs in 40–50% of mCRPC cases. Loss of the gene leads to activation of the PI3K/AKT pathway and is associated with worse prognosis and reduced benefit from androgen receptor (AR) blockade.

Interestingly, among men with PTEN loss, assessment of rPFS by next-generation sequencing (NGS) rather than IHC showed a wider separation of survival curves in favor of the combination.

“I think it’s very promising data on AKT inhibition in prostate cancer (PCa), particularly in the NGS-defined group of PTEN loss,” commented Dr. Grönberg in his discussion of the trial.

“But I think it’s too early to tell; the subgroup that benefits from this treatment must be better defined, and we need to also see more mature data from this very important trial,” he added.

“Ipatasertib is an oral small molecule that binds to the adenosine triphosphate (ATP)-binding pocket of all 3 AKT isoforms. The drug inhibits AKT serine-threonine kinase activity and is shown to improve the antitumor effects of AR blockade in PCa models,” De Bono explained.

“Reciprocal cross-talk between AR and PI3K/AKT signaling enables PCa cell survival, while dual blockade has superior antitumor activity.”

For the IPATential 150 trial, investigators enrolled 1,101 men with asymptomatic or mildly symptomatic mCRPC untreated for advanced PCa. Men included 521 with and 580 without PTEN loss.

Men were stratified by PTEN loss by IHC, prior taxane therapy, PSA only progression, presence of liver and/or lung metastases, and geographic region. They were randomly assigned to receive abiraterone 1g daily plus daily ipatasertib 400 mg (547 men) or placebo (554 men).

**Study results**

After a median follow-up of 19 months, men with PTEN loss had a median rPFS of 18.5 vs. 16.5 months, respectively, with combination vs. abiraterone treatment alone. The one-year event-free rate was 64.4 vs. 63.3%, respectively, with combination vs. abiraterone treatment alone, translating into a stratified hazard ratio (HR) for progression with ipatasertib plus abiraterone of 0.77 (P=0.0335, a statistically significant result).

In the ITT population, median rPFS with ipatasertib/ abiraterone vs. abiraterone/placebo was 16.6 and 19.2 months, respectively. The one-year event-free rates were 65.3 and 63.0% respectively, translating into a 0.84 HR for the combination.

However, the P value (0.0431) for this analysis did not reach the prespecified P value for statistical significance, which was 0.01, meaning this coprimary endpoint was not met.

As noted, rPFS in the PTEN-loss population, as defined by NGS, was a secondary endpoint. With combination vs. abiraterone/placebo treatment, rPFS was 19.1 and 14.2 months respectively, translating into an HR of 0.65 favoring the combination (P=0.0206, a statistically significant difference).

Response rates with the combination were much higher than those with abiraterone alone. In the PTEN loss analysis, objective response rates, determined according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, were 61 vs. 39% for men treated with ipatasertib/abiraterone and abiraterone alone. The respective rates in the ITT population were 61 and 44%.

In the PTEN loss by IHC group, PSA response rates were 84 vs. 72%. In the ITT group, they were 81 vs. 76%. Time to PSA progression was also significantly better in the combination arm in both analyses. HRs were 0.69 (P=0.0013) and 0.73 (P <0.0001) in the PTEN-loss and ITT populations, respectively. No significant differences in time to cytotoxic chemotherapy was noted by treatment arm or population.

“Overall survival data were not mature at the data cutoff. In the current analysis, no difference in overall survival between treatment arms, was seen,” De Bono said.

**Toxicity**

Grade 3/4 adverse events were reported in 70.1 vs. 39% men treated with ipatasertib/abiraterone vs. abiraterone/placebo. Twenty-four men (4.4%) with combination treatment died during the study, as did 20 (3.7%) men with abiraterone alone.

Adverse events leading to discontinuation of study treatment occurred in 21.1 vs. 5.1% of men in the combination vs. placebo arms. Adverse events leading to dose reductions occurred in 39.9 and 6.2%, respectively. Adverse events with a 2% or greater difference between treatment arms – all of which occurred at higher rates among men treated with the combination – included rash/maculopapular rash, diarrhea, hyperglycemia (high blood sugar), elevated liver transaminase levels, and dehydration.

De Bono noted that prophylactic use of loperamide for diarrhea and antihistamine for cutaneous adverse events may help avoid the discontinuation of drug treatment.

In his discussion, Grönberg pointed out that only about 18% of men in each treatment arm had received prior taxane therapy, which is a lower percentage than is typically seen in practice. “An interesting observation – when we look at prior taxane-based therapy, in those exposed to taxanes before, there was no effect on PFS compared to those who were not exposed to taxane-based therapy,” he said.

“This finding raises the possibility that prior taxane therapy can make patients less sensitive to AKT inhibitors, which should be explored further,” he added. He also pointed to the rPFS analysis by NGS, which was conducted in only 205 of 1,101 men.

“In my view, most likely NGS is a better way to define PTEN loss, and I urge the authors and the company to try to collect [NGS data for] the other 900 patients to do this analysis,” Grönberg said.

Presented at the ESMO 2020 Annual Meeting, Abs. LBA4 Medscape Medical News 24 September 2020

Get the Latest on COVID-19 and Prostate Cancer

Including resources, tips on holding virtual meetings, and an ongoing series of informational articles with some important comments regarding the coronavirus, cancer patients, and safety from Dr. Mark A. Moyad at www.ustoo.org/covid
Post-radiotherapy (RT) ipilimumab led to a small but persistent long-term survival advantage in a placebo-controlled trial in metastatic castration-resistant prostate cancer (mCRPC). The trial failed to meet the primary endpoint of median overall survival (OS), but a preplanned long-term analysis showed a 2- to 3-fold improvement at 2, 3, 4, and 5 years in the ipilimumab arm. A piecewise hazard model showed a changing survival hazard ratio (HR) over time in favor of ipilimumab, ranging from 1.49 at 0 to 5 months to 0.66 beyond 12 months.

“Long-term analyses of survival are rarely reported in mCRPC studies, although this is of even greater importance for immunotherapy trials, because a delayed effect on the immune system is expected,” Karim Fizazi, MD, of Gustave Roussy Institute in Villejuif, France, and coauthors stated in the journal European Urology. “This global study was the first phase III trial testing ipilimumab in men with mCRPC that included long-term follow-up, and the primary endpoint of OS was not improved at the initial analysis.”

“This intention-to-treat analysis with longer follow-up shows that beyond the crossing of the (survival) curves at 7 to 8 months, there is persistent separation of the curves favoring the ipilimumab plus RT arm. This favorable impact of ipilimumab plus RT on OS was associated with an increased number of men alive at 2 years and beyond, some of whom had complete responses to treatment.”

Lawrence Fong, MD, of the University of California San Francisco, agreed with the authors that clinical trials in mCRPC often have limited follow-up for survival, which means that potential long-term benefits with immunotherapy are missed.

“Despite a perception that immunotherapy has limited activity in prostate cancer (PCa), the trial showed that more than twice as many men had PSA responses with the addition of ipilimumab to RT (13 vs. 5%),” Fong added.

Fizazi and coauthors reported final results from a randomized trial to compare RT for bone metastases plus ipilimumab or placebo in 800 men who had already received docetaxel for mCRPC. The primary analysis conducted after median follow-up of 9-10 months, showed median OS of 10-11 months in the 2 treatment arms, as opposed to a hypothesized 5-month improvement with added ipilimumab (15 vs. 10 months). Progression-free survival (PFS) and response were significantly higher in the ipilimumab arm.

Preplanned long-term follow-up in the trial showed statistically significant improvement in mean OS in months (95% Confidence Interval [CI]) at landmark analyses from 2-5 years.

“The challenge has been to identify reliable biomarkers associated with response and potential long-term benefit. Several molecular markers, such as tumor mutational burden and mismatch repair deficiency, have shown little correlation with response to immunotherapy.

“One of the challenges is that PCa has a much lower mutational burden vs. lung cancer or melanoma or some of the other ‘checkpoint inhibitor-sensitive’ cancers,” said Fong. “High microsatellite instability and CDK12 mutations have shown some promise as markers of response to immunotherapy but confirmatory research is still needed,” he added.

The Prognostic Impact of Intraductal Carcinoma of the Prostate: A Systematic Review and Meta-Analysis

Miura N, Mori K, Mostafaei H, Quhal F, Motlagh RS, Pradere B, Laukhtina E, et al.

J Urol 204: 909-17, 2020

Purpose: Systematic review and meta-analysis aimed to assess prognostic impact of intraductal carcinoma of the prostate (ICP) in men with prostate cancer (PCa).

Materials and Methods: A systematic search was performed according to the Preferred Reporting Items for Systematic Review and Meta-Analysis statement. We searched PubMed®, Web of Science™, the Cochrane Library and Scopus® up to October 2019. The end points were biochemical recurrence (BCR)-free, cancer specific and overall survival (OS).

Results: We identified 32 studies with 179,766 men. Thirty-one studies containing 179,721 men with localized and advanced PCa were eligible for meta-analysis. In localized PCa, intraductal disease was associated with adverse outcomes including lower BCR-free survival (pooled Hazard Ratio [HR] 2.09, 95% Confidence Interval [CI] 1.75-2.50) and cancer specific survival (CSS) (pooled HR 2.93, 95% CI 2.25-3.81).

In advanced PCa, OS was lower in men with vs. without ICP (pooled HR 1.75, 95% CI 1.43-2.14). Subgroup analysis by specimen type revealed that ICP is a significant negative prognostic factor in both biopsies and prostatectomy specimens. Moreover, subgroup analyses based on the histopathological [microscopically assessed] definitions of ICP indicated that intraductal disease was significantly associated with lower BCR-free, cancer specific and overall survival for almost all definitions.

Conclusions: Intraductal disease is a histopathological feature of biologically and clinically aggressive PCa. It confers worse oncologic outcomes in both localized and advanced PCa, whether assessed in biopsy or prostatectomy specimen. The pathologist should assess for and report on the presence of intraductal disease in all prostate specimens. The urologist and radiation oncologist should consider this adverse feature in their clinical decision making.
**Reserve PARP Inhibitors for mCRPC with BRCA Mutations (Continued from page 2)**

But as more recently reported, overall survival was significantly improved with olaparib for men in the BRCA/ATM cohort, but there was no significant survival benefit among men with other HRR gene mutations.

Schweizer’s editorial was published a few weeks before these final PROfound results were reported at the European Society of Medical Oncology 2020 Virtual Congress. But even before these additional data were reported, they wrote the following:

“On the basis of published studies, there are limited data to support use of olaparib in the absence of BRCA1/2 mutations, and without other indications of HR repair deficiency, these men would be better served by participating in clinical trials or receiving a therapy that is beneficial in unselected patients (e.g., taxane-based chemotherapy).”

Pomerantz said that his center tries whenever possible to perform genetic profiles of mCRPC tumors, in addition to assessing the patient’s genetic background. “Cancer is a disease of two genomes,” he explained. “We’re always dealing with two genomes: the germline genome – the genome inherited from your parents – and the somatic genome, the deranged, mutated genome of the tumor.”

He said some germline and somatic DNA-damage repair mutations can make prostate tumors susceptible to PARP inhibition, but further trials are needed to determine the ultimate role of PARP inhibitors in advanced PCa.

“I think there’s still a big knowledge gap here,” Schweizer said. “We need to really focus on clinical trials to better delineate which biomarkers are really appropriate for selecting patients for these drugs.”

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08 October 2020

**Impact of Biopsy Compliance on Outcomes for Patients on Active Surveillance for Prostate Cancer**


*J Urol* 204: 934-40, 2020

**Purpose:** Active surveillance (AS) or prostate cancer (PCa) relies on regular PSA tests and AS biopsies. Compliance rates with biopsies vary but the subsequent impact on oncologic outcomes is not known. The objective of this study was to determine if non-compliance with negative confirmatory biopsy impacts PCA-specific outcomes.

**Materials and Methods:** A retrospective analysis was performed on a prospective single-arm cohort of men enrolled in AS for PCa between 1995 and 2018 with a median 9.1 year of followup. A total of 1,275 men were enrolled and 1,043 who were followed a minimum of 3 years were included in the analysis. Men were stratified by compliance with a confirmatory biopsy within 24 months of enrollment in AS. The primary outcome was recurrence-free survival. Secondary outcomes included metastasis-free survival and cause specific survival.

**Results:** Of men included in the analysis, 425 were treated for localized PCa. Those patients non-compliant with the confirmatory biopsy had higher rates of recurrence after treatment (19 vs. 12%, Hazard Ratio [HR] 1.64, 95% Confidence Interval [CI] 1.19-2.26, p=0.003) and metastases (7 vs. 2%, HR 3.56, 95% CI 1.8-7.0, p=0.0003) even after accounting for age, PSA and Grade Group. Cause specific survival was not significantly different between the two groups. The results were consistent even in the subset of men with Grade Group 1 disease at study entry.

**Conclusions:** Noncompliance with a confirmatory biopsy compromises the control of PCa in men followed on AS. Patients and physicians should be aware of the importance of adhering to protocol for men on AS.

**More Prostate Cancers are Being Diagnosed at a Later Stage**

While men can take solace in a new government report that shows prostate cancer (PCa) cases have declined overall in the past 2 decades, the same analysis finds that the opposite is true for advanced PCa cases.

In fact, the proportion of PCa cases diagnosed at an advanced stage doubled between 2003 and 2017 from 4 to 8%, according to research by the U.S. Centers for Disease Control (CDC) led by Dr. David Siegel.

Why the spike in advanced PCa? Dr. Anthony D’Amico, a professor of radiation oncology at Harvard Medical School in Boston, said the increase was an inevitable consequence of a 2012 recommendation from the U.S. Preventive Services Task Force (USPSTF) against routine PCa screening with PSA.

“We realized in 2012 we would expect to see distant metastases [cancer that has spread] go up 2-3 years later and precede death by a couple of years,” he explained. “That’s exactly what this report found,” D’Amico noted.

“That trend will continue for a couple more years from now before we start to see a plateauing and eventually a decrease in distant disease,” he said. That’s because USPSTF’s reversal of the recommendation didn’t happen until [2018], “We should have PSA brought back.

“We’re diagnosing less low-risk cases now, so from my perspective PSA should be brought back so that men with low-risk cancer and doctors can discuss whether they want treatment or not, knowing what the side effects are.” D’Amico said.

The CDC study also delved into racial differences for prostate cancer survival. The researchers found that five-year survival was highest among Asian/Pacific Islanders (42%), followed by Hispanics (37%), American Indian/Alaska Natives (32%), Black men (32%), and white men (29%).

“Understanding PCa rates and survival can help guide treatment and survivor care planning,” Siegel said.

“This study did not look at PSA testing trends, but past studies have noted use of PSA testing decreasing,” Siegel said. “There are a lot of factors, including reduced PSA testing that might contribute to the incidence trends we reported in this study.”

The findings were published October 16, 2020 in the CDC’s *Morbidity and Mortality Weekly Report* (MMWR).

HealthDay Today
16 October 2020
same time as were the RADI-
CALS-RT and GETUG-17 trials.
“Trials results are concordant
suggesting ART does not im-
prove post-RP event-free sur-
vival in high-risk PCa,” said
Andrew Kneebone, MBBS, Roy-
al North Shore Hospital, Syd-
dey, Australia, and colleagues.
“It now appears preferable to
wait until the cancer recurs,
heralded by PSA rising to ≥0.2
ng/mL before commencing RT.

This would spare many men
from potential RT-related side
effects,” they suggest.

**Meta-Analysis Results**
The ARTISTIC meta-analysis
was prospectively designed
before results of the three RT
trials were known. Collectively,
the analysis included 2,153
men from the trials. All results
showed no improvement in
PSA-driven event-free survival
with use of ART vs. SRT. Indeed,
there was only a 1% point
difference in the 5-year event-
free survival rate at 89 and 88%
for ART and early SRT, respec-
tively.

“Our findings suggest that
post-RP, men whose PCa is
organ-confined or has spread
only to nearby tissues or organs
can safely be spared routine
post-RP RT and its associated
side effects,” lead author Claire
Vale, MD, MRC Clinical Trials

**Low Bone Health Testing Rates After Prostate Cancer Treatment** (Continued from page 1)
The researchers used the
Régie de l’assurance maladie
du Québec (RAMQ) – a Cana-
dian public healthcare ad-
ministrative database – to
review patient demographic
and billing information for
22,033 men with PCa who
began receiving ADT be-
between January 2000 and De-

dember 2015. Of those,
3,910 (17.8%) received a
BMD test at any point during
the study period. The largest
increase in testing rates oc-
curred around 2003 and
2004, coinciding with the
publication of several articles
and guidelines recommend-
ing BMD screening in this set
of patients. People age 80
and older, with metastatic
disease, or living in rural are-
as were less likely to be
screened.

“While we have known for
many years that types of ADT
used to treat PCa carry an
increased risk of osteoporo-
sis, this study identifies spe-
cific populations that might
not undergo recommended
screening prior to hormone-
based therapies,” comment-
ed Joshua M. Lang, MD, MDs,
Associate Professor of Medi-
cine, Carbone Cancer Center,
University of Wisconsin.

“These populations are es-
pecially vulnerable, including
our older men located in
rural areas of the country.”
Dr. Lang, a Member NCCN
Guidelines® Panel for Pro-
sate Cancer, who was not
involved in this research,
continued: “The importance
of screening is even more
critical given the availability
of medications that can slow
or reverse osteoporosis. The
NCCN Guidelines for Prostate
Cancer specifically recom-
 mend screening for these
patients and this report
demonstrates that more
work is needed to advocate
for and implement screening
of vulnerable patient popula-
tions.”

NCCN Plymouth Meeting, PA
October 7, 2020
QUESTION FROM PROSTATE CANCER SURVIVOR:
I was wondering if you could go over the changes that occur after nerve sparing prostate cancer surgery?

RESPONSE FROM DR. JEFFREY ALBAUGH:
Thank you for your question and I would be happy to review that information with you. Erectile dysfunction is common after surgery, radiation or hormone androgen deprivation therapy. After surgery, in particular, the nerves for erections become inflamed and can take up to five years and an average of two years to recover. This can be a source of frustration. From a psychological standpoint, there are other issues that may come into play during sex after prostate cancer treatment. Some men may fear they won’t be able to get an erection, or feel like a failure if they can’t perform. Erectile dysfunction—even if temporary—can have a negative impact on some men’s sense of manhood. Worry and stress only add to the problem. Some men may have fears about leaking urine during sex (this can happen sometimes, but it is harmless since urine is sterile anyway). Men and their partners may be fearful of pain or discomfort during lovemaking, which can be another distraction. It may take some experimentation to find what works best for both of you. Remember, sex is supposed to be fun, so explore and enjoy each other during this time of rediscovering new ways of pleasuring each other.

Some other changes may also occur. If your prostate was surgically removed, no ejaculate will come out of your body after surgery. That’s because the prostate and seminal vesicles have been removed, and there’s no longer a pathway for seminal fluid. You should still be able to have the orgasm/climax sensation and men report that it is still very enjoyable after surgery or radiation. Some men experience temporary penile shrinkage after surgery. Sometimes this can also occur with other treatments, such as radiation or hormone androgen deprivation therapy. Men often describe this to me as “their penis has disappeared into their body” sort of like a turtle’s head disappears into their body.

It may help to approach sex after prostate cancer with the goals of connectedness with your partner and pleasure. You don’t need an erection for either of those two things. If you are prepared for these changes, they will be less surprising. Knowledge is empowering for both you and your partner. No one knows definitely who will and will not experience continuing sexual issues. Putting pressure on yourself to perform sexually can make sex stressful and frustrating for both you and your partner. Keeping the lines of communication open (including discussing what’s working and what isn’t) is also important. If you don’t experience the results you hoped for right away when you have sex after prostate cancer surgery, try not to be discouraged because it can take several years for recovery to occur. In the meantime, you and your partner can be sexual in many other ways and this can be very gratifying in terms of intimacy and sex. You can also explore erectile dysfunction treatments with your urology healthcare provider.

You can access the new edition of my book or download a free copy of my original book at www.drjeffalbaugh.com.

Watch Dr. Albaugh’s presentation on sexual health and intimacy from the Prostate Cancer Pathways for Patients and Caregivers event recorded at NorthShore University HealthSystem in Skokie, IL on November 3, 2018 at https://www.youtube.com/watch?v=Hiq0dDEb110&t=4483s.

Read previous issues of Between the Sheets at www.ustoo.org/BTS.

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:
Us TOO International
Between the Sheets
2720 S. River Road, Suite 112
Des Plaines, IL 0018
Broccoli and Prostate Cancer: What’s the Connection?
If you’ve been reading about prostate cancer for a while, you have probably heard that broccoli is good for your prostate. Let’s dive into the science behind this thinking.

This is a good time to review some of the different types of scientific studies used in making recommendations for patients. We’ve got “preclinical” studies, or experiments in a lab with cell lines or animals. These studies can give us a sense of how (say) a chemical in broccoli affects prostate cancer cells in a test tube. Observational, or epidemiologic studies, follow large groups of people for many years and try to associate behaviors or exposures with health outcomes. The relevant example here is consumption of broccoli and development of prostate cancer, or, for patients diagnosed with prostate cancer, recurrence of the disease. Then we have interventional studies, where patients agree to take a specific medicine, or even to eat a food (broccoli!), and be followed over time to see what happens. There are limitations to each of these types of studies; you can read more about the “science of science” on www.pcf.org.

Why study broccoli and prostate cancer? Broccoli, as a cruciferous vegetable, is a rich source of natural plant chemicals called glucoraphanins, which are converted to isothiocyanates in the body. They’ve been shown in preclinical studies to help rid the body of cancer-causing toxins, interrupt pathways that cause inflammation, and act as antioxidants to protect cells and DNA from damage caused by free radicals.

So, that sounds promising! What do we see when we observe large groups of men over time? Some studies suggest that men who ate cruciferous vegetables were at lower risk of developing prostate cancer. There are lots of reasons to recommend a diet high in plant-based foods like crucifers. Men with prostate cancer are at risk for heart disease, based on their age and gender. Men on hormone therapy for prostate cancer are at risk for weight gain, which further increases their risk of heart disease. And there is strong observational evidence that a plant-based diet, including broccoli, decreases heart disease. Should you eat broccoli along with other plant foods to reduce your risk of death from heart disease? Absolutely!

Last, we’ve got the “gold standard” of intervention trials. One interesting study (https://academic.oup.com/ajcn/article/109/4/1133/5455624), led by PCF-funded investigator Dr. Richard Mithen, involved 49 men on active surveillance who were randomized to consume a broccoli “soup” – with regular broccoli or with broccoli containing enhanced amounts of glucoraphanin. After 12 months, researchers noted potentially beneficial, less cancer-promoting changes in genes in prostate tissue of the men taking the glucoraphanin-rich soup. Some substances, including antioxidants like lycopene, accumulate in the prostate. Another study (http://www.nnuh.nhs.uk/news/2019/08/new-study-to-test-the-benefits-of-broccoli-and-garlic-for-prostate-health) of broccoli and garlic supplements in men scheduled for prostate biopsy is nearing completion. We need more data, but these are fascinating examples of how food has the potential to act like medicine.

For more information visit www.pcf.org, email info@pcf.org, or call 1-800-757-2873.
These are certainly strange times, and the need to connect with others is more important than ever, especially for men who are affected by prostate cancer and their loved ones. While living with restrictions related to COVID, these men and women continue to deal with important treatment decisions or management of side effects associated with prostate cancer treatment. Us TOO and AnCan are proud to offer Prostate Cancer Connections, a series of educational and interactive webinars which will bring people together virtually and safely to access empowering, decision-making information and personal connections in a time of social distancing.

For the third of our three webinars, we offer a discussion on Imaging and Prostate Cancer.

Prostate Cancer Connections, Episode 3: Imaging and Prostate Cancer Webinar
Presented by Us TOO International and AnCan

About Our Guest Speaker:
Dr. Brian T. Helfand is the Richard Melman and Ron Chez Family Chair and Chief of Urology at NorthShore University HealthSystem in Evanston, Illinois. He is an Associate Professor at the University of Chicago and former Adjunct Professor at Northwestern University. He holds MD and PhD degrees, and is head of clinical and research programs focused on prostate cancer. Dr. Helfand has authored more than 200 peer reviewed manuscripts. Currently, his interests are devoted towards using novel imaging techniques and biomarkers, including genetics, to help guide clinical decision making for men with newly diagnosed and advanced prostate cancer.

To Register, Please Visit www.ustoo.org/connections
For Sponsorship Opportunities, Please Email ustoo@ustoo.org

Join us for Prostate Cancer Connections

Episode 3 in a Series of 3: Imaging and Prostate Cancer Webinar
Tuesday, November 24, 2020
7:00-8:30pm Central

Register at: www.ustoo.org/connections

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