US TOO® PROSTATE CANCER EDUCATION & SUPPORT

HOTSHEET

JUNE 2013

AUA AND ASTRO ISSUE JOINT GUIDELINES FOR POSTSURGERY RADIOTHERAPY

For the first time ever, the two medical organizations most responsible for the treatment of prostate cancer in the United States have issued a joint guideline. The American Society for Radiation Oncology (ASTRO) and the American Urological Association (AUA) announced the publication of a guideline on radiation therapy (RT) after radical prostatectomy (RP) – both adjuvant and salvage – at the AUA 2013 Annual Scientific Meeting held in San Diego, CA.

"The purpose of this guideline is to provide a clinical framework for the use of RT after RP in patients with and without evidence of prostate cancer recurrence," write the guideline authors, led by ASTRO's Richard K. Valicenti, MD, from the University of California Davis Comprehensive Cancer Center in Sacramento, and the AUA's Ian M. Thompson, MD, from the Cancer Therapy and Research Center at the University of Texas Health Science Center at San Antonio.

"We hope the guidelines will facilitate discussion between physicians and patients about the use of RT," Dr. Valicenti stated. He said that the discussion should include the benefits, adverse events, and quality of life associated with the treatment.

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NEW AUA GUIDELINE FOR CASTRATION RESISTANT PROSTATE CANCER

The American Urological Association (AUA) has issued a new guideline for the management of castration-resistant prostate cancer (CRPC) that provides a "rational basis" for treatment decisions.

Those decisions are now "complex" because a group of treatment options for metastatic CRPC (mCRPC) has emerged in a short period of time, according to a press release issued at the 2013 AUA Annual Scientific Meeting, held in San Diego, CA.

The treatment options in mCRPC include 4 new therapies that have been approved since 2010: sipuleucel-T (Provenge®), cabazitaxel (Jevtana®), abiraterone (Zytiga®), and enzalutamide (Xtandi®). These therapies, along with docetaxel (approved in 2004), have all been shown to improve overall survival in mCRPC.

"Prior to 2004, once patients failed primary androgen deprivation, treatments were administered solely for palliation," write the guideline authors, led by Michael S. Cookson, MD, from Vanderbilt -Ingram Cancer Center in Nashville, TN. The guidelines are much needed, according to a clinician not involved with their writing. "There is a lack of clarity as to the best method for treating CRPC," said Willie Underwood III,

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AUA ISSUES NEW GUIDELINES ON PSA SCREENING

New guidelines on prostate cancer screening, issued last month by the American Urological Association (AUA), are supportive of routine use of the prostate-specific antigen (PSA) test in healthy men, but only for a specified age group, and only after discussion between a man and his physician. Specifically, the new guidelines state that men 55 to 69 years of age **who are at average risk** and asymptomatic can consider PSA screening. They should speak to their physician about the benefits and harms of testing to determine the best course of action.

This is a major difference from the guidelines issued last year by the US Preventative Services Task Force (USPSTF), which recommended against any routine use of the PSA test, concluding that any benefit is outweighed by harm. "We recognize that there are some men who could benefit from screening," said Ballentine Carter, MD, professor of urology and oncology at the Johns Hopkins Medicine and director of adult urology at the Brady Urological Institute in Baltimore, Maryland, who chaired the guideline committee.

"In the age group that we identified – 55 to 69 – there is evidence that there may be more benefit than harm," Dr. Carter told Medscape Medical News. But only

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CANCER IMMUNOTHERAPY: AN OVERVIEW

By James L. Gulley, MD, PhD, FACP

With the approval of sipuleucel-T (Provenge®) for the treatment of metastatic castrate-resistant prostate cancer, interest in the field of cancer immunotherapy has grown significantly. Until recently, the only treatment shown to improve overall survival (OS) for prostate cancer patients was chemotherapy. Now, men have a number of options with approved targeted therapies such as abiraterone (Zytiga®) and enzalutamide (Xtandi®), and some promising new immunotherapies under development. A targeted immunotherapy candidate, PROSTVAC®, showed an 8.5 month improvement in median overall survival (OS) vs. controls in a randomized, placebo controlled Phase 2 study[1], and a global Phase 3 trial is now underway.

In general, cancer immunotherapies work to train the body's own immune system to recognize and destroy cancer cells. These therapies include cancer vaccines (also known as therapeutic vaccines) which have substantially fewer and less severe side effects than chemotherapy yet can lead to clinically meaningful improvements in OS. However, as these are still a relatively new therapeutic option, many patients are unsure about what these types of therapy have to offer and how they could ultimately change the way we treat prostate cancer (and eventually other cancers).

First, it is important to understand how immunotherapies differ from other treatment options and therefore must be evaluated differently. While clinical trials of immunotherapies for prostate cancer (such as Provenge and PROSTVAC®) have demonstrated clinically meaningful improvements in OS, these studies have not been associated with an improvement in progression-free survival (PFS). This can be attributed in part to cancer immunotherapies directly targeting the immune system, which in turn enable the body to recognize and destroy the prostate tumor cells. It may take some time to generate a clinically significant response following a vaccine, however because the body can make memory cells, this response can be active long after this active immunotherapy is given. Thus while there may not be significant changes short term, even a slowing of the tumor growth rate can lead to substantial improvement in OS long term. This is an important concept in understanding expectations of clinical responses following immunotherapy and has changed the way immunotherapy studies are designed with approval endpoints looking primarily at the more important improvement in OS rather than the less clinically relevant PFS.

Studies have also strongly suggested that cancer immunotherapies may be more effective in earlier stage prostate cancer, where the immune system may be in a better position to respond and any slowing of the tumor growth rate could offer a greater benefit. In one Phase 2 study, men receiving PROSTVAC® exceeded their predicted median survival time, but those with a predicted survival of ≥18 months upon enrollment saw a much greater *increase* in their survival time above that predicted than those whose predicted survival was <18 months. Another recently published study with sipuleucel-T suggested that men with lower PSA values also had a bigger OS impact from immunotherapy than men with higher PSA values. Studies such as these support the theory that these well tolerated immunotherapies may best be used early in the treatment armamentarium in asymptomatic or minimally symptomatic men, prior to chemotherapy which is associated with a substantially worse side effect profile.

Furthermore, another promising aspect of cancer immunotherapies is the idea of combination therapies. The use of multiple immunotherapy treatments and/or combination with traditional treatments (such as androgen deprivation therapy or chemotherapy) could provide further clinical benefit by bringing together two or more "mechanisms of action" to attack the cancer. However, further studies will need to address questions regarding simultaneous versus sequential approaches to therapy, as well as which combinations may be the most effective for different patients.

Finally, even with the marketing approval of new treatment options in recent years,

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AUA SCREENING GUIDELINES

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in that age range, he emphasized; for other age groups, the panel could not recommend routine screening.

Another difference is that the AUA guidelines reviewed the evidence from an individual perspective, not from a public health perspective, Dr. Carter explained. "The point of the guidelines is to help urologists inform an average-risk man who is asymptomatic."

The AUA guidelines are "not a response" to the USPSTF or any other guidelines, he noted. The process for drawing up the AUA guidelines began 2 years ago. It was based on a rigorous systematic literature review by a multidisciplinary team, involving medical and radiation oncologists, general internists, epidemiologists, and urologists, he said.

The AUA guidelines state that PSA screening is not recommended for men younger than 40 years, for men 40 to 54 years who are at average risk, for men 70 years and older, and for men with a life expectancy of less than 10 to 15 years. It is recommended that men in these age groups (younger than 55 years or 70 years and older) who are at a higher risk for prostate cancer (e.g., because of a family history of disease or by virtue of their race) speak to their physician about the benefits and risks of PSA testing.

"There is less evidence here of benefit," Dr. Carter said, but these men who are at higher risk need to know the benefits and harms of screening, he added.

The new guidelines supersede and replace the section on prostate cancer detection in the 2009 AUA best-practice document, which recommended screening start at age 40. That document was based on opinion and clinical evidence, whereas these new clinical guidelines are based on evidence from a systematic literature review, Dr. Carter explained.

In the new guidelines, "our statements do not go beyond the evidence," he said. The quality of the evidence for benefit was moderate (grade B), whereas the quality of the evidence for harm was high (grade A)," he noted. "The panel felt that it would not be reasonable to go beyond the evidence and make statements based on opinion."

Medscape Medical News, 8 May 2013

DOC MOYAD'S WHAT WORKS & WHAT IS WORTHLESS COLUMN, ALSO KNOWN AS "NO BOGUS SCIENCE" COLUMN

"If you are a former smoker please stay away from dietary supplements with beta-carotene in them. Food sources are fine, but the supplements are not! "

Mark A. Moyad, MD, MPH, Univ. of Michigan Medical Center, Dept. of Urology

Editors' note: Us TOO has invited certain physicians and others to provide information and commentary for the *HotSheet* to enrich its content to empower the reader. This column contains the opinions and thoughts of its author and is not necessarily those of Us TOO International.

Bottom Line: One of the largest studies of dietary supplements to prevent the progression of macular degeneration (AREDS2) was just published[1] and fish oil was not beneficial and beta-carotene may have increased the risk of lung cancer in former smokers! Yikes! This is an important column for current, former and even non-smokers that at times less is really more!

Less is more (Moyad is always saying that, especially to his kids when they ask for money)! One of the most surprising findings in a large dietary supplement studies occurred in the 1990s when the Alpha-Tocopherol Beta-Carotene Cancer Prevention (ATBC) trial, a randomized study of 50 mg of alpha-tocopherol and/or 20 mg of beta-carotene on over 29,000 male chronic smokers was stopped. Participants receiving beta-carotene had a significant increase in the risk of lung cancer incidence and dying from all causes compared to placebo. This study was designed originally because plenty of epidemiologic research suggested beta-carotene could reduce the risk of lung cancer.

Yet, soon after the ATBC stopped, the Carotene and Retinol Efficacy (CARET) Trial, a randomized study using 30 mg of beta-carotene in individuals with a history of smoking or asbestos exposure, was also stopped for precisely the same reasons as ATBC! A significant increase in lung cancer diagnoses and overall death occurred in the supplement vs. placebo arm. The third large prevention trial of beta-carotene, the Physicians' Health Study (PHS), did not show anything positive or negative, but PHS was not just conducted in smokers. A total of 11% were current and 39% were former smokers, and 50 mg of beta carotene was utilized every other day (blood levels were also lower in beta-carotene from supplementation in PHS). In other words, researchers received a real indication that an excess of certain supplements or antioxidants in certain populations could potentially increase the risk of cancer and early death. This was again a substantial change in the paradigm of thinking that really impacted my thoughts and beliefs forever.

Hot off the press comes the results of the AREDS2 trial that showed that fish oil does NOT reduce the progression of macular degeneration. However, in this same trial the group that was taking 15 mg of beta-carotene in their supplement had a significant increase in the risk of lung cancer (23 vs. 11 cases or 2.0% vs. 0.9%) and most of the lung cancer cases were in former smokers! Is it possible that higher doses of beta-carotene in dietary supplements (15 mg or more) increases the risk of lung cancer in former and current smokers!? YES! It is possible!

So, if you are a former smoker check your supplements to make sure they contain little or no beta-carotene. If you are a current smoker please stop smoking now! If you have never smoked always remember that in many situations less is more! Eating healthy foods high in beta-carotene has not been a safety issue in former and current smokers-only the supplements! Yikes! No room for jokes here folks! This one is really scary! I bet there are a lot of men and women, and men with prostate cancer that are former smokers that have a good deal of beta-carotene in some of their multivitamin or other supplements. Yikes!

Reference:

1. The Age-Related Eye Disease Study 2 (AREDS2) Research Group. Lutein + zeaxanthin and omega-3 fatty acids for age-related macular degeneration: The AREDS2 randomized clinical trial. JAMA 5 May 2013, online first.

AUA/ASTRO POST-RP RADIOTHERAPY GUIDELINE *(Continued from page 1)*

The data-dense document considered 324 research articles and is the fruit of the Radiotherapy after Prostatectomy Panel, a collaboration that was created in 2011 by the 2 groups. Only studies in which PSA data were provided for at least 75% of men were included in the guideline. The recommended strategies and approaches are derived from evidence-based and consensus-based processes in the reviewed articles. "This document constitutes a clinical strategy and is not intended to be interpreted rigidly," write the guideline authors.

The literature that undergirds the guideline has a "major limitation" – the "lack of a large number of randomized controlled trials to guide decision-making in patients with and without evidence of recurrence," they note. There was a similar data problem regarding the appropriate use of androgen-deprivation therapies (ADT), so the guidelines include no instructions about ADT.

The lack of top-flight data means that the guideline has only 1 statement with evidence strength of grade A (high quality, high certainty). In short, the guideline's statements are based mostly on less stellar quality/certainty data or on expert opinion.

The guideline document offers 9 major statements, which fall into different categories – clinical principles (wide agreement by urologists), recommendations (grade C; low-quality and certainty evidence), standards (grade A or B; high/moderate-quality and certainty evidence), and options (non-directives).

"This guideline provides a very practical approach for the clinician to help guide in patient decision-making that will result in the very best patient outcomes." Dr. Thompson said in a press statement.

The new guideline will be published in the August 1 print issue of the International Journal of Radiation Oncology * Biology * Physics, the official scientific journal of ASTRO, and in the August print issue of The Journal of Urology, the official journal of the AUA.

Medscape Medical News, 10 May 2013

NINE GUIDELINE STATEMENTS

1	Inform patients undergoing RP for localized prostate cancer of the potential for adverse pathologic findings that portend a higher risk for cancer recurrence *(clinical principle)*
2	Inform patients with adverse pathologic findings (including seminal vesicle invasion, positive surgical margins, and extraprostatic extension) that ART reduces the risk for biochemical (PSA) recurrence, local recurrence, and clinical progression of cancer, compared with RP alone *(clinical principle)*
3	Offer ART to patients with adverse pathologic findings at the time of RP because of the above-stated benefits *(standard; evidence strength, grade A)*
4	Inform patients that PSA recurrence after surgery is associated with a higher risk for the development of metastatic prostate cancer or death from the disease *(clinical principle)*
5	Define biochemical recurrence as a detectable or rising PSA value after surgery that is at least 0.2 ng/mL, with a second confirmatory level that is at least 0.2 ng/mL *(recommendation; evidence strength, grade C)*
6	Consider a restaging evaluation in the patient with a PSA recurrence *(option; evidence strength, grade C)*
7	Offer salvage RT to patients with PSA or local recurrence after RP in whom there is no evidence of distant metastatic disease *(recommendation; evidence strength, grade C)*
8	Inform patients that the effectiveness of RT for PSA recurrence is greatest when given at lower levels of PSA *(clinical principle)*
9	Inform patients of the possible short-term and long-term urinary, bowel, and sexual adverse effects of RT, as well as the potential benefits of controlling disease recurrence (clinical principle).

HIGH-DOSE PROSTATE RADIOTHERAPY: BETTER LOCAL CONTROL, NOT SURVIVAL

For the first time in a randomized trial, dose-escalated radiation therapy (RT) for prostate cancer resulted in better local control at 10 years, but did not translate to better overall survival (OS). Study results were reported at the 2nd European Society for Radiotherapy & Oncology (ESTRO) Forum by Joos Lebesque, MD, a radiation oncologist at the Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam.

The phase 3 trial enrolled 664 men with prostate cancer (T1b-T4) from 4 Dutch hospitals between 1997 and 2003. Men were randomly assigned to receive either 78 Gy (n = 333) or 68 Gy (n = 331) of RT in 2 Gy per fraction using three-dimensional conformal RT. Results showed that freedom from biochemical/clinical failure was better in the higher-dose group according to American Society for Therapeutic Radiology and Oncology (ASTRO) criteria (45.9% vs 38.4%; $P = 0.025$) or Phoenix guidelines (48.5% vs 43.1%; $P = 0.045$).

Local failure, one of the secondary endpoints, was observed significantly less in the higher-dose group (14 vs 27 events; $P = 0.036$). "This is the first time after a follow-up of 9 years that we notice a difference in local failure," he noted. However, "for the most important secondary endpoints [disease-specific survival and overall survival] there was no difference. This was a big disappointment for us," Lebesque stated.

Mary Gospodarowicz, MD, Medical Director of the Princess Margaret Cancer Centre at the University Health Network in Toronto, ON, Canada and co-moderator of the session commented, "for early-stage disease you need 20-year data to comment on OS." I think he needs a larger cohort of patients over a longer period of time," she stated.

Dr. Lebesque acknowledged that longer follow-up might have revealed a survival difference, if there is one, and he suggested that the wide inclusion criteria may have obscured this potential trend.

Reference:

Second ESTRO Forum, abstract OC-0048, presented 20 April 2013

GENE TEST FOR PROSTATE CANCER SHOWS PROMISE

A genetic test can predict the aggressiveness of prostate cancer, a new study shows. The 17-gene test predicts whether tumors will progress to high-grade or postsurgical stage III disease. The results of the study were presented at the American Urological Association 2013 Annual Scientific Meeting.

"We think this will allow patients and doctors to make more confident decisions," stated study coauthor Eric Klein, MD. "That will be a boon to everyone and it will save the system money."

The researchers used RT-PCR to quantify gene expression from manually dissected prostate cancer tissue. They began with 732 candidate genes from 441 men obtained after radical prostatectomy (RP), and calculated the association between these genes and the occurrence of high-grade or stage III (pT3) cancer.

They identified 288 genes predictive of clinical recurrence, regardless of Gleason score patterns. From these 288 genes, they quantified 81 in a needle biopsy study of 167 men. This confirmed the strong association between the genes and adverse pathology. They used multivariate analysis to narrow the genes of interest to 17 from multiple biologic pathways, including stromal response, cellular organization, androgen, proliferation, and reference genes.

A validation study assessed biopsies from 395 men suitable for active surveillance (AS) with tumors as small as 1 mm. They found that they could predict high-grade and/or pT3 disease independently of the Cancer of the Prostate Risk Assessment Post-Surgical (CAPRA-S) nomogram or other standard pretreatment factors (P = 0.002).

The test enabled them to increase the number of patients in their study population identified as very low risk – and therefore suitable for AS – from less than 10% to 26%. In other words, they were able to reclassify more than a third of patients, originally classified as low risk on the basis of clinical factors, as very low risk. This enabled men to pursue AS.

The researchers also identified aggressive disease in need of immediate treatment in about 10% of patients who had been classified as low risk or very low risk. There are already some gene tests for prostate cancer, but they are only useful for determining the risk for cancer recurrence in men who have already been treated for prostate cancer.

Our 17-gene test "is useful in patients who have been newly diagnosed with prostate cancer," said Dr. Klein. "Right now, we don't have good tools to distinguish cancers that are going to do well from those that will need treatment."

Genomics Health began selling the test, known as the Oncotype Dx Genomic Prostate Score (GPS), after the data was presented at the AUA meeting. It will cost $3820 per patient, said Steven Shak, MD, chief medical officer of Genomic Health. He said he expects insurance to pay for the test because similar Oncotype Dx tests for use in breast and colon cancer are now reimbursed. He argued that it could save money by reducing unnecessary treatment. "We expect it to be cost-effective," he said. "It should triple the number who choose AS."

This test is one of several promising new technologies for determining which prostate cancers pose the greatest risk, said Jeffrey Hahn Reese, MD, a clinical professor of urology at Stanford University in Palo Alto, California, who was not involved in the study. "It's going to have to be validated at a number of institutions," he stated. "What we have seen in the past is that some of these fly and some of them don't. I think you're going to see a lot more of these because it's what we need."

This study was funded by Genomics Health. Dr. Klein is a paid consultant to the company and to other companies developing genetic tests for prostate cancer. Dr. Reese has disclosed no relevant financial relationships.

Reference:

AUA 2013 Annual Scientific Meeting, abstract 2131, presented 8 May 2013

MIDLIFE PSA TEST PREDICTS FUTURE PROSTATE RISK

A screening PSA test in middle age predicted the risk of prostate cancer (PCa) mortality decades later, but was less predictive of metastatic disease, investigators in a multinational study reported. During a 27-year median follow-up, 44% of PCa deaths occurred in men who had PSA values in the highest 10th percentile (≥1.6 µg/L) at ages 45 to 49 or 51 to 55, reported Hans Lilja, MD, of Memorial Sloan-Kettering Cancer Center in New York City, and colleagues online in the *British Medical Journal*.

"Measurement of PSA concentration in early midlife can identify a small group of men at increased risk of PCa metastasis several decades later," Lilja's group wrote. "Careful surveillance is warranted in these men. Given existing data on the risk of death by PSA concentration at age 60, these results suggest that three lifetime PSA tests – mid to late 40s, early 50s, and 60 – are probably sufficient for at least half of men," they added.

Recent studies by Lilja and others have suggested that a single screening PSA test predicts long-term risk for clinically relevant PCa. By extension, a baseline PSA concentration might help distinguish men who would benefit from subsequent PSA evaluations from those who would not, the authors continued.

In an attempt to develop an evidence-based strategy for PCa screening, investigators analyzed data from the Malmö Preventive Project, a Swedish cohort that formed the basis for a previous study showing that PSA level at 60 can predict the risk of PCa mortality by age 85.

Men, ages 27 to 52, provided blood samples at enrollment during 1974 to 1984, and a subgroup provided a second sample 6 years after the first. The analysis involved 21,277 men who provided baseline samples and 4,922 who provided two samples. None of the men had PSA tests to screen for PCa, but the samples were archived for future evaluation.

A total of 9,108 men provided samples before 44 and 12,169 provided samples at 44 to 51. Men who provided a second sample were 51 to 55 at the time. Overall, baseline PSA had a significant asso-

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MIDLIFE PSA TEST

(Continued from page 5)

ciation with PCa metastasis as much as 30 years later (P <0.005). The baseline PSA value also was predictive of subsequent risk of PCa mortality.

Men in the 90th percentile of PSA values at 45 to 49 (≥1.6 µg/L) accounted for the single largest share of PCa deaths (44%) during follow-up. Similar results were observed for men 51 to 55 whose PSA levels were in the 90th percentile for the age group (≥2.4 µg/L).

Risk of metastatic PCa could not be ruled out among men who had PSA values below the median at 45 to 49 (0.68 µg/L) or at 51 to 55 (0.85 µg/L). Men in the younger age group had a 15-year risk of metastatic PCa of 0.09% and the older group had a risk of 0.28%. "Because of the limited number of events in this analysis, it would ... seem likely that only a few tumors would become incurable between the ages of 40 and 45," the authors said. "Therefore, it is difficult to justify initiating PSA testing at age 40 for men with no other relevant risk factor.

"In contrast, the risk of metastases within 15 years was much higher (1.6%) for men in the highest 10th at age 45 to 49 and 5.2% at age 51 to 55, suggesting that not starting PSA-based screening until age 51 to 55 would leave an important proportion of men at a increased risk of later being diagnosed with an incurable cancer," they said.

The authors acknowledged that their study population was mostly white so the results may not apply to other races or ethnicities.

The results do add to a substantial body of evidence supporting risk stratification in PCa screening, said Guilherme Godoy, MD, of Baylor College of Medicine in Houston. The study also supports using a baseline PSA test to guide patient counseling and future testing. "If an initial screening PSA test is done when a patient is 40 to 50 and the PSA is low, we can tell the patient that probably the risk of having cancer in the future is low," said Godoy, who was not involved in the study.

"If a man has no other risk factors, such as race or family history, we can probably do less frequent PSA testing... reducing overdiagnosis and overtreatment…"

AUA GUIDELINES FOR CRPC TREATMENT

(Continued from page 1)

MD, MPH, from the Roswell Park Cancer Institute in Buffalo, NY.

The guidance is especially important given the publicity that has accompanied the new therapies, as well as their cost. "When a drug comes out with a lot of hype, every patient wants that drug."

A large part of the new guideline is recommendations for 6 different types of patients. These "index" patients represent the most common clinical scenarios in men whose prostate cancer is not responsive to traditional androgen-deprivation therapy (ADT).

The profiles of the index patients comprise symptoms, performance status (PS), presence or absence of metastases, and whether or not docetaxel (Taxotere®) has been administered.

The guideline authors acknowledge that treatment is rapidly changing, and advise clinicians to use it in conjunction with the "current literature" and an individual patient's treatment goals.

The table below lists each index patient and their associated recommendations. Because the skeletal system is the most common site for prostate cancer metastasis, the guideline also makes recommendations regarding bone health. Supplemental calcium and vitamin D can be used to prevent fractures and either denosumab (Xgeva®) or zoledronic acid (Zometa®) can be given to prevent skeletal-related events (SREs).

"Prostate cancer deaths are typically the result of mCRPC, a painful disease," said Dr. Cookson in a press statement. "In recent years, a number of new treatments and therapeutic agents have entered the market that have been shown to minimize adverse effects and pain and prolong survival in some patients, but the fact remains that mCRPC is the terminal stage of prostate cancer."

Medscape Medical News, 9 May 2013

CRPC INDEX PATIENTS AND THEIR ASSOCIATED RECOMMENDATIONS

Index (patient type)		Clinical profile	Primary therapy	Secondary therapy
1	Asymptomatic non-metastatic CRPC	↑ PSA with castrate testosterone & no measurable mCRPC on radiographic imaging	Observation with continued ADT	1st generation antiandrogen, or ketoconazole Nizoral®) +steroid
2	mCRPC with minimal or no symptoms and no previous Taxotere (TAX)	↑ PSA with castrate testosterone & mCRPC detected on radiographic imaging	Zytiga+prednisone (pred), TAX, or Provenge	1st generation antiandrogen, Nizoral+ steroid, or observation
3	Symptomatic mCRPC with good PS and no previous chemotherapy	↑ PSA with castrate testosterone, mCRPC is only cause of symptoms (e.g., pain)	TAX, Zytiga+pred	Nizoral+steroid, mitoxantrone, or radionuclide therapy
4	Symptomatic mCRPC with poor PS and no previous chemotherapy	Symptomatic mCRPC not eligible for clinical trials due to poor PS (ECOG 3 or 4)	Zytiga+pred	Nizoral+steroid, or radionuclide therapy Chemotherapy if poor PS is directly related to mCRPC
5	Symptomatic mCRPC with good PS & progressive disease on TAX	Focus is to maintain good PS and avoid significant toxicity from additional treatments	Zytiga+pred (if not given prior to TAX), Jevtana, or Xtandi	Nizoral+steroid can be given if primary therapy is not available
6	Symptomatic mCRPC with poor PS and disease progression on TAX	Men with poor PS (ECOG 3 or 4) in their final months of life	Palliative care	For selected men, Zytiga+pred, Xtandi, or Nizoral+ steroid

DOCTOR CHODAK'S BOTTOM LINE *(Ref Key: article #, page #, column #)*

Gerald Chodak, MD www.prostatevideos.com

Editors' note: Us TOO has invited certain physicians and others to provide information and commentary for the *HotSheet* to enrich its content to empower the reader. This column contains the opinions and thoughts of its author and is not necessarily those of Us TOO International.

a1p1c1 The AUA has been very active in the past few weeks providing policy statements for the management of several aspects of prostate cancer. Three are described in this month's *HotSheet*. The first is a joint report in collaboration with the American Society for Radiation Oncology in which they provide nine statements about adjuvant radiation after radical prostatectomy with varying levels of support. Unfortunately, only one is based on randomized clinical data. Until the full report is published any critique must be tempered, however, as written, the statements are broad and in my opinion, they do not really provide enough information that will enable patients to decide what to do. What they lack is any numerical information about benefits and risks. The most important statement based on randomized data is that adjuvant radiation after surgery for adverse pathological findings does improve survival; however, the statement should include the odds of benefitting, which is about one out of every nine men who get treated. Statement 4 indicates that a PSA recurrence is associated with a higher risk for metastases or death but patients should be provided with the approximate odds each will occur with and without the adjuvant treatment. Equally important is the need to present patients with the odds of developing short and long-term urinary, bowel and sexual problems and the potential odds of reducing disease recurrence if adjuvant therapy is used. Without more detailed information, patients really will be unable to make a truly informed decision because they cannot decide if the benefits are worth the risks.

The Bottom Line: Having a more uniform message between urologists and radiotherapists about adjuvant radiation after radical prostatectomy can potentially benefit patients, but it should include more specific information about the odds of getting good and bad results to be really helpful.

a2p1c2 The second guideline from the AUA is about managing castrate resistant prostate cancer (CRPC). As indicated in the article, four new therapies are already available and more are likely to appear in the near future. Presently, no studies on optimal sequencing have been conducted and there may not be much incentive for pharmaceutical companies to conduct them.

To begin with, any man with bone metastases is advised to receive Calcium and Vitamin D plus Zometa or Xgeva to protect the bones. Although there are clear advantages in favor of Xgeva, they are not included in the report. Several examples of patient profiles are shown that would benefit from different treatments, which does offer some help but there are several shortcomings. For example, in Case I for a man with a rising PSA on hormone therapy without metastases, they advise secondary therapy with an antiandrogen or ketoconazole, but not one study has ever demonstrated a survival benefit with either treatment and ketoconazole is not FDA approved for that purpose. Cases 2 and 3 both include men with symptoms from metastases and it is unclear how they are different, although the implication is that men in case 3 have more than minimal symptoms. More clarity would be provided by including information about performance status. Case 2 also lacks guidance about either sequencing or combinations of therapy and I find it surprising on the AUA website that they assign level "A" supporting evidence for Zytiga/prednisone but level "B" for TAX and Provenge even though all three were FDA approved based on Level A studies. If a man is going to receive Provenge, the statement should have talked about giving it before chemotherapy because that is the way it was approved and there is little data showing its effect after Taxotere. Another question is whether it should be given before Zytiga because no data exist about the effect of Provenge if given after Prednisone. For patient 3, the guidance talks about men with "good performance status" without specifically defining that category as including men with a status of 0-2 and excluding 3 and 4. In Case 4, Zytiga/prednisone are recommended for a man with symptomatic disease and poor performance status, however, the randomized studies specifically excluded men with moderate or severe pain or those using narcotics. In Case 5, one wonders why the statement provided equal guidance for Jevtana, Zytiga/prednisone, and Xtandi rather than delaying the use of Jevtana until after the other two options due to its much higher incidence of severe and or dangerous side effects.

The Bottom Line: The management of CRPC has become much more complicated due to a growing number of treatment options and the guidance provided by the AUA is a good step in helping men but in its present form it contains several shortcomings.

a6p4c3 The study reported by Lebesque and co-workers provides interesting but perhaps not definitive information about the value of using higher doses of radiation to the prostate. The authors randomized men with stage T1b-T4 disease to receive two different doses of 3D-CRT. They found no impact on survival at 20 years. The weaknesses of the study, however, are that they combined a broad range of clinical stages and did not include hormone therapy with the higher risk group even though randomized studies have proven a survival benefit. The study would be more reliable if the patients had been stratified at entry to allow a proper analysis. A subset analysis did not show any benefit for the higher dose in men with a PSA under 10 ng/mL. Perhaps the most important finding from this study that has broad implications for other clinical trials is that **a reduction in PSA recurrence and local recurrence did not translate into a survival benefit**. The reason this matters is that so many studies with newer forms of radiation are using these two outcomes as a surrogate for survival and this study is just one more example of why that assumption is invalid.

The Bottom Line: The most important message from this study is that lowering PSA and local recurrence do not prove

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DOCTOR CHODAK'S BOTTOM LINE *(Continued from page 7)*

that a treatment will prolong survival.

a7p5c1 As more doctors acknowledge the fact that many men with prostate cancer are getting over treated, there is a clear need to identify the dangerous and not so dangerous tumors. The latest entry is the new but costly Oncotype DX Genomic Prostate Score or GPS. Unlike medical therapies, the FDA does not need to approve tests such as this one for them to be commercially available. That is clearly a problem. This test is based on a small number of patients and contains no long term information about what will happen to men managed with this test in terms of their survival. That is clearly needed to know if the test is worth the high expense. It is not going to give men a yes or no answer. Instead it will give an approximate probability of the tumor being high risk or low risk.

The Bottom Line: Although a test that improves on Gleason score for predicting tumor aggressiveness is needed, much more data are needed to know whether the GPS is worth the expense.

a8p5c3 Risk assessment is becoming the new catchword that is replacing screening. Lilja and co-workers analyzed stored blood samples from Sweden and found that men with a PSA over 1.6 ng/mL between the ages of 45-49 accounted for 44% of eventual prostate cancer deaths. The authors are suggesting that a single test in mid to late 40's, early 50's and 60 are enough to screen most men. Although this might lessen the screening burden it is unclear how high it will remain. Most importantly, this analysis in no way helps determine the impact of this approach on reducing prostate cancer mortality. That would require a study similar to the ones done in Europe and the United States. Since many of the cancer deaths occurred in men not meeting this cutoff, one cannot assume that any benefit for screening would occur in this group compared to those with a lower PSA level who eventually died of their disease.

The Bottom Line: A search for an improved way to screen for prostate cancer is clearly needed, but at this time, not enough information is available to determine if substituting only 3 PSA levels

CANCER IMMUNOTHERAPY

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clinical studies still serve a crucial role in helping us understand prostate cancer and expand our therapeutic arsenal.

One of the most exciting clinical studies currently underway, the PROSPECT trial for PROSTVAC®, is an example. Men considering whether a clinical trial is right for them should speak with their doctor about their options. In many cases, a man may be eligible to participate in a clinical study and still receive other already approved treatments, either during or afterward. To find out more about clinical trials, I invite you to visit the *National Cancer Institute*'s informational website (http://www.cancer.gov/clinicaltrials), which currently lists more than 700 prostate cancer studies that are accepting patients.

Reference:

1. Kantoff, PW, Shuetz TJ, Blumenstein BA, et al. Overall survival analysis of a Phase II randomized controlled trial of a poxviral-based PSA-targeted immunotherapy in metastatic castration-resistant prostate cancer. J Clin Oncol 2010; 28: 1099–1105.

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