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HOTSHEET

FEBRUARY 2014

QIGONG IMPROVES FATIGUE IN PROSTATE CANCER SURVIVORS

The practice of Qigong significantly improves fatigue in older men with prostate cancer, compared with a stretching regimen, according to a new study published online October 30 in the *Journal of Cancer Survivorship*.

The favorable outcome adds to a small but growing body of evidence indicating that the ancient Chinese practice is uniquely suited to improve this vexing problem – especially in elderly patients.

Qigong consists of "slow, flowing movements, coordinated with deep breathing, and a meditative focus to balance the flow of 'Qi' or life energy for overall well-being," write the study authors, led by Rebecca Campo, MD, from the Huntsman Cancer Institute at the University of Utah in Salt Lake City.

Dr. Campo and colleagues randomized 40 men (average age, 74 years) to hour-long classes of either Qigong or stretching twice a week. At baseline, all of the men had "significant fatigue" and a lifestyle classified as sedentary. At the end of the 12-week trial, the Qigong group had significantly greater improvements in the primary outcome of fatigue than the stretching group ($P = 0.02$). There were also greater improvements in the Qigong group in the secondary outcome of distress, measured on the somatization, anxiety, and Global Severity Index

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PAIN DRUGS USED IN PROSTATE GLAND REMOVAL LINKED TO CANCER OUTCOME

The methods used to anesthetize prostate cancer patients and control pain when their prostate glands are surgically removed for adenocarcinoma may affect their long-term cancer outcomes, a study led by Mayo Clinic has found. Opioids, painkillers commonly given during and after surgery, may suppress the immune system's ability to fight cancer cells. The research suggests that supplementing general anesthesia with a spinal or epidural painkiller before a radical prostatectomy (RP) reduces a patient's need for opioids after surgery, and this finding was associated with a lower risk of cancer recurrence. The findings are published online in the *British Journal of Anaesthesia*.

The immune system's strength is especially important in cancer surgery because surgical manipulation of a tumor may spread cancer cells. The immune system can be impaired by general anesthesia, the overall stress surgery places on the body and by post-surgical systemic opioid use. The study found better outcomes in RP patients who had general anesthesia supplemented with spinal or epidural delivery of a long-acting opioid such as morphine, than in those who received general anesthesia only.

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RESEARCHERS REVEAL POTENTIAL BIOLOGICAL FACTOR CONTRIBUTING TO RACIAL DISPARITIES IN PROSTATE CANCER

Researchers have uncovered a potential biological factor that may contribute to disparities in prostate cancer incidence and mortality between African-American and non-Hispanic white men in the US, according to results presented at the Sixth American Association of Cancer Research Conference on the Science of Cancer Health Disparities in Racial/Ethnic Minorities and the Medically Underserved.

"The causes of prostate cancer disparities are numerous, complex, often interrelated, and only partially understood," said David P. Turner, PhD, assistant professor in the Department of Pathology and Laboratory Medicine at the Medical University of South Carolina. "We have identified a potential relationship between sugar-derived metabolites and cancer that may provide a biological link with socioeconomic and environmental factors known to contribute to prostate cancer disparities.

"As our bodies use the sugars that we consume for energy they generate waste products, or metabolites, including molecules called advanced glycation end products (AGEs)," Turner stated. "AGEs naturally accumulate in our tissue as we

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CLINICAL ACTIVITY AND TOLERABILITY OF ENZALUTAMIDE IN PATIENTS WITH METASTATIC, CASTRATION-RESISTANT PROSTATE CANCER WHO PROGRESS AFTER DOCETAXEL AND ABIRATERONE TREATMENT

Badrising S, et al

Cancer 30 December 2013; Epub

Background: Enzalutamide (Enz) and abiraterone acetate (AA) are hormone treatments proven to have a survival advantage in patients with metastatic, castration-resistant prostate cancer (mCRPC) who previously received docetaxel (Doc). Recently, limited activity of AA after Enz and of Enz after AA was demonstrated in small cohort studies. Here, the authors present the activity and tolerability of Enz in patients who previously received AA and Doc in the largest cohort to date.

Methods: The efficacy and tolerability of Enz were investigated in men with progressive, mCRPC who previously received Doc and AA. Toxicity, progression-free survival (PFS), time to prostate-specific antigen (PSA) progression, and overall survival (OS) were retrospectively evaluated.

Results: Sixty-one patients were included in the analysis. The median age was 69 years (interquartile range [IQR], 64-74 years), 57 patients (93%) had an Eastern Cooperative Oncology Group performance status from 0 to 2, 48 patients (79%) had bone metastases, 33 patients (54%) had lymph node metastases, and 13 patients (21%) had visceral metastases. The median duration of Enz treatment was 14.9 weeks (IQR, 11.1-20.0 weeks), and 13 patients (21%) had a maximum PSA decline ≥50%. The median PFS was 12.0 weeks (95% confidence interval [CI], 11.1-16.0 weeks), the median time to PSA progression was 17.4 weeks (95% CI, >16.0 weeks), and the median OS was 31.6 weeks (95% CI, >28.7 weeks). Enz was well tolerated, and fatigue and musculoskeletal pain were the most frequent grade ≥2 adverse events. The PSA response to Doc and AA did not predict the PSA response to Enz.

Conclusions: Enz has modest clinical activity in patients with mCRPC who previously received Doc and AA. PSA response to Doc and AA does not predict for PSA response to Enz.

PROSPECTIVE COMPARISON OF COMPUTED TOMOGRAPHY, DIFFUSION-WEIGHTED MAGNETIC RESONANCE IMAGING AND [11C] CHOLINE PET/CT FOR PREOPERATIVE LYMPH NODE STAGING IN PROSTATE CANCER PATIENTS

Heck M, Souvatzoglou M, Retz M, et al

Eur J Nucl Med Mol Imaging 3 December 2013; Epub

Purpose: The aim of this study was to prospectively compare diffusion-weighted magnetic resonance imaging (DWI) and [11C]choline PET/CT with computed tomography (CT) for preoperative lymph node (LN) staging in prostate cancer (PCa) patients.

Methods: Between June 2010 and May 2012, CT, DWI and [11C]choline PET/CT were performed preoperatively in 33 intermediate- and high-risk PCa patients undergoing radical prostatectomy (RP) and extended pelvic lymph node dissection (ePLND) including obturator fossa and internal, external and common iliac fields. Patient- and field-based performance characteristics for all three imaging techniques based on histopathological results are reported. Imaging techniques were compared by means of the area under the curve (AUC).

Results: LN metastases were detected in 92/1,012 (9 %) LNs from 14/33 (42%) patients. On patient-based analysis, sensitivity, specificity and accuracy for CT were 57, 68 and 64%, respectively, for DWI were 57, 79 and 70%, respectively, and for [11C]choline PET/CT were 57, 90 and 76%, respectively. On field-based analysis, these numbers for CT were 47, 94 and 88%, respectively, for DWI were 56, 97 and 92%, respectively, and for [11C]choline PET/CT were 62, 96 and 92%, respectively. Neither DWI nor [11C]choline PET/CT performed significantly better than CT on pairwise comparison of patient- and field-based results.

Conclusion: All three imaging techniques exhibit a rather low sensitivity with less than two-thirds of LN metastases being detected on patient- and field-based analysis. Overall diagnostic efficacy did not differ significantly between techniques, whereas distinct performance characteristics, especially patient-based specificity, were best for [11C]choline PET/CT followed by DWI and CT.

QIGONG REDUCES FATIGUE

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subscales of the Brief Symptom Inventory 18 (P <0.05 for all).

This study is the first to assess Qigong for fatigue in older prostate cancer survivors, the authors note. The results are "consistent" with results from previous studies indicating that the practice improves fatigue in breast cancer patients and a variety of other types of cancer survivors, they report.

"Cancer patients are very, very good candidates for Qigong," according to Olga Gonzalez, MSTOM, LAc, an acupuncturist in private practice in New York City, who was not involved in the study. She is also a certified teacher of Wild Goose Qigong, a particularly ancient form of the practice that has roots in Taoism.

"Qigong is one of the branches of Chinese medicine and is considered to be as healing as acupuncture," she stated in an interview. Qigong can be practiced from a seated or standing position, she explained. "No matter what your ability is, you can start." When Qi increases and/or flows, blood flow is generated, which helps blood deficiencies and blood stagnation, both of which contribute to fatigue, insomnia, irritability, dry skin, hair loss and thinning, headache, and other symptoms in cancer patients, she said.

Gonzalez explained that, ideally, Qigong should be practiced outdoors. If practicing indoors, windows should be open to enhance the flow of Qi from nature. The practice provides a connection to one's self, one's community, and nature. "It's all one," said Gonzalez. "Nature will regenerate itself, if given a chance. It's the same thing with the body."

A large proportion (69%) of the Qigong group had a "minimally important" difference in fatigue (at least 3 points), whereas only 31% of those in the stretching group did, the authors report. In other words, meaningful improvement in the Qigong group was seen in most of the men.

This study is distinguished from other studies of Qigong in cancer patients because it had an active control group, the authors point out. The structure of

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USE OF STATINS AND THE RISK OF DEATH IN PATIENTS WITH PROSTATE CANCER

Yu O, Eberg M, Benayoun S, et al

J Clin Oncol 32: 5–11, 2014

Purpose: To determine whether the use of statins after prostate cancer diagnosis is associated with a decreased risk of cancer-related mortality and all-cause mortality and to assess whether this association is modified by prediagnostic use of statins.

Patients and methods: A cohort of 11,772 men newly diagnosed with nonmetastatic prostate cancer between April 1, 1998, and December 31, 2009, followed until October 1, 2012, was identified using a large population-based electronic database from the United Kingdom. Time-dependent Cox proportional hazards models were used to estimate adjusted hazard ratios (HRs) with 95% CIs of mortality outcomes associated with postdiagnostic use of statins, lagged by one year to account for latency considerations and to minimize reverse causality, and considering effect modification by prediagnostic use of statins.

Results: During a mean follow-up time of 4.4 years (standard deviation, 2.9 years), 3,499 deaths occurred, including 1,791 from prostate cancer. Postdiagnostic use of statins was associated with a decreased risk of prostate cancer mortality (HR, 0.76; 95% CI, 0.66 to 0.88) and all-cause mortality (HR, 0.86; 95% CI, 0.78 to 0.95). These decreased risks of prostate cancer mortality and all-cause mortality were more pronounced in patients who also used statins before diagnosis (HR, 0.55; 95% CI, 0.41 to 0.74; and HR, 0.66; 95% CI, 0.53 to 0.81, respectively), with weaker effects in patients who initiated the treatment only after diagnosis (HR, 0.82; 95% CI, 0.71 to 0.96; and HR, 0.91; 95% CI, 0.82 to 1.01, respectively).

Conclusion: Overall, the use of statins after diagnosis was associated with a decreased risk in prostate cancer mortality. However, this effect was stronger in patients who also used statins before diagnosis.

NO OVERALL SURVIVAL BENEFIT WITH ADDITION OF SUNITINIB TO PREDNISONE IN METASTATIC CASTRATION-RESISTANT PROSTATE CANCER

In a phase III trial reported in the *Journal of Clinical Oncology*, Michaelson et al assessed the addition of the antiangiogenesis agent sunitinib (Sutent®) to prednisone in patients with progressive metastatic castration-resistant prostate cancer (mCRPC) after docetaxel-based chemotherapy. No significant improvement in overall survival (OS) was observed with the addition of sunitinib.

In this double-blind, placebo-controlled trial, 873 patients were randomly assigned 2:1 to receive prednisone at 5 mg twice daily and either sunitinib at 37.5 mg/d continuously (n = 581) or placebo (n = 285). The primary endpoint was OS. Two interim analyses were planned.

The sunitinib and placebo groups were balanced for age (median, 69 and 68 years), Eastern Cooperative Oncology Group performance status (0 and 1 in 50% and 50% in both), Gleason score (8 –10 in 51% and 45%, ≤ 6 in 13% and 15%), disease progression (PSA-only progression in 54% and 50%, radiographic progression in 46% and 50%), prior VEGF inhibitor therapy (2% in both), number of prior systemic therapies (one in 86% in both, two in 10% and 11%), and reason for stopping docetaxel (progression in 91% and 92%, intolerance in 9% and 8%).

The study was stopped early after a second interim analysis indicated that an OS difference between groups was statistically improbable. After median follow-up of 8.7 months, median OS was 13.1 months in the sunitinib group vs 11.8 months in the placebo group (hazard ratio [HR] = 0.914, P = 0.168). Progression-free survival (PFS) was significantly longer in the sunitinib group (median, 5.6 vs 4.1 months, HR = 0.725, P < .001). The objective response rate (no complete responses) was 6% vs 2% (odds ratio [OR] = 3.56, P = 0.040) and the stable disease rate was 26% vs 30%.

Treatment-related adverse events of any grade were more common in the sunitinib group (94% vs 62%), with the most common nonhematologic adverse

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BIOMARKER MAY EXPLAIN RACIAL DISPARITY

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grow older, and they have been implicated in diseases associated with aging such as diabetes, heart disease, and Alzheimer's disease. They can also cause increased inflammation and the generation of potentially harmful chemicals known as reaction oxygen species, which both promote cancer.

"Critically, a common source of the AGEs that accumulate in our bodies is the foods we eat, which has significant implications for cancer health disparities and our overall health.

"We found that AGE levels were highest in African-American men with prostate cancer," said Turner. "Because obesity, poor eating habits, and an inactive lifestyle all promote AGE accumulation, and these factors are often more evident in African-Americans, we hypothesize that there is a link between these factors that could help explain why African-American men are more likely to develop prostate cancer and die from the disease."

Turner and colleagues examined circulating and intratumoral AGE levels in 16 African-American and 16 non-Hispanic white men with prostate cancer. They found that AGE levels were higher in serum from cancer patients compared with individuals without cancer. When analyzing AGE levels in prostate tumor samples, levels were highest in tumor samples from African-American men. In addition, AGE levels in prostate tumors correlated with levels of a molecule to which AGEs bind to mediate their effects, called receptor for AGE (RAGE)

"We think that the AGE-RAGE signaling pathway promotes prostate cancer and that increased AGEs accumulation may represent a biological mechanism promoting prostate cancer disparity," said Turner.

Presented at the Sixth American Association of Cancer Research Conference on the Science of Cancer Health Disparities in Racial/Ethnic Minorities and the Medically Underserved, abstract PR10

Medical News Today, 11 December 2013

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

"STEP RIGHT UP & TAKE YOUR BEST SHOT AT A DAILY MULTIVITAMIN – The piñata of dietary supplements?!"

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:

Should I take a daily multivitamin? I get only this question 100 times a week and the answer is "yes" more than ever before for me because it may reduce the risk of cancer and cataracts (the 2 big Cs). And, it might correct some minor nutrient deficiencies, but keep in mind that Centrum Silver® (or a children's multivitamin) is one of the cheapest multivitamins in America and has most of the evidence, and taking more than one pill a day is not needed. Oh, and to all the "experts" that claim multivitamins are worthless, please just learn a little more from the research then give me a call, but I won't answer the phone! Hey do you want to know the real piñata of the pill world right now? It is the multivitamin my friends! It is open season on this poor pill with a variety of bone headed "experts" taking a whack at it! Come on and step right up – take your best shot! Wack! Wack! One medical journal that will remain nameless[1] (sorry, no way!) not only published the recent research that showed Centrum Silver does not impact cognition, but also in the same issue on December 23, 2013 allowed an editorial to be published without ANY rebuttal that was scathing and unusually candid about how multivitamins are simply worthless ("stop wasting money…")!

Wow! That was really harsh! However, let me put this into objective perspective without trying to be histrionic. If you really thought a Centrum would impact cognitive function better than placebo within 10 years in healthy older doctors whose average BMI is 25, less than 4% are smokers, less than 9% are diabetics and most of whom doing vigorous exercise weekly and eat five servings of fruits and veggies daily then I have swampland with gold embedded in it that I want to sell you in Ann Arbor, Michigan! It is ridiculous to think this pill could prevent Alzheimer's and most other diseases in perfectly healthy individuals. However, what was surprising is that this is the same clinical trial that found a modest, but significant reduction in the risk of cancer in those with and without a personal history of cancer when taking this multivitamin compared to placebo, and this was one of the primary endpoints of the study.[2] This is also the same study that found a reduction in the risk of the most common type of cataracts and cataract surgery when taking a multivitamin, and there is adequate research to suggest it could correct some minor nutritional deficiencies (vitamin D, B12, B6, etc…).[3] Otherwise there has not been any other phase-3 like trials of multivitamins in the U.S., or really around the world!

In other words, the folks jumping on the "lets beat up the multivitamin" bandwagon are really acting in an immature, ignorant, silly and non-evidence based fashion. Patients and other health care professionals do not need physicians/researchers to act like Democrats and Republicans fighting on 2 different television channels but rather they need objectivity and education on what to do with all this mess! The multivitamin chaos was not just created by some members of the supplement industry, but also by some members of my own profession. Ask yourself these questions: Are you willing to pay pennies a day to slightly reduce your risk of cancer and cataracts (the number 1 cause of blindness in the world and one of the most costly annual Medicare procedures) with a pill that has the same side effects as a placebo that does not show any evidence to prevent other diseases right now? If the answer is "yes" then great and if the answer is "no" then that is okay too! My answer is "yes."

References:

1. Grodstein F, O'Brien, J, Kang J-H, et al. Ann Intern Med 2013;159:806-14.
2. Gaziano JM, Sesso HD, Christen WG, et al. JAMA 2012;308:1871-80.
3. Christen W, Glynn RJ, Manson JE, et al. Ophthalmology 20 Nov 2013 Epub.

ABIRATERONE ACETATE PLUS PREDNISONE VERSUS PREDNISONE ALONE IN CHEMOTHERAPY-NAIVE MEN WITH METASTATIC CASTRATION-RESISTANT PROSTATE CANCER: PATIENT-REPORTED OUTCOME RESULTS OF A RANDOMISED PHASE 3 TRIAL

Basch E, Autio K, Ryan, CJ, et al

Lancet Oncology 14: 1193–1199, 2013

Background: Abiraterone acetate (AA) plus prednisone (P) significantly improves radiographic progression-free survival in asymptomatic or mildly symptomatic, chemotherapy-naive patients with metastatic castration-resistant prostate cancer (mCRPC) compared with P alone. We describe analyses of data for patient-reported pain and functional status in a preplanned interim analysis of a phase 3 trial.

Methods: Between April 28, 2009, and June 23, 2010, patients with progressive, mCRPC were enrolled into a multinational, double-blind, placebo-controlled trial. Patients were eligible if they were asymptomatic (score of 0 or 1 on item three of the Brief Pain Inventory Short Form [BPI-SF] questionnaire) or mildly symptomatic (score of 2 or 3) and had not previously received chemotherapy. Patients were randomly assigned (1:1) to receive oral AA (1 g daily) plus P (5 mg twice daily) or placebo plus P in continuous 4-week cycles. Pain was assessed with the BPI-SF questionnaire, and health-related quality of life (HRQoL) with the Functional Assessment of Cancer Therapy – Prostate (FACT-P) questionnaire. We analysed data with prespecified criteria for clinically meaningful pain progression and deterioration in HRQoL. All patients who underwent randomization were included in analyses. This study is registered with ClinicalTrials.gov, number NCT00887198.

Findings: 1,088 patients underwent randomization: 546 were assigned to AA plus P and 542 to placebo plus P. At the time of the second prespecified interim analysis, median follow-up was 22.2 months. Median time to progression (TTP) of mean pain intensity was longer in patients assigned to AA plus P (26.7 months [95% confidence interval [CI] 19.3–not estimable]) than in those assigned to placebo plus P (18.4 months [14.9–not estimable]; hazard ratio [HR] 0.82, 95% CI 0.67–1.00; p=0.0490), as was median TTP of pain interference with daily activities (10.3 months [95% CI 9.3–13.0] vs 7.4 months [6.4–8.6]; HR 0.79, 95% CI 0.67–0.93; p=0.005). Median TTP of worst pain was also longer with AA plus P (26.7 months [95% CI 19.4–not estimable]) than with placebo plus P (19.4 months [16.6–not estimable]), but the difference was not significant (HR 0.85, 95% CI 0.69–1.04; p=0.109). Median time to HRQoL deterioration was longer in patients assigned to AA plus P than in those assigned to placebo plus P as assessed by the FACT-P total score (12.7 months [95% CI 11.1–14.0] vs 8.3 months [7.4–10.6]; HR 0.78, 95% CI 0.66–0.92; p=0.003) and by the score on its prostate-cancer-specific subscale (11.1 months [8.6–13.8] vs 5.8 months [5.5–8.3]; HR 0.70, 95% CI 0.60–0.83; p<0.0001).

Interpretation: AA plus P delays patient-reported pain progression and HRQoL deterioration in chemotherapy-naive patients with mCRPC. These results provide further support for the efficacy of abiraterone in this population.

POPULATION BASED STUDY OF PREDICTORS OF ADVERSE PATHOLOGY AMONG CANDIDATES FOR ACTIVE SURVEILLANCE WITH GLEASON 6 PROSTATE CANCER

Vellekoop A, Loeb S, Folkvaljon Y, Pär Stattin P

J Urol 191: 350–357, 2014

Purpose: Approximately a third of prostate cancer cases with a Gleason score of 6 are upgraded at radical prostatectomy. We studied trends and predictors of upgrading and up staging among men with Gleason 6 prostate cancer who were potential candidates for active surveillance in a population based cohort.

Materials and Methods: From 2007 to 2011, 13,159 men were diagnosed with Gleason 6, clinical stage T1c/T2 prostate cancer in the NPCR (National Prostate Cancer Register of Sweden). Of these men 4,500 underwent radical prostatectomy, including 2,205 with data on the extent of prostate cancer in the biopsy cores. Logistic regression was used to examine variables associated with adverse pathology (defined as upgrading to Gleason 7 or greater, or up staging to pathologic stage T3 or greater) in the full group and in potential candidates for active surveillance using six current published protocols.

Results: Among Swedish men with clinically localized Gleason 6 prostate cancer approximately 50% had adverse pathology at radical prostatectomy. Of the men who met the study inclusion criteria of six different active surveillance protocols, adverse pathology was present in 33% to 45%. Predictors of adverse pathology were older age, higher prostate specific antigen, prostate specific antigen density greater than

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OPIOIDS AND CANCER OUTCOME

(Continued from page 1)

"We found a significant association between this opioid-sparing technique, reduced progression of the prostate tumor and overall mortality," says senior author Juraj Sprung, M.D., PhD, a Mayo Clinic anesthesiologist.

Researchers used Mayo Clinic's RP registry, anesthesia database and electronic medical records to identify men who had prostate gland surgery for adenocarcinoma from January 1991 through December 2005. Reports of recurrence of cancer, cancer spread and death were confirmed with patients' physicians.

While promising, the findings must be tested in randomized trials, Dr. Sprung says: "Provided future studies confirm what we have found in this study, maybe down the line this would be a standard of care for pain management in patients undergoing cancer surgery."

Science Daily, 17 December 2013

CLINICAL SIGNIFICANCE OF CANCER IN RADICAL PROSTATECTOMY SPECIMENS: ANALYSIS FROM A CONTEMPORARY SERIES OF 2900 MEN

Samaratunga H, Delahunt B, Yaxley J, et al

Pathology 46(1):11–14, 2014

Summary: With prostate specific antigen (PSA) testing, up to 49% of detected tumours are small and in some of these cases there is a possibility that the tumor will remain clinically insignificant during the patient's remaining lifetime. The current study was performed to characterize the extent of cancer in men treated by radical prostatectomy (RP) in a community without population-based PSA screening in the United Kingdom. Clinical and pathological data of 2,900 patients who underwent RP between 2008 and 2012 were analysed. Specimens were entirely embedded and evaluated by routine hematoxylin and eosin staining. Tumors were graded using recent modifications to the International Society of Urological Pathology (ISUP) modified Gleason grading system, and staged according to the ISUP recommendations. Tumors were considered pathologically insignificant if organ confined, with a volume of <0.5cc and a Gleason score (GS) of <7.

The mean age of patients in the series was 63 years (range 32-79 years) and the mean pre-operative PSA was 7.16 ng/mL (range 0.4–69). In total, 2,614 (90.1%) were classified as cT1; however, insignificant tumours were found in only 150 (5.2%) patients following examination of the RPspecimen. A total of 2,681 cases (92.4%) had a final GS of ≥7, 1,144 (39.4%) had extraprostatic extension (EPE), of which 88.7% were classified as established; 669 (23.1%) had a tumour volume of >3cc and 284 (9.8%) had surgical margin positivity. Seminal vesicle involvement was seen in 159 (5.5%) cases. Of 693 patients who had a lymphadenectomy, 31 (4.5%) had lymph node metastases. There were 212 (7.3%) men aged ≤50 years (mean age 47 years). Of these, 194 were classified as cT1 while 192 (90.6%) were found to have significant cancer on examination of the radical prostatectomy specimen.

Although 90.1% of tumors in our series were cT1, we have shown that an overwhelming majority of tumors were found to be pathologically significant following RP, with a high proportion of cases showing high stage disease, seminal vesicle involvement and lymph node metastasis. These results suggest that, contrary to estimates from international trials, ad hoc PSA testing is associated with low levels of over-treating.

NO SURVIVAL BENEFIT FROM ADDED SUNITINIB *(Continued from page 4)*

events being diarrhea, decreased appetite, nausea, fatigue, hand-foot syndrome, altered taste and vomiting. The most common grade 3 or 4 adverse events were fatigue (9% vs 1%), asthenia (8% vs 2%), and hand-foot syndrome (7% vs 0%).

Sunitinib dose reduction was required in 32% of patients, and adverse events led to study drug discontinuation in 27% of the sunitinib group. A total of 57 patients (10%) in the sunitinib group and 30 patients (11%) in the placebo group died during the study, with most deaths (72% and 80%) due to prostate cancer.

As related by the authors, the findings are similar to those in another recently reported study (Cancer and Leukemia Group B 90401), which showed that the addition of the antiangiogenic agent bevacizumab (Avastin®) to docetaxel and prednisone improved PFS without improving OS in mCRPC. They noted, "The reason that improved [PFS] does not appear to translate to [OS] benefit with antiangiogenic agents is not clear. The magnitude of [PFS] may be too small to affect [OS], or other factors may be involved."

Investigators concluded: "The addition of sunitinib to prednisone did not improve [OS] compared with placebo in docetaxel-refractory [mCRPC]…. Antiangiogenic agents may yet have a role to play in treating patients with [mCRPC], but their future development in this area will require enhanced patient selection by using predictive biomarkers of response to guide therapy in a rational manner."

The ASCO Post, 18 December 2013

A PHASE II TRIAL OF PERSONALIZED PEPTIDE VACCINATION IN CASTRATION-RESISTANT PROSTATE CANCER PATIENTS: PROLONGATION OF PROSTATE-SPECIFIC ANTIGEN DOUBLING TIME

Noguchi M, Moriya F, Suekane S, et al

BMC Cancer 30 Dec 2013; Epub

Background: Cancer vaccine is one of the attractive treatment modalities for patients with castration-resistant prostate cancer (CRPC). However, because of delayed immune responses, its clinical benefits (besides for overall survival), are not well captured by the World Health Organization (WHO) and Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Several surrogate markers for evaluation of cancer vaccine, including prostate-specific antigen doubling time (PSADT), are currently sought. The purpose of this study was to assess prospectively the PSA kinetics and immune responses, as well as the efficacy, safety, and biomarkers of personalized peptide vaccination (PPV) in progressive CRPC.

Methods: One hundred patients with progressive CRPC were treated with PPV using 2-4 positive peptides from 31 candidate peptides determined by both human leukocyte antigen (HLA) class IA types and the levels of immunoglobulin G (IgG) against each peptide. The association between immune responses and PSADT as well as overall survival was studied.

Results: PPV was safe and well tolerated in all patients with a median survival time of 18.8 months. Peptide-specific IgG and T-cell responses strongly correlated with PSADT ($p < 0.0001$ and $p = 0.0007$, respectively), which in turn showed correlation with overall survival ($p = 0.018$). Positive IgG responses and prolongation of PSADT during PPV were also significantly associated with overall survival ($p = 0.001$ and $p = 0.004$) by multivariate analysis.

Conclusions: PSADT could be an appropriate surrogate marker for evaluation of the clinical benefit of cancer vaccine. Further randomized trials are needed to confirm these results.

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

Gerald Chodak, MD Author, Winning the Battle Against Prostate Cancer , Second Edition 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 benefits of unconventional therapies in men with prostate cancer continue to be debated, in part because of a lack of randomized studies. The study by Campo and co-workers appears to provide some interesting data about the value of Qigong compared to stretching exercises to treat fatigue in elderly men with this disease. They found that after 12 weeks, men performing Qigong had less fatigue than the control group, less distress and less anxiety. The study only included 40 men, however, and would need to be confirmed by a much larger study with carefully matched groups. Potential weaknesses of this study include a very wide age range (58–93) and an unclear treatment history to document the percentage receiving androgen deprivation therapy. Additionally, although not statistically significant, 80% of men in the Qigong group, compared to only 65% of the stretching group, remained on the program. Lastly, significantly higher class attendance occurred in the Qigong group. These imbalances could easily account for the findings.

The Bottom Line: Qigong may offer men with prostate cancer some relief of their fatigue but more definitive data are needed to validate these findings.

a2p1c2 Does the use of opioids for a few days after radical prostatectomy (RP) affect survival and tumor recurrence? Scavonetto and co-workers addressed this question by doing a retrospective comparison with men having spinal or epidural supplementary anesthesia. They found better outcomes when opioids were avoided. As the authors' acknowledge, this study design does not permit firm conclusions so additional data would be needed to confirm the findings. For now, results seem interesting and deserve further study.

The Bottom Line: Avoiding opioids during and after a RP may offer some survival benefit to men with prostate cancer but more data are needed.

a4p2c2 Abiraterone and enzalutamide are two new, valuable treatments for men with progressive metastatic castrate resistant prostate cancer (mCRPC). Abiraterone is now approved to treat men before chemotherapy, and based on results of a recent study, enzalutamide is likely to gain that approval, too. When that happens, doctors will need to know which of these drugs should be used first to achieve the best overall survival. Perhaps both together may even prove to be the optimal approach. For now, important data are needed to find out the best order for these drugs. The study by Badrising and co-workers shows us that using enzalutamide after abiraterone results in only a modest benefit for following this drug with enzalutamide. To truly assess the best order of these drugs, a randomized study will be needed and hopefully that will appear soon. Until then, the optimal sequence will remain unclear, assuming enzalutamide gains approval soon.

The Bottom Line: Important studies are needed to determine the optimal sequencing of abiraterone and enzalutamide in men with CRPC.

a5p2c3 Fortunately for most men with newly diagnosed prostate cancer, the likelihood of having lymph node metastases is very low resulting in the ability to avoid removing them during a radical prostatectomy. For those at higher risk, the question is whether preoperative imaging studies can identify who should have their lymph nodes removed. The study by Heck and co-workers attempts to address this question. They performed CT, Choline PET/CT and diffusion-weighted MRI in a group of high-risk patients and found no significant difference in the sensitivity or accuracy of the different methods. None of the methods was capable to clearly identify who should or should not have a complete node dissection.

The Bottom Line: Men with a significant risk of pelvic lymph node metastases still need a formal dissection because neither CT, Choline PET/CT nor MRI is sufficiently accurate.

a6p3c2 Are statin drugs good for men with prostate cancer? The study by Yu and co-workers is another uncontrolled study with long follow-up again showing a benefit to men in terms of overall and prostate cancer mortality. A greater benefit occurred in men who were on one of these drugs before their cancer diagnosis. Does this mean men should take a statin even if their cholesterol is normal? That is still unclear. Two weaknesses acknowledged by the authors are the lack of data on tumor grade and tumor stage. They attempted to adjust for these based on the treatments received but that still does not insure that the findings are reliable. Once again, only a randomized study can make that determination. It is surprising that no study has occurred given the repeatedly positive findings from uncontrolled studies.

The Bottom Line: More data is provided that statins will benefit men with prostate cancer but true proof still requires a prospective, randomized trial.

a9p5c2 What criteria define candidates for active surveillance (AS). The study by Vellekoop provides new data suggesting that the criteria used by many doctors may not be correct because 33-45% of the men actually have worse pathology following removal of their prostate. PSA density greater than 0.15 and more than 4 mm of cancer in prostate biopsy cores were risk factors for worse results. Unfortunately, using the final pathology report is not an adequate method to determine who is a good candidate. Although it is true that men with a Gleason score of 7 or extra capsular disease have a higher progression rate than men with Gleason 6, it is not uniformly bad. Data showing the odds of developing metastatic disease or dying from prostate cancer in a group of men who were thought to be good candidates for active surveillance but instead had surgery is what is needed.

The Bottom Line: Additional data about long-term outcomes are needed to better identify which patients should not undergo active surveillance.

a10p6c2 The study by Samaratunga attempts to address the question of whether non-routine PSA testing will lead to an over-diagnosis of prostate cancer. They analyzed the results of 2,900 men treated in a community set-

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THE BOTTOM LINE

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ting and found that only 5% were classified as clinically insignificant using the definition of a tumor volume less than 0.5 cc and a Gleason score less than 7. Unfortunately, these are not reliable classifications, as a high percentage of men with a high volume tumor or Gleason 7 cancer will not suffer from recurrence of their disease.

The Bottom Line: Defining clinically insignificant cancer based on a volume less than 0.5 cc or a Gleason score less than 7 will underestimate the percentage of men in this category.

a11p6c3 A new treatment approach is called personalized Peptide Vaccination or PPV. Noguchi, et al have published several papers using this treatment and in the current paper they suggest that PSA doubling time might be useful for identifying men that are responding. To confirm this, survival results from a randomized study will be needed.

The Bottom Line: Personalized peptide vaccine has some promising preliminary data and hopefully it can be confirmed in a prospective study.

QIGONG

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the control group's stretching class was the same as that of the Qigong class in terms of intensity and group format. In addition, both classes consisted of sitting and standing exercises, and all participants were given DVDs of their intervention to encourage home practice.

Class attendance was significantly better in the Qigong group than in the stretching group (P = 0.04). The study retention rate was also better in the Qigong group (80% vs 65%).

It was not surprising that Qigong was more satisfying and appealing to the men than stretching, said Gonzalez. Stretching is an "external exercise" in which the breath is typically not consciously worked with, as it is in Qigong.

"If you do stretching that is not in tune with the energy you have, you might overdo it and expend more energy than you generate, which is unhealthy," Gonzalez explained. Qigong literally means working with energy. "You want it to flow, you want it to increase," she said.

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0.15 ng/mL/cm^3, palpable disease and extent of cancer greater than 4 mm on biopsy cores. Larger prostate volume had an inverse relationship with adverse pathology.

Conclusions: More than one-third of men meeting the most stringent active surveillance criteria had adverse pathology at radical prostatectomy in this population based cohort. Active surveillance programs should consider prostate specific antigen density and extent of cancer on biopsy for patient selection.

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