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Affected by Prostate Cancer?



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Hot SHEET

Us TOO INTERNATIONAL Prostate Cancer Education and Support Network

Aspirin May Lower Risk of Lethal Prostate Cancer

But confirmation needed before a firm recommendation can be made

Men with prostate cancer had almost a 40% lower risk of dying of the disease if they were taking aspirin for cardiovascular protection, a large cohort study showed.

The hazard ratio for prostate cancer death was 0.61 (95% CI 0.47-0.78) for men who reported taking aspirin more than three times a week versus those who reported less frequent or no aspirin use. Aspirin prophylaxis also was associated with a 24% reduction in the hazard for lethal

prostate cancer, defined as metastatic disease or death. Total prostate cancer and the risk of high-grade or locally advanced disease did not decrease with aspirin use.

However, regular aspirin use did not affect the likelihood of developing prostate cancer in the first place, nor was there an association with any of the other risk categories of prostate cancer included in the analysis.

The findings require further study and confirmation but suggest that men already taking aspirin for cardiovas-

cular benefits "could have one more reason to consider regular aspirin use," Christopher B. Allard, MD, of Harvard's T.H. Chan School of Public Health and Brigham and Women's Hospital in Boston, reported at the Genitourinary Cancers Symposium (GuCS).

"Regular aspirin intake may inhibit lethal prostate cancer, probably by preventing cancer progression," Allard said during a press briefing that preceded GuCS, which began

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Blood Test May Guide Prostate Cancer Therapy

An experimental blood test showed promise for identifying prostate cancers that were unlikely to respond to treatment with newer hormonal therapies, according to a preliminary clinical study.

Men with heterogeneous (wide variation in appearance and genetic make-up) circulating tumor cells (CTCs) on the test, described as a "liquid biopsy," had a median progression-free survival (PFS) of five months when treated with abiraterone (Zytiga®) or enzalutamide (Xtandi®) compared with 17 months for men whose CTCs were homogeneous (consistent characteristics). Heterogeneity also correlated with overall survival (OS).

The extent of heterogeneity in CTCs did not influence response to taxane chemotherapy, reported Howard Scher, MD, of Memorial Sloan Kettering Cancer Center in New York City, at the Genitourinary Cancers Symposium (GuCS).

"Single CTC morphology, protein, and genomic characterization are feasible and can be used to assess tumor heterogeneity," Scher said during a press briefing that preceded GuCS. "High CTC heterogeneity identifies men with shorter survival times on abiraterone and enzalutamide but not taxane chemotherapy. A noninvasive liquid biopsy that enables the characterization of individual cells from a man with metastatic cancer can be used to guide treatment selection."

"The results require validation in larger studies, which already are in development, but preliminary findings are fascinating and suggest that the liquid biopsy has potential for addressing the

(Continued on page 6)

Comparing Chemical and Surgical Castration for Prostate Cancer

Surgical castration to remove the testicles (orchiectomy) of men with metastatic prostate cancer (PCa) was associated with lower risks for adverse effects compared with men who underwent medical castration with gonadotropin-releasing hormone agonist (GnRH) therapy, according to an article published online by *JAMA Oncology*.

Androgen-deprivation therapy (ADT), achieved by surgical or medical castration, has been a cornerstone in the management of metastatic PCa for the past 50 years. But the use of bilateral orchiectomy (BO) has been nearly eliminated in the US because of cosmetic and psychological concerns.

Quoc-Dien Trinh, M.D., of Brigham and Women's Hos-

pital and Dana-Farber Cancer Institute, Boston, and coauthors compared adverse effects of GnRH and BO in 3,295 men with metastatic PCa (66 or older) between 1995 and 2009. The authors analyzed six major adverse effects, which were picked based on their effect on a patient's quality of life, the potential for increased health care costs, and on a previously described association with ADT use. The six adverse effects were: any fractures, peripheral artery disease, venous thromboembolism, cardiac-related complications, diabetes and cognitive disorders.

Of the 3,295 men, 87% (n=2,866) were treated with

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Comparison of Hypofractionated High-Dose Intensity-Modulated Radiotherapy Schedules for Prostate Cancer: Results from the Phase III Randomized CHHiP Trial

Non-inferiority demonstrated for 60 Gy versus 74 Gy

A modest hypofractionated radiotherapy (RT) protocol demonstrated noninferiority to conventional treatment and can be considered a new standard of care in men with low- and intermediate-risk prostate cancer, investigators concluded here.

Over a follow-up period of about five years, a 3-Gy schedule of 60 Gy in 20 fractions proved non-inferior to 74Gy in 37 fractions, with respect to biochemical failure/prostate cancer recurrence and overall survival. The schedules had similarly low rates of acute and late side effects, reported David P. Dearnaley, MD, at the Genitourinary Cancers Symposium (GuCS).

“We believe that modified hypofractionation, using 60 Gy in 20 fractions delivered with high-quality RT, can now be recommended as a new standard of care in men with this type of intermediate- and low-risk cancer,” he said. “The low side effect profile, in general, probably reflects the technique of RT and the strict use of dose constraint and quality assurance.”

The findings come from the multicenter, randomized CHHiP (Conventional or Hypofractionated High dose Intensity Modulated Radiotherapy in Prostate Cancer; CRUK/06/016) trial.

CHHiP investigated two 3-Gy hypofractionated radiotherapy dose schedules in 3,216 men with T1b to T3N0M0 localized prostate cancer, following hormonal treatment for three to six months, which was optional in men with low-risk disease, defined as stage T1c/T2a and a Gleason score ≤ 6 and a serum PSA level ≤ 10 ng/mL.

Men enrolled in CHHiP had a risk of seminal vesicle involvement $\leq 30\%$ and a serum PSA value ≤ 30 ng/mL, and were randomized in a 1:1:1 fashion to standard RT delivered using 74 Gy in 37 fractions over 7.4 weeks or one of two experimental hypofractionated regimens: 60 Gy in 20 fractions over four weeks or 57 Gy in 19 fractions over 3.8 weeks.

Toxicity was assessed before hormone therapy; before RT; weekly during RT; at weeks 10, 12 and 18; and then at 26 weeks and every six months for five years.

Median age of men was 69 years; 73% had intermediate-risk, 15% had low-risk and 12% had high-risk prostate cancer; 62% had a Gleason score of 7 and 35% had a Gleason score ≤ 6 and 55% had stage T2 and 36% had stage T1 disease. The median PSA level prior to hormone therapy was 10 ng/mL.

Five-year progression-free survival was 88.3% in the 74-Gy arm, 90.6% in the 60-Gy arm, and 85.9% in the 57-Gy arm. The 60-Gy schedule met the non-inferiority criterion compared with the 74-Gy schedule (HR 0.84, 90% CI 0.68-1.03, $P=0.004$), but the 57-Gy schedule did not (HR 1.20, 90% CI 0.99-1.46, $P=0.96$).

Mortalities were 8.6%, 6.8%, and 8.1% in the standard, 60-Gy and 57-Gy arms, respectively, with no significant difference between arms.

Compared with standard RT, bowel toxicity was worse for both hypofractionated schedules ($P<0.001$ in each arm). There was no significant difference in acute bladder or acute bowel toxicity

between the hypofractionation schedules. The hypofractionated schedule had favorable late-toxicity.

“The 60-Gy in 20 fractions was associated with a small increase in late bowel side effects compared to 57 Gy, but not compared to 74 Gy,” said Dearnaley. The two-year RTOG grade 2+ bowel toxicity was 5.4% in the 60-Gy arm and 4.4% in the 57-Gy arm ($P=0.39$), and the rates at five years were 5.2% and 3.9% ($P=0.32$), respectively.

The rates of grade 2+ bladder toxicity were 13.7% in the 60-Gy arm and 10.8% in the 57-Gy arm at two years ($P=0.07$), with corresponding five-year rates 13.2% and 11.2% ($P=0.35$), respectively. “Of note, bladder symptoms were less common at two and five years compared with pretreatment,” he said. There was no difference between the three treatment groups in sexual dysfunction.

Hypofractionation may not necessarily be a superior treatment, but the data clearly establish that “modest hypofractionation regimens are noninferior for biochemical failure with modest to no change in toxicity,” said invited discussant Daniel A. Hamstra, MD, PhD, of the Texas Center for Proton Therapy in Irving. “This is probably ready for prime time.”

Hamstra added, “Questions that remain to be answered include, what is the correct regimen, should it be shorter, and how do we implement this in the US?”

Presented at the 2016 GuCS; Abstract 2

MedPage Today
9 January 2016

Men Unclear on Sexual Function after Prostatectomy

Many unaware of sexual adverse effects, recovery issues

Men who underwent radical prostatectomy (RP) had unrealistic expectations about how well they would function sexually postoperatively, especially men who had robot-assisted radical prostatectomy (RARP), according to survey results.

In a survey of 336 men who had undergone RP, only 38% of respondents accurately recollected whether they had had a nerve sparing procedure three months after undergoing either an open RP

or the robotic equivalent, reported Serkan Deveci, MD, of Memorial Sloan Kettering Cancer Center in New York City, and colleagues.

Only 70% of men who had undergone an open RP and 60% of their robotic counterparts were aware that they were rendered anejaculatory by their surgery ($P=0.065$), they published online in *BJU International*.

Few if any men in either group were aware that the nature of an orgasm could

change following the surgery ($P=0.09$), that they could have pain on orgasm ($P=0.2$), or that they could leak urine at the moment of climax ($P=0.15$).

None of the patients who had undergone RARP and only 10% of those who had undergone an open procedure recalled being told that there was a potential for loss of penile length ($P<0.01$). And no patient in either group was aware of the association between RP and Pey-

ronie's disease that can be caused by scar tissue formation post-RP.

"Patients who have undergone RP have unrealistic expectations with regard to postoperative sexual function," the authors wrote. "We encourage all clinicians to utilize written instructions to transmit sexual health information to patients, lest they receive the orally transmitted information in a state

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Doc Moyad's What Works & What is Worthless Column, Also Known As "No Bogus Science" Column

"Vitamin D in high dosages might increase the risk of falls and Go Blue?!"

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

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

Bottom Line:

Less is still more! We need to wait for a few more major clinical trials but in the meantime taking more than 800 or 1000 IU of vitamin D per day is not supported by overall research and it could increase your risk of falls!¹ The jury is still out but the jury is certainly nervous about more vitamin D for better health, and now I can explain why Michigan easily beat Florida in football and why number 2 gets more attention than number 1?!

How many times have I been warning folks about not taking too much of any supplement without some good evidence to suggest a benefit over harm?! I have built a career on these warnings (and also on my middle age model-like good looks) and written countless times over the years about not getting too excited about any supplement or drug (same thing, when there is good clinical research performed on a pill...aka supplement=drug and drug=supplement).

I have watched as countless folks push higher and higher blood levels of vitamin D with supplements. Why oh, why?? It is easy to forget that vitamin D functions like a hormone. When has getting mega-doses of a hormone been healthy in an otherwise healthy person? It is also easy to forget that the vitamin D blood test appears to drop in some individuals the sicker they get over time. So, it is not vitamin D that is making people super healthy but super healthy people make vitamin D look good.

Now, along comes this one-year randomized trial of monthly doses of vitamin D (800 vs. 2,000 IU per day by the math) and the higher dosage appeared to increase the risk of falls in men and women 70 years and older that already had a prior fall. Now, critics will point out that giving a large monthly dose of vitamin D rather than daily dosages is more dangerous, and we need to wait for one or two more major trials that give vitamin D daily and not

monthly, and this is true.

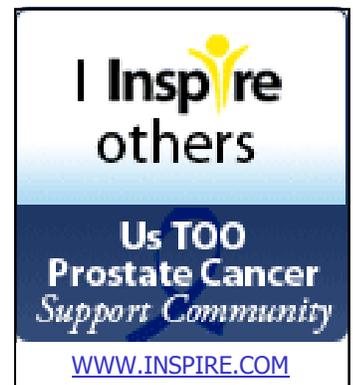
However, what critics do not point out is that the benefit of taking higher daily dosages of vitamin D supplements (more than 800-1,000 IU per day for example) has not been shown to outweigh the negatives in otherwise healthy folks. So, until research provides more pieces of this puzzle to give a clearer picture of the situation, being conservative is the way to go. I mean, do we really need another selenium and vitamin E situation? The answer is "no."

Oh, and by the way my column is the perfect segue for saying "Coach Harbaugh for President!" Michigan 41 and Florida 7 at the Citrus Bowl 2016! I bet you we won so easily because our players do not get excessive amounts of vitamin D before the game but the Florida players obviously did! I mean...heck they live in Florida—the vitamin D capital of the world! You know Florida, the place where every time I visit my folks and get into an elevator (while eating a sandwich)

someone is talking to someone else in the back of the elevator really loudly, and being extremely and excruciatingly descriptive about their latest uncomfortable or even fabulous bowel movement. Man, I love Florida - the only place where number two always gets more attention than number one (now that is a funny joke—sorry mom and dad, don't worry, I am certain no one reading my column knows that you live in Longboat Key, FL)!

Reference:

1. Bischoff-Ferrari HA, Dawson-Hughes B, Orav EJ, et al. *JAMA Intern Med* 4 January 2016 [Epub].



Surgery Bests Radiotherapy for Localized Prostate Cancer: Meta-analysis

Radical prostatectomy (RP) provides a better chance of survival than radiotherapy (RT) for men with clinically localized prostate cancer, according to a meta-analytic review of relevant research.

"In the past, studies that have compared the success rates of RP or RT have been confusing because of their methods," Senior Author Dr. Robert Nam from Odette Cancer Centre, Sunnybrook Research Institute, University of Toronto, Canada, noted in a statement.

"We have evaluated all the good-quality data comparing RP and RT, and the results are pretty conclusive; in general, RP results in better mortality rates than RT. Nevertheless, there are times when RT may be more appropriate than surgery, so it is important that a patient discusses treatment options with his clinician," Dr. Nam said.

The meta-analysis, online December 15 in *European Urology*, included 19 studies of "low to moderate" risk of bias involving up to 118,830 men with localized prostate cancer who had either RP or RT (external beam RT alone or with brachytherapy).

The overall risk of death was higher for men treated with RT compared to those treated with surgery (10 studies, adjusted hazard ratio 1.63; $p < 0.00001$), the researchers report. Prostate cancer-specific death was also higher with RT than RP (15 studies, aHR 2.08; $p < 0.00001$).

"Subgroup analyses by risk group, RT regimen, time period, and follow-up length did not alter the direction of results," the researchers say. This is the most robust meta-

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Adding Hormonal Therapy To Salvage RT Ups Prostate Cancer Survival Metastasis, cancer-specific survival also reduced in high-risk disease

Antiandrogen therapy (AAT) using daily bicalutamide improved overall survival (OS) modestly among men with high-risk prostate cancer who received salvage radiotherapy (RT) after radical prostatectomy (RP).

Men randomized to daily bicalutamide for 24 months in the RTOG 9601 clinical trial had 10-year OS of 82% vs. 78% in the placebo arm (hazard ratio [HR] 0.77, 95% CI 0.59-0.99, $P=0.04$). The bicalutamide group also had reduced rates of metastatic prostate cancer and death from prostate cancer, William U. Shipley, MD, reported here at the Genitourinary Cancers Symposium (GuCS).

"Treatment was tolerated quite well and with a high completion rate, not only for RT but the daily pills for two years," said Shipley, of Massachusetts General Hospital in Boston, MA.

From March 1998 to March 2003, 760 men with high-risk prostate cancer were randomized to receive RT (64.8 Gy) plus bicalutamide or placebo. Eligible patients had stage pT3 N0 or pT2 N0 disease with positive margins, elevated PSA to a maximum of 4.0 ng/mL, and negative abdominal/pelvic findings on computed tomography and bone scans.

The cohort had a median age of 65, positive margins in 75%, median entry PSA of 0.6 ng/mL and a median interval between RP and first detectable PSA of 1.4 years.

Shipley reported that 97% in the AAT arm and 95% in the placebo arm completed their RT protocols, and 84% and 93%, respectively, completed taking their daily oral tablets. The primary reason for not completing daily bicalutamide was gynecomastia. He

said that 70% of men randomized to bicalutamide had some degree of this.

The incidence of metastatic prostate cancer was reduced from 19% to 11% in the placebo and bicalutamide arms, respectively (HR 0.63, 95% CI 0.46-0.87, $P=0.005$). Death from prostate cancer occurred in 4.5% of men randomized to AAT vs. 10.1% of those randomized to placebo (HR 0.49, 95% CI 0.32-0.74, $P < 0.001$). "The number needed to treat to save one man from dying of prostate cancer is 12," said Shipley. "It's quite low."

Multivariable analysis for OS revealed that AAT was a significant predictor of improved survival ($P=0.025$), and study entry PSA ≤ 1.5 ng/mL ($P=0.003$), age ≥ 65 years ($P < 0.001$) and Gleason score 8 to 10 ($P < 0.001$) were significant predictors of worse OS. AAT demonstrated significant benefit on major endpoints in several subgroups.

- PSA level > 1.5 ng/mL: AAT was associated with an HR of 0.45 (95% CI 0.25-0.81, $P=0.007$) for OS and an HR of 0.36 (95% CI 0.15-0.84, $P=0.014$) for time to metastatic prostate cancer
- Gleason grade 7 disease: AAT was associated with an HR of 0.69 (95% CI 0.49-0.98, $P=0.039$) for OS.
- Positive surgical margins: AAT was associated with an HR of 0.87 (95% CI 0.53-1.41, $P=0.038$) for OS and an HR of 0.56 (95% CI 0.38-0.84, $P=0.005$) for time to metastatic prostate cancer
- Gleason grade 8 to 10: AAT improved the time to metastatic prostate cancer (HR 0.35, 95% CI 0.18-0.67, $P=0.001$)

The incidences of late genitourinary (GU) and gastrointestinal (GI) toxicity were not

different between the two arms. GU \geq grade 2 toxicity occurred in 32% of each arm and GU \geq grade 3 toxicity occurred in 7% of each arm. The rates of GI \geq grade 2 toxicity were 20% in the AAT arm and 16% in the placebo arm, and the rates of GI \geq grade 3 toxicity were 3% and 2%, respectively.

"The RTOG 9601 trial expands the established role of androgen deprivation therapy with RT therapy in high-risk prostate cancer to now include men who have previously had surgery," said discussant Daniel A. Hamstra, MD, PhD, of the Texas Center for Proton Therapy in Irving, TX. "This is the first Level I evidence looking at the addition of hormonal therapy to RT for men who've undergone RP," he said. "This is a treatment that has a 'wow' impact."

"The optimal duration of AAT in this setting is unknown," said Hamstra. A three-arm trial known as RADICALS being conducted in Great Britain may provide an answer; one arm of the trial is being randomized to six months of hormonal therapy plus RT after RP while another arm receives two years of hormonal therapy (the third arm is randomized to RT alone).

Presented at the 2016 GuSC; Abstract 3

MedPage Today
11 January 2016



Reaching Men Through the Universal Language of Beer.™

Aspirin May Lower the Risk of Lethal Prostate Cancer

(Continued from page 1)

in San Francisco January 7th. “Men with prostate cancer who took aspirin regularly after diagnosis had a significantly reduced risk of death.”

The findings do not, however, give men license to begin using aspirin specifically to prevent prostate cancer, he suggested. “More work is needed to identify particular subsets of men most likely to benefit from aspirin and to determine the optimal aspirin dose. Men should always consult their physician before considering aspirin use.”

“Although prostate cancer has a reputation as a slow-growing cancer, the 25,000 men who die of the disease annually offer a reminder that the condition often is progressive,” said press briefing moderator Sumanta Pal, MD, of City of Hope in

Duarte, CA. He also emphasized the limitations of the study and its results.

“While this work is provocative, it is important to keep in mind that the findings are from an observational study, where surveys and reviews of hospital records were used to obtain information,” Pal said. “These studies are certainly thought-provoking, but are perhaps best followed by clinical trials where we compare use of aspirin to either no treatment or perhaps to a placebo.”

“It’s also critical to keep in mind that aspirin can have some potentially severe consequences, such as bleeding,” Pal continued. “With those caveats in mind, it’s important to have a detailed discussion of the pros and cons of aspirin therapy with

your own physician prior to using the drug for prostate cancer-related purposes.”

Multiple studies have suggested that regular aspirin use may reduce the risk of several types of cancer, including prostate cancer. Clinical guidelines for several organizations recommend aspirin for cardioprotection, but until last year, no organization had recommended aspirin for cancer prevention. In September 2015 the United States Preventive Services Task Force recommended regular aspirin use to reduce the risk of colorectal cancer.

“Previous studies of aspirin and prostate cancer yielded conflicting data,” Allard said. Moreover, none of the studies had focused specifically on prevention of lethal prostate cancer. To address the

issue, they analyzed data for 22,071 men enrolled in the Physicians’ Health Study. In addition to the relationship between aspirin use and lethal prostate cancer, study objectives included the incidence of total prostate cancer, Gleason score 8-10, and advanced cancer (T3b-T4 or N1 or M1).

During 27 years of follow-up (533,261 person-years), 3,193 men had new diagnoses of prostate cancer, and 403 of the cancers proved to be lethal. In multivariate analysis, men who used aspirin regularly had a 24% lower risk of progression to lethal prostate cancer (HR 0.76, 95% CI 0.62-0.93).

Presented at the 2016 GuCS, abstract 306

MedPage Today
5 January 2015

Comparing Chemical and Surgical Castration for Prostate Cancer

(Continued from page 1)

GnRHa and 13% (n=429) were treated with BO. The overall three-year survival for GnRHa treatment and BO was 46% and 39%, respectively. Results indicate that BO was associated with lower risks of any fractures, peripheral artery disease and cardiac-related complications compared with medical castration with GnRHa. No statistically significant difference was found between BO and GnRHa for diabetes and cognitive disorders.

Men treated with GnRHa for 35 months or more were at the greatest risk of experiencing any fracture, peripheral artery disease, venous thromboembolism, cardiac-related complications and diabetes, according to the results. The authors note limitations to the study, primarily its retrospective design which relies

on historical data.

“In some patients who need permanent androgen suppression, surgical castration may represent a suitable alternative to GnRHa. However, other considerations must be contemplated when deciding between medical or surgical castration (i.e., young age, intermittent ADT),” the study concludes.

Johann S. de Bono, MB, ChB, MSc, FRCP, PhD, FMedSci, and coauthors from the Institute of Cancer Research and the Royal Marsden National Health Service Foundation Trust, England wrote an accompanying editorial.

“Despite their retrospective nature, studies such as this are critically important, because they increase awareness of these concerns,” they stated. “Because men with metastatic PCa are living

longer than ever, it is imperative that we minimize the risk of harm from therapies. Physicians treating patients with PCa must familiarize themselves with how to prevent and treat these complications ...”

The editorialist continued, “The current article by Sun et al adds fuel to an already controversial debate and the discredit brought by the reimbursement issues. When there is more than one reasonable option, clinical decisions must be guided by the patient’s values and preferences. In the absence of clear evidence to the contrary, patients are likely to continue to overwhelmingly favor GnRHa over orchiectomy,” de Bono and colleagues concluded.

Medical News Today
23 December 2015

RP vs. RT

(Continued from page 4)

analysis to date of studies comparing surgery and RT for localized prostate cancer, they point out.

“The important thing about this research is that it gives physicians and patients additional information to consider when making the decision about how to treat localized prostate cancer,” Dr. Nam added in his statement.

Dr. Nicolas Mottet, chairman of the European Association of Urology Prostate Guideline Panel, added, “This systematic review suggests that survival is better after surgery compared to various forms of RT.”

“However, definitive proof needs a large well-conducted randomized control trial,” Dr. Mottet said.

Reuters Health
18 December 2015

Liquid Biopsy & Drug Therapy *(Continued from page 1)*

challenge of choosing the most effective therapy for metastatic castration-resistant prostate cancer (mCRPC) as the disease evolves and changes over time," said press briefing moderator Sumanta Pal, MD, of City of Hope in Duarte, CA.

The ability to link certain tumor cell characteristics to treatment response or lack of response "has incredible value because we have a number of new treatments for patients with advanced prostate cancer, but right now have little means of personalizing therapy and offering the right treatment for the right patient" Pal said. "The proposed studies to validate this work could put this tool to personalize therapy in our hands."

To examine the potential utility of CTC analysis, investigators evaluated 221 blood samples obtained from 179 patients with mCRPC prior to treatment with abiraterone, enzalutamide, or docetaxel. Scher and colleagues performed a cell-by-cell analysis of a subset of CTCs in an attempt to develop predictive biomarkers to guide therapeutic decision making for patients with mCRPC.

The study employed a blood test that analyzed tumor cells with respect to morphology, protein chemistry, and genomics. Investigators tracked the clinical parameters of PSA level, time on drug, radiographic PFS, and OS.

The blood test revealed 9,225 CTCs. A subset of 741 CTCs from 31 men underwent individual sequencing, including analysis of whole-genome copy number variability to determine clonality and gene amplification or deletion. Investigators ranked the blood samples on the basis of the extent of cell

heterogeneity or diversity, using methodology associated with the Shannon Index, a validated scale for calculating biodiversity.

Comparing heterogeneity and clinical parameters, Scher and colleagues could stratify men into high- and low-heterogeneity groups. The results showed that CTC heterogeneity increased with the number of prior lines of therapy a man had received. However, the impact of CTC heterogeneity on clinical outcome varied by the type of treatment received.

Scher reported that both radiographic PFS and OS had significant inverse associations with CTC heterogeneity in men treated with abiraterone or enzalutamide but not those treated with docetaxel.

Comparing men treated with abiraterone or enzalutamide with high and low heterogeneity scores yielded a hazard ratio (HR) of 2.2 for radiographic PFS (95% CI 1.2-4.1, P=0.00182) and 5.5 for OS (95% CI 2.4-12.8, respectively P<0.0001). Men with a high heterogeneity score had a median radiographic PFS and OS of five and nine months, respectively vs. 17 months and not yet reached for the low-heterogeneity group.

In the subgroup of men treated with docetaxel or cabazitaxel, high heterogeneity was not associated with worse radiographic PFS (HR 0.89, P=0.758) or OS (HR 1.6, P=0.182).

The authors concluded that analysis of CTCs might help identify biomarkers of tumor heterogeneity and guide more efficient and effective use of available therapies.

MedPage Today
8 January 2016

Risk-Based Patient Selection Can Reduce MRI Use after Negative Prostate Cancer Biopsy

Some men with suspected prostate cancer after a negative biopsy may be able to avoid subsequent MRI, new research from the Netherlands suggests.

Risk-based patient selection may reduce by half the number of multiparametric MRIs (mpMRIs) after a negative PSA- and/or digital rectal exam-driven transrectal ultrasound (TRUS)-guided random biopsy, researchers reported online in *European Urology* on December 3rd.

"Not all men with a sustained suspicion of prostate cancer after a negative biopsy (based on a high PSA level) should receive an MRI. We should do a proper assessment of the prostate cancer risk with the Rotterdam Prostate Cancer Risk Calculator (RPCRC), for example, before deciding which men should receive an MRI," said lead study Dr. Arnout R. Alberts from Erasmus University Medical Center in Rotterdam.

"The number of radiologists with expertise in prostate MRI is limited. Moreover, MRI scans are expensive, and the scan and subsequent biopsy can be burdensome for patients," he told Reuters Health by email.

Dr. Alberts and colleagues studied 122 consecutive men who received an mpMRI scan and MRI-TRUS fusion targeted biopsy to examine any suspicious lesions found by negative TRUS-guided random biopsy.

The team retrospectively stratified men according to the RPCRC biopsy advice to compare targeted biopsy outcomes after risk-based selection with standard (PSA- and/or digital rectal exam-driven) selection.

Upfront RPCRC-based selec-

tion would have avoided 62 (51%) of the mpMRIs and two (25%) of eight low-grade PCa diagnoses. It would have missed three (10%) of 31 high-grade PCa diagnoses.

The area under the curve of the RPCRC for prostate cancer was 0.76 and for high-grade disease it was 0.84.

Of the 60 men with a positive RPCRC biopsy advice, 10% had low-grade prostate cancer and 47% had high-grade disease on targeted biopsy; 3% of the 62 men with negative advice had low-grade and 5% had high-grade prostate cancer.

Dr. Douglas S. Scherr, professor of urology at Weill Cornell Medical Center/NY-Presbyterian Hospital in New York City, stated, "Risk stratifying is an essential component to any valid PSA screening program. Without it, we will overdiagnose insignificant disease. These findings fit in line with the whole concept of risk stratification that is now starting to take shape as it relates to prostate cancer screening."

"This was an important study mainly regarding cost: MRIs are quite expensive. By avoiding about half of them, we can save a significant number of health care dollars and avoid over-diagnosing insignificant disease," said Dr. Scherr, who was not involved in the research.

"I think most practitioners should consult with any of the number of risk calculators (Rotterdam, Prostate Cancer Prevention Trial (PCPT), etc.) prior to deciding whether to pursue MRI-guided fusion biopsy," he added.

Reuters Health
21 December 2015

Doctor Chodak's Bottom Line *(Page number and first few words of article title)*

Gerald Chodak, MD, Author, *Winning the Battle Against Prostate Cancer*, Second Edition <http://www.prostatevideos.com/>

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

P1 "Aspirin May Lower..."

Several studies have suggested a benefit for men with prostate cancer taking non-steroidal anti-inflammatory agents (NSAIDs). In this issue, Allard et al. report a reduced risk of dying from prostate cancer in men who were taking aspirin at least three times per week compared to less frequent use. The authors are careful to discourage men from starting aspirin in the absence of other recommended reasons. The problem, of course is that it is an observational study, not one specifically designed to determine if aspirin is truly beneficial. Furthermore, dosing was not pre-determined. As is the case with other NSAIDs, only a well-designed randomized study will be able to determine if real benefits occur with aspirin use.

The Bottom Line: Aspirin taken three times per week may improve survival but more studies are needed for confirmation.

P1 "Blood Test..." Among the challenges of treating men with advanced prostate cancer is how to select the next treatment after ADT. The options include chemotherapy with docetaxel or cabazitaxel, enzalutamide or abiraterone. Many people feel that chemotherapy is likely to have more side effects so one of the other two drugs should be used first. Unfortunately, not all men will benefit from the non-chemotherapy options. Finding a way to identify this would be very beneficial by sparing men from a treatment that will not help while avoiding a delay in the use of one of the options that could prolong survival. Scher and co-workers reported some early data in which they

looked at circulating tumor cells (CTCs) and measured the variability of the cancer cells, which they divided into two groups. Men with very heterogeneous cells had a lower survival compared to low heterogeneity only if they were being treated with enzalutamide or abiraterone but not with chemotherapy. This finding could help identify those men who should go directly to chemotherapy without first receiving enzalutamide or abiraterone, but further validation is needed.

The Bottom Line: CTCs measured in a blood sample could be used to determine whether a patient will not respond to immediate enzalutamide or abiraterone, but more work is needed.

P1 "Comparing Chemical..."

For years, doctors have believed that surgical and medical castration had similar effects on men with metastatic prostate cancer. However, more recently, studies have suggested more side effects from LHRHa. Another new study by deBono and co-workers adds more information suggesting more side effects compared to orchiectomy. However, this study was retrospective and the sample sizes were hugely different. For those reasons, many other unknown factors could have influenced the results and therefore for now both options should be offered to men faced with the need for ADT.

The Bottom Line: More information is needed to determine if orchiectomy is superior to an LHRH agent.

P2 "Hypofractionated vs..."

An ongoing study is looking at shortening the duration of RT with hypofractionation using

either 57 Gy in 19 fractions or 60 Gy in 20 fractions compared to 74 Gy in 37 fractions. The authors found that at five years, clinical recurrence was not inferior with the 60 Gy but was inferior with 57 Gy. Before routinely recommending 60 Gy, however, more information is definitely needed. One problem is that the results were not stratified by Gleason score. Gleason 6, which often does not need treatment was included, so the results may be misleading. Secondly, biochemical recurrence is not always a reliable predictor of OS. Therefore, the studies need further follow-up to assess this outcome before firm conclusions can be made.

The Bottom Line: More information is needed to truly prove that hypofractionation has similar OS compared to traditional RT.

P3 "Men Unclear on Sexual"

A critical component of patient counseling regarding the treatments for localized prostate cancer includes the incidence of all potential side effects. Since no standardized approach is currently used, patient awareness will be greatly dependent on the information that is provided by either the doctor or nurse involved in his care. The study by Deveci et al. suggests that patient knowledge regarding sexual function was very poor in terms of when and if their erections would return and whether they would need intracavernosal injections, or if their penis would decrease in length. The authors point out that this study did not document the information actually provided to the patients so it is possible that patients simply did not remember the

information given to them. Nevertheless, this study illustrates a deficiency that needs to be avoided. That could be done by the major organizations such as the AUA and ASTRO by developing standardized information sheets that could be given to all men prior to therapy with documentation. Although men still might not remember the facts and figures, at least there would be an assurance that the information was provided prior to a patient selecting his therapy.

The Bottom Line: More work is needed to properly counsel men about the potential sexual side effects following all therapies for localized prostate cancer.

P4 "Surgery Bests RT..." Surgery or radiation; which is better for localized prostate cancer? The study by Nam and co-workers suggests that surgery is significantly better than radiation. They conducted a meta-analysis of 19 published reports to arrive at their conclusion. Unfortunately, none of these was from randomized studies, so it is quite possible that a number of biases caused this observation other than surgery being the better therapy. The abstract does not provide enough caution about this potential bias.

The Bottom Line: This meta-analysis has potential flaws that makes the conclusion potentially incorrect.

P4 "Adding Hormonal..."

Men who develop a rising PSA after RP are faced with receiving either early or late RT. For those who wait until the PSA rises before considering RT, the question is how

(Continued on page 8)

Men Unclear on Sexual Function Post-RP *(Continued from page 3)*

of anxiety where failure to process the information may be highly likely.”

“The study sheds light on the importance of managing expectations for men undergoing surgical therapy for prostate cancer,” said Charles Ryan, MD, of the University of California San Francisco. “It suggests that clinicians involved in recommending such therapies should be aware of this ‘expectation gap’ during the time that they counsel patients about upcoming treatments.”

The survey participants had a mean age 64 and sought consultation at a sexual medicine clinic within three months of RP. The study population comprised 216 men, who had undergone open RP, and 120 men who had RARP. All men were asked to complete a questionnaire regarding their expectations about recovery of sexual function following RP.

“Patient knowledge regard-

ing post-RP sexual function was poor with significant differences between the open and the RARP groups,” Deveci and colleagues observed. For example, men who had undergone RARP expected that they would recover EF in six months compared with 12 months for men who had undergone an open RP (P=0.02). More RARP patients (75%) expected that their EF would return to normal baseline levels than men who underwent open RP (50%, P=0.01) and felt that they would be much less likely to need intracavernosal injections to achieve an erection (4%) compared with men undergoing open RP (20%, P=0.01). Limitations to the study include lack of an instrument to define patient expectations, and investigators’ inability to differentiate between what patients were told and what patients remembered. Another limita-

tion was investigators’ inability to ascertain if some patients did their own research before or after they had seen their surgeon and prior to undergoing the procedure.

“These data are illuminating and should give us reason to think about our approach to the education of the patient prior to radical prostatectomy,” Deveci’s group noted.

“Irrespective of whether we as clinicians routinely have a sexual dysfunction discussion or not, patients are not remembering or appreciating the information the way it is intended and undertake the operation with poor expectations regarding multiple domains of sexual health”

“Surgeons should be encouraged to be thorough in counseling patients prior to RP and to document that [at least] such a discussion was held,” they wrote.

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The Bottom Line

(Continued from page 7)

to maximize survival. An ongoing randomized study is comparing RT alone vs. RT plus 24 months of bicalutamide, 150 mg/day. This study found a small but significant improvement in survival and metastases in the combination therapy group. Overall side effects were similar. At 10 years, the difference in overall survival and cancer specific survival was significantly higher in the men getting the combination therapy. However, the differences were small; 4% higher overall survival, 7% lower risk of metastases and 5.5% lower cancer mortality in 10 years. That means only about one out of 25 men are truly benefitting.

The Bottom Line: Twenty-four months of bicalutamide along with external RT offers a small but significant improvement in survival.

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