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**Affected by Prostate Cancer?**



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# Hot SHEET

Us TOO INTERNATIONAL Prostate Cancer Education and Support Network

## Long-Term ADT Best for Locally Advanced Prostate Cancer

Continuing androgen deprivation therapy (ADT) for an additional 24 months improves all disease end points during 15 years of follow-up compared with short-term ADT in men with locally advanced prostate cancer treated with radiotherapy (RT). This is the conclusion from the final report of the RTOG 9202 trial. The study was presented at the American Society for Radiation Oncology (ASTRO) 57th Annual Meeting.

David Beyer, MD, from the University of Arizona, in

Tucson, and president-elect of ASTRO was asked to comment on the study. On the basis of RTOG 9290 results, he stated, "As long as we select the right patient – and the study was in locally advanced prostate cancer – long-term ADT should be the standard of care," he said.

During a press briefing, trial investigator Colleen Lawton, MD, vice-chair, Department of Radiation Oncology, Medical College of Wisconsin said, "One of the questions patients always want answered is, 'Am I going to die of this cancer?' And the answer from this trial is, 'if you've had long-term hormone therapy, we can reduce that chance significantly.'"

RTOG 9202 was a randomized, multi-institution study involving 1,554 men with clinical stage T2c to T4 prostate cancer. "Men could not have any extra pelvic lymph node involvement and their PSA level had to be less than 150 ng/mL at study entry," said Dr. Lawton. In addition, none of the men had previously received chemotherapy or hormone therapy.

Men were randomly assigned to receive four months of goserelin and flutamide beginning two months prior to receiving RT (short-term ADT) or the same ADT regimen followed by an additional 24 months of goserelin

*(Continued on page 4)*

## 24 Months of AAT Improves Survival for Men with Cancer Recurrence after Prostatectomy

It is well established that a rising serum PSA level is an indication of cancer progression in men diagnosed with prostate cancer and treated with radical prostatectomy (RP). For these men, adding 24 months of antiandrogen therapy (AAT) during and after salvage radiotherapy (RT) statistically improves overall survival compared with treating them with salvage RT alone, according to the long-term results of a clinical trial conducted by the Radiation Therapy Oncology Group (RTOG), now conducting research as NRG Oncology. The RTOG 9601 study results presented at the plenary session of the 57th Annual Meeting of the American Society for Radiation Oncology (ASTRO) also revealed that the addition of AAT to salvage RT reduces prostate cancer death and the development of metastatic prostate cancer without increasing radiation toxicity.

"Over the last 25 years, many men with intermediate-risk prostate cancer have undergone RP, yet many will face recurrence subsequently with a rising PSA," says lead study author William U. Shipley, MD, FACR, FASTRO, who is the Andres Soriano Distinguished Professor of Radiation Oncology at the Massachusetts General Hospital and Harvard Medical School, both in Boston. "Our results show that salvage RT plus peripheral androgen blockade (AAT with bicalutamide), when compared with RT plus a placebo, improved long-term overall survival and reduced death from prostate cancer without adding significantly to RT toxicity. Because prostate cancer progresses slowly,

*(Continued on page 4)*

## FDA Approves First Focused Ultrasound System for Treating the Prostate

The US Food and Drug Administration has approved SonaCare Medical's Sonablate 450 focused ultrasound system for the ablation of prostate tissue. Focused ultrasound enables treatment of organ-confined prostate disease while preserving surrounding healthy tissue, without radiation or surgery. The technology has been successfully used to treat a wide variety of diagnoses, including benign prostatic hyperplasia (BPH), partial gland cancer, localized whole-gland prostate cancer and recurrent prostate cancer.

Focused ultrasound is a non-invasive, radiation-free meth-

od to treat localized prostate cancer. Using real-time image guidance, the physician directs a focused beam of ultrasound energy to a selected volume in the patient's prostate gland. The energy heats the targeted tissue at the focal point and thermally coagulates the targeted cells within seconds. This process is repeated until the selected volume or the entire gland is destroyed.

Focused ultrasound treatments are performed with no incisions, leading to few complications and minimal discomfort, enabling patients to

*(Continued on page 5)*

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## Five-Point Likert Scaling on MRI Predicts Clinically Significant Prostate Carcinoma

Harada T, Abe T, Kato F, Matsumoto R, Fujita H, et al

**BMC Urol. 2015; 15(91)**

**Background:** To clarify the relationship between the probability of prostate cancer scaled using a five-point Likert system and the biological characteristics of corresponding tumor foci.

**Methods:** We studied 44 men undergoing 3.0-Tesla multiparametric MRI before laparoscopic radical prostatectomy. Tracing based on pathological and MRI findings was performed. The relationship between the probability of cancer scaled using the five-point Likert system and the biological characteristics of corresponding tumor foci was evaluated.

**Results:** A total of 102 tumor

foci were identified histologically from the 44 specimens. Of the 102 tumors, 55 were assigned a score based on MRI findings (score one: n = three; score two: n = three; score three: n = 16; score four: n = 11; score five: n = 22), while 47 were not pointed out on MRI. The tracing study revealed that the proportion of >0.5 cm<sup>3</sup> tumors increased according to the upgrade of Likert scores (one or two: 33%; three: 68.8%; four or five: 90.9%,  $\chi^2$  test,  $p < 0.0001$ ). The proportion with a Gleason score >7 also increased from scale two to scale five (scale two: 0%; scale three: 56.3%; scale four:

72.7%; scale five: 90.9%,  $\chi^2$  test,  $p = 0.0001$ ). On using score three or higher as the threshold of cancer detection on MRI, the detection rate markedly improved if the tumor volume exceeded 0.5 cm<sup>3</sup> (<0.2 cm<sup>3</sup>: 10.3%; 0.2–0.5 cm<sup>3</sup>: 25%; 0.5–1.0 cm<sup>3</sup>: 66.7%; >1.0 cm<sup>3</sup>: 92.1%).

**Conclusions:** Each Likert scale favorably reflected the corresponding tumor's volume and Gleason score. Our observations show that "score three or higher" could be a useful threshold to predict clinically significant carcinoma when considering treatment options.

## Magnetic Resonance Imaging on Disease Reclassification among Active Surveillance Candidates with Low-Risk Prostate Cancer – A Diagnostic Meta-Analysis

Guo R, Cai L, Fan Y, Jin J, Zhou L, Zhang K

**Prostate Cancer Prostatic Dis. 2015; 18: 221–228**

**Background:** Active surveillance (AS) is an increasingly important attempt to avoid overtreatment of patients who harbor clinically insignificant disease while offering curative treatment to those in whom disease is reclassified as higher risk after an observation period and repeat biopsy. We aim to evaluate the diagnostic performance of magnetic resonance imaging (MRI) in predicting upgrading on confirmatory biopsy in men with low-risk prostate cancer (PCa) on AS.

**Methods:** We searched the PubMed for pertinent studies up to November 2014. We used standard methods recommended for meta-analyses of diagnostic test evaluations. The analysis was based on a summary receiver operating characteristic (SROC) curve.

Meta-regression analysis was used to assess effects of some confounding factors on the results of the meta-analysis. The potential presence of publication bias was tested using the Deeks' funnel plots.

**Results:** Seven studies provided the diagnostic data on MRI and AS of PCa, comprising 1,028 patients. The pooled estimates of MRI on disease reclassification among AS candidates were as follows: sensitivity, 0.69 (95% confidence interval (CI), 0.44–0.86); specificity, 0.78 (95% CI, 0.53–0.91); positive likelihood ratio, 3.1 (95% CI, 1.6–6.0); negative likelihood ratio, 0.40 (95% CI, 0.23–0.70); and diagnostic odds ratio, 8 (95% CI, 4–16). The P-value for heterogeneity was <0.001. We found that the SROC curve is positioned toward the desira-

ble upper left corner of the curve, and the area under the curve was 0.79 (95% CI, 0.76–0.83). For a pretest probability of 0.20, the corresponding positive predictive value (PPV) was 0.44 and the negative predictive value (NPV) was 0.91. MRI may reveal an unrecognized significant lesion in 33.3% of patients, and biopsy of these areas reclassified 14.6% of cases as no longer fulfilling the criteria for AS. In addition, when no suspicious disease progression (66.3%) was identified on MRI, the chance of reclassification on repeat biopsy was extremely low at 6.1%.

**Conclusions:** MRI, especially multiparametric (MP)-MRI, has a moderate diagnostic accuracy as a significant pre-

(Continued on page 3)

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

"Landmark PSA screening study = the benefits of Fiber & Exercise?! What??!!!"

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:

Let's stop arguing about PSA screening for one second and appreciate the two unappreciated findings from the PLCO (prostate, lung, colorectal, and ovarian cancer) screening trial (PSA screening study). DIETARY fiber (especially from cereal and fruits) appeared to reduce the risk of colon cancer, and physical activity/exercise reduces the risk of having to get up at night to go number 1 (aka urinate or pee-pee)!<sup>1,2</sup> Where are the commercials or media headlines from these two unappreciated findings (sarcasm alert, sarcasm alert...)?! ALSO THIS IS MY 100<sup>TH</sup> COLUMN!!!

Do you remember the USPSTF conclusion that PSA screening should not be done based on the results of two major screening studies—one from Europe and one from the US, known as the PLCO? What few realized was that

regardless of whether or not you agree with the findings from the PLCO (that did not find a benefit to PSA screening) there is one thing we can all agree on. And that is the fact that the PLCO researchers did a heck of a job also looking at other things that could impact your health. In other words, the PLCO group did a fabulous job of also looking at other factors apart from the obvious ones that received all the positive and negative attention (PSA screening stuff)! So, while many people are out there complaining or not about PSA screening based on the PLCO study we should all take a minute or really a lifetime to appreciate two other amazing findings from this same clinical study, which are:

1. Dietary (not supplements or pills or expensive powders) fiber primarily from cereals and fruit appeared to reduce the risk of distal

2. Exercise/physical activity appears to help you pee pee better and helps to empty your bladder so you do not have to get up at night as much.

Where are the commercials for these findings? Of course, there are no commercials. But these are important findings that of course I agree with and should be almost or as important as arguing about PSA screening. That is why I decided to give these findings a commercial by placing them in the US TOO *Hot SHEET* because this is Hot Sheet (get it)! If you want better colon health, then eat more fiber! You want to empty your bladder like a racehorse or elephant, then exercise daily!

NOW THAT WOULD BE AN AMAZING COMMERCIAL!!! And, the first 100 callers get a free copy of a Dr. Moyad T-shirt that says "I am just a

regular guy on fiber" on the front of the shirt, and on the back of the shirt it says "Exercise makes my bladder as happy as a dog stuck in an elevator with a group of squirrels." Okay... this is a verbose T-shirt, but who cares? This is my 100<sup>th</sup> column in the *Hot SHEET* so I am allowed to do what I want! Man, I love this stuff!!!

### References:

1. Kunzmann AT, Coleman HG, Huang WY, et al. Dietary fiber intake and risk of colorectal cancer and incident and recurrent adenoma in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. *Am J Clin Nutr* 2015; 102: 881–890.
2. Wolin KY, GVrubb RL, Pakpahan R, et al. Physical activity and benign prostatic hyperplasia-related outcomes and nocturia. *Med Sci Sports Exerc* 2015; 47: 581–592.

## DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer

Mateo J, Carreira S, Sandu S, et al

**N Engl J Med** 373: 1697–1708

**Background:** Prostate cancer is a heterogeneous disease, but current treatments are not based on molecular stratification. We hypothesized that metastatic, castration-resistant prostate cancers with DNA-repair defects would respond to poly (adenosine diphosphate [ADP]–ribose) polymerase (PARP) inhibition with olaparib.

**Methods:** We conducted a phase 2 trial in which patients with metastatic, castration-resistant prostate cancer were treated with olaparib tablets at a dose of 400 mg twice a day. The primary end point was the response rate, defined either as an objective response according to Response Evaluation Criteria in Solid Tumors, version 1.1, or as a reduction of at least 50% in the prostate-specific antigen level or a confirmed reduction in the circulating tumor-cell count from five or more cells per 7.5 ml of blood to less than five cells per 7.5 ml. Targeted next-generation sequencing, exome and transcriptome analysis, and digital polymerase-chain-reaction testing were performed on samples from mandated tumor biopsies.

**Results:** Overall, 50 patients were enrolled; all had received prior treatment with docetaxel, 49 (98%) had received abiraterone or enzalutamide, and 29 (58%) had received cabazitaxel. Sixteen of 49 patients who could be evaluated had a response (33%; 95% confidence interval, 20 to 48), with 12 patients receiving the study treatment for more than six months. Next-generation sequencing identified homozygous deletions, deleterious mutations, or both in DNA-repair genes – including BRCA1/2, ATM, Fanconi's anemia genes, and CHEK2 – in 16 of 49 patients who could be

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## MRI Reclassification

(Continued from page 2)

dictor of disease reclassification among AS candidates. The high NPV and specificity for the prediction of biopsy reclassification upon clinical follow-up suggest that negative prostate MRI findings may support a patient remaining under AS. Although the PPV and sensitivity for the prediction were relatively low, the presence of a suspicious lesion >10 mm may suggest an increased risk for disease progression.

**SALVAGE RT Plus AAT** (Continued from page 1)

follow-up of over 12 years was necessary to demonstrate a statistically better patient survival with combined AAT and RT.”

With a median follow-up now of 12.6 years, the study results showed the actuarial overall survival at 10 years was 82% for the RT plus AAT arm and 78% for the RT plus placebo arm (P = 0.036). The 12-year incidence of prostate cancer-related deaths was 2.3% for the RT plus AAT arm, compared with 7.5% for the RT plus placebo arm. At 12 years, metastases occurred in 51 (14%) men in the RT plus AAT arm vs. 83 (23%) men in the RT plus placebo arm. Additionally, late bladder and bowel toxicity were low and similar in both groups, whereas 70% of men in the RT plus AAT arm reported swelling of the breasts, compared with 11% in the RT plus placebo arm.

Conducted at sites across the US and Canada from 1998 to 2003, RTOG 9601 enrolled 761 men with prostate cancer who had undergone RP

and subsequently developed elevated PSA levels. The men were randomized to receive either salvage RT plus placebo (377 men) or salvage RT plus AAT (384 men).

“Further statistical analyses, which are underway, may identify subgroups of patients who may not benefit from hormone therapy added to salvage RT and other subgroups for whom it may be especially beneficial. “Also, because antiandrogen therapy, which suppresses testosterone production, is now used more commonly than peripheral androgen blockade with AAT, its use should be evaluated,” says Shipley in regard to next research steps for the population of post-RP patients referred for salvage RT.

Shipley also emphasizes the clinical researchers’ gratitude for the willingness of men to participate on this and other randomized trials and for the essential role they play in advancing cancer care.

*Medical News Today*  
20 October 2015

**High-Grade Prostate Cancer Linked to Elevated Cardiovascular Risk**

Men having prostate cancer (PCa) found on biopsy are more likely to have a high-grade Gleason score if they are at moderate or high cardiovascular risk (CVR), according to Italian investigators.

In a prospective study, Cosimo De Nunzio, MD and colleagues of Ospedale Sant'Andrea, Sapienza University of Rome enrolled 584 men who underwent 12-core prostate biopsies. Of these, 406 (70%) had moderate or high CVR and 237 (40.6%) had PCa found on biopsy. The PCa group included 157 men with moderate or high CVR and 80 with low or no CVR, a non-significant difference.

Of the 237 men with PCa, 113 had a Gleason score of 6 and 124 had a Gleason score of 7 or higher. Ninety-two (75%) of 124 men had a moderate or high CVR.

Moderate or high CVR was not associated with PCa risk overall, but was associated with a significant 2.1 times increased risk of having Gleason 7 or higher disease, researchers reported online ahead of print in *Prostate Cancer and Prostatic Diseases*.

Investigators defined CVR on the basis of the following risk factors: systolic and diastolic blood pressure (BP), high-

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**RT Plus Long-Term ADT** (Continued from page 1)

after completion of the RT protocol (long-term ADT). RT was delivered at a dose of 44 Gy to 46 Gy to the pelvic nodes and in doses of 65 Gy to 70 Gy to the prostate. The median follow-up period for 1,520-protocol-eligible men was 19.6 years. At 15 years, the group receiving long-

points strongly favored long-term ADT, with better overall survival of 21 vs. 17%, for the long-term vs. the short-term group, investigators observe. “Our findings reinforce the benefit of longer ADT for men with locally advanced prostate cancer,” Dr. Lawton said. “More men with ad-

**Outcomes at 15 Years Post-RT Vs. Length of ADT**

	Long-Term	Short-Term	Hazard Ratio	P Value
Disease-free survival	16	10	0.72	<0.001
PSA failure (cumulative)	45	61	0.57	<0.001
Local progression	13	23	0.53	<0.001
Distant metastases	17	26	0.61	<0.001
Disease-specific survival	84	78	0.67	0.002
Overall survival	30	27	0.72	0.120

term ADT continued to show favorable outcomes compared with the group undergoing short-term ADT.

Furthermore, for a subgroup of 337 men with a Gleason score of 8–10 at study outset, all disease-specific end

vanced prostate cancer should be considered for and may benefit from long-term ADT,” she said.

*Presented at the ASTRO 57<sup>th</sup> Annual Meeting, abstract 97*  
*Medscape Medical News*  
22 October 2015

**Benefit of Nexrutine for Cancer Prevention**

Hussain SS, Patel D, Ghosh R, Kumar AP

**Current Pharmacology Reports. 21 March 2015; Epub**

The current standard of care for prostate cancer (PCa) includes hormone therapy, radiation therapy and radical prostatectomy, each with its own set of undesirable side effects. In this regard there is an unmet need to develop strategies that can prevent or delay the development of clinical PCa. One potential area involves the use of natural compounds involving botanicals.

Along these lines we have found that Nexrutine®, a dietary supplement derived from Phellodendron amurense bark extract, has PCa prevention activity. The "extract" nature of this botanical, which constitutes a blend of several active protoberberine alkaloids, allows it to target several pathways deregulated in PCa simultaneously. In this review, we will emphasize the prospective translational benefit of Nexrutine as a chemopreventive agent for PCa management as it was first identified and has been exhaustively studied with reference to PCa. Therefore the focus of this review is on the use of Nexrutine in PCa. In addition, we have summarized the emerging evidence regarding the use of Nexrutine in other tumor models to demonstrate the potential benefits of Nexrutine.

## Liquid Biopsy Assay May Predict Drug Resistance in Prostate Cancer Patients

Researchers from the University of Trento in Italy and the Institute of Cancer Research of London in the UK have shown that a next-generation sequencing-based assay that evaluates alterations to the androgen receptor (AR) genes from prostate cancer patients' blood may be able to explain why men with castration-resistant prostate cancer (CRPC) develop resistance to androgen inhibitors.

Reporting the results of a 97-man study in *Science Translational Medicine*, researchers found that men without alterations to the AR gene before starting abiraterone had significantly longer overall and progression-free survival (PFS) compared to men with mutations in the AR gene, or with copy number gains of AR. In addition, they identified two point mutations associated with the development of resistance.

Mutations to the AR gene tend to be rare in prostate cancer before primary androgen deprivation therapy (ADT), but emerge with castration resistance. Researchers wanted to test whether mutations to and copy number gains of AR were associated with resistance to abiraterone. Because obtaining serial biopsy samples would be very invasive and challenging, they settled on a noninvasive approach to evaluate circulating tumor DNA (ctDNA) in plasma.

Researchers sequenced the entire coding region of the AR gene in 217 plasma samples from 80 men with CRPC who were being treated with the AR inhibitor abiraterone in an attempt to determine the molecular drivers of resistance. From 97 total men, they were able to obtain enough ctDNA to evaluate 217 samples from 80 men.

The team found that pre-treatment samples tended to have less ctDNA than samples analyzed at disease progression. In addition, men with a lower ctDNA burden tended to have better outcomes.

The team found that 81/217 (37%) samples from 32/80 (40%) men had a copy number gain to AR. In addition, 41 plasma samples from 16 men had somatic nonsynonymous mutations to AR. The team also identified two point mutations that were not present in baseline samples, but occurred over the course of treatment. Seven men developed these mutations in the AR gene, which the researchers hypothesized occurred due to selective pressure from abiraterone treatment. By contrast, men with AR copy number gains did not experience any further gains of the gene during treatment. Overall, men with either a copy number gain of AR or point mutations to AR fared worse than men with a normal AR gene. Out of 80 men, 36 (45%) had either a copy number gain or a point mutation. Those men were 4.9 times less likely to have a PSA decline greater than 50% after abiraterone treatment and were 7.8 times less likely to have a PSA decline of 90% after treatment. Like men with a lower ctDNA burden, those with normal AR also had significantly longer PFS and overall survival when compared to men with an AR gain or point mutation.

The study is important because men with prostate cancer typically start ADT, but the majority eventually progress and develop CRPC. Typically, these men begin second-line hormonal treatment with drugs such as abi-

*(Continued on page 6)*

## HIFU for Prostate Treatment *(Continued from page 1)*

return to daily activities rapidly. Because there is no radiation involved, the procedure can be repeated, if necessary.

"For men with conditions like prostate cancer, the option of a non-invasive procedure that can selectively target and treat diseased tissue is very appealing," says Neal Kassell, MD, chairman of the Focused Ultrasound Foundation.

"American men have been traveling overseas for focused ultrasound treatment for prostate diseases for years, and we are pleased that they will now have access to this innovative treatment at leading centers in the US."

In addition to Sonablate, EDAP's Ablatherm focused ultrasound system for treating the prostate is under FDA review and may be approved soon. Focused ultrasound devices have been cleared to treat the prostate in more than 40 countries since the first approval in 2000. Several systems for focused ultrasound ablation of prostate tissue are commercially available or being researched in other geographic areas with differing guidance methods

(ultrasound vs. magnetic resonance imaging) and approach (transrectal or transurethral).

"I believe that we are at a pivotal point in prostate care," said Michael Koch, MD, Sonablate trial investigator and chairman of the Department of Urology at Indiana University.

"Simultaneous advances in imaging, fusion technologies, and now more focused therapies are going to allow us to precisely diagnose prostate conditions and ablate these targeted areas rather than perform whole gland prostate surgery, which carries a significant burden on quality of life. Focused ultrasound will become the work-horse of subtotal prostate therapy."

More than 50,000 men around the world have been treated with focused ultrasound for prostate cancer, which is the leading clinical application of the technology. More than 50% of the men who have undergone focused ultrasound around the globe have had prostate disease treated.

*Medical News Today  
16 October 2015*

## High-Grade PCa and CVR *(Continued from page 4)*

density lipoprotein and triglyceride levels, glycemia, abdominal obesity, and family history of premature cardiovascular disease. Men with grade two hypertension (HTN, 160/100 mm Hg or higher), those with grade one HTN (systolic BP 140–159 mm Hg or diastolic BP 90–99 mm Hg) and one or two risk factors, or men with three or more risk factors apart from BP were considered to have moderate or high CVR.

Of the 584 study subjects, 223 (38.1%) had metabolic syndrome as defined according to the Adult Treatment

Panel III. Among men with PCa, metabolic syndrome was significantly more prevalent when a man's tumor Gleason score was  $\geq 7$  vs.  $\leq 6$  (50.8 vs. 32.7%).

Study limitations included that this was a single-center study with a limited male population having a significant proportion of men with moderate or high CVR. Also, results apply only to men undergoing prostate biopsy, and cannot be extrapolated to all men at risk for PCa.

*Renal & Urology News  
15 October 2015*

## Costs of Treating Low-Risk Prostate Cancer Analyzed

Researchers at a large tertiary care center have discovered what it really costs to treat low-risk prostate cancer at their institution. Their results were published online November 2<sup>nd</sup> in the journal *Cancer*. Estimated cost of treating prostate cancer vary widely. For example, costs of a radical prostatectomy (RP) can range from a low of \$10,000 to over \$135,000, Aaron Laviana, MD, from the University of California, Los Angeles (UCLA), told Medscape Medical News.

That huge discrepancy prompted Dr. Laviana and his colleagues to determine the cost across the entire care process, from the time a man checks in for his first appointment to post treatment follow-up testing. They started with detailing the costs associated with RP for localized, low-risk prostate cancer.

"All the cost studies that have been done have been arbitrary," Laviana said in an interview. "There is no exact measurement. Some studies are based on hospital charges, others on reimbursement, but when you get down to the nitty gritty of what these costs include, you find out that oftentimes, they don't include anesthesia costs, or surgeon costs, or nursing costs. It's a bundled, arbitrary payment," he said.

"We need to break down each individual cost and see how these all play a role. Often, a man will get a medical

bill, and it just says, 'hospital.' Even when one asks for an itemized bill, it can still be very murky. You hear stories about someone getting several stitches that cost thousands of dollars, and wonder why. This study sheds light on how all the costs are being formulated," Dr. Laviana said.

The UCLA team used a technique called time-driven activity-based costing, which is used to detail costs for doing business in industry, for each phase of care from the initial urologic visit through 12 years of follow-up.

Treatments included robot-assisted laparoscopic RP (RALP), cryotherapy, high-dose-rate and low-dose-rate brachytherapy, intensity-modulated radiation therapy (RT), stereotactic body RT, and active surveillance, which included both traditional transrectal ultrasound (TRUS) biopsy and multiparametric-MRI/TRUS fusion biopsy.

"We broke down each of the individual processes for every treatment modality, starting from when the patient was first seen at the clinic, checked in by a clerk, in the waiting room, going to the examining room, noting the amount of time each physician took with each patient, how much time the nurse took, what their salaries were. We wrote down every single step as the cost per minute," Dr. Laviana said. "We also analyzed the cost per minute of space, the cost of rent, we took the blueprint and calculated the square footage and how much each proportion of a urology clinic went towards the overall rent. We tried to make it as precise as possible."

The analysis showed a substantial cost variation at five years, ranging from \$7,298 for AS to \$23,565 for IMRT.

The cost variations remained throughout the 12 years of follow-up. LDR brachytherapy, at \$8,978, was notably less expensive than HDR brachytherapy, at \$11,448. Stereotactic body radiation therapy, at \$11,665, was notably less expensive than IMRT, with the cost savings attributable to shorter procedure times and fewer visits required for treatment.

Both equipment costs and an inpatient stay, at \$2,306, contributed to the high cost of RALP, at \$16,946. Cryotherapy (\$11,215) was more costly than LDR brachytherapy, largely because of increased single-use equipment costs (\$6,292 vs. \$1,921). The cost of AS became equivalent with LDR brachytherapy after seven years of follow-up.

"The relatively low cost of AS, which uses repeated PSA testing and prostate biopsies to monitor for development of more aggressive disease in younger, healthier patients who might benefit from delaying treatment, was the biggest surprise uncovered by our analysis," Dr. Laviana noted. "These costs apply only to those at UCLA. They will be different for each hospital, based on how much their rent is, how much their staff is paid and other factors," he added.

"Next we will analyze the costs of treating high-risk prostate cancer and metastatic prostate cancer," Dr. Laviana said. "Few people have a good sense of what our costs are. There is so much waste in the operating room. We are using equipment, but no one has a solid sense of what the costs are. We're just ordering labs and ordering tests, but there is a huge disconnect there. But we should have a better sense of what we are order-

ing, how much it matters, and how much it costs, rather than just saying, okay, get this," he said.

Researchers now plan to link cost analyses to outcomes. "We may think it is cheaper to withhold some treatment and opt to do others based on cost, but we also need to be sure there are no differences in health outcomes when we do this," he said.

*Medscape Medical News*  
5 November 2015

## Liquid Biopsies

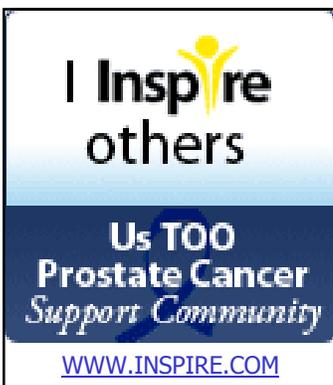
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raterone, which inhibits the AR gene. However, these drugs are not curative and men usually develop resistance within one year, according to an accompanying editorial from the University of Washington and Johns Hopkins University that comments about the study.

Other studies have previously supported a link between AR gain and resistance to abiraterone, however, one previous study also found AR gains to be associated with abiraterone sensitivity, the authors wrote. "Future studies may shed light on the explanation for this discordance, including possible genomic differences between prostate tumors and plasma DNA," they wrote. In addition, they wrote that an expanded sequencing panel might uncover additional mutations that explain abiraterone resistance.

The Editorialists wrote, "Understanding the molecular events driving this drug resistance is critical and may enable the identification of new therapeutic targets and biomarkers for use in clinical decision-making."

*GenomeWeb.com*  
4 November 2015



## Doctor Chodak's Bottom Line (Reference Key: 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 "24 months of AAT..."

Information continues to accrue regarding the optimal management of men with a rising PSA after radical prostatectomy (RP). Randomized studies have shown a small but significant survival benefit from early radiation therapy (RT). Shipley et al are now reporting the results of a randomized study comparing salvage RT plus placebo to salvage RT plus two years of antiandrogen therapy with bicalutamide 150 mg/day.

The addition of bicalutamide showed a small but significant improvement in survival at 12 years of only 4%. That means 25 men had to be treated with the antiandrogen to prevent one from dying in 12 years. There was a greater reduction in metastatic rates; only 11 men had to be treated to prevent one from getting metastases.

An important question not answered by the study is whether the RT was necessary; could two years of the antiandrogen alone have achieved similar results? Another study will be needed to address that issue. Fortunately, toxicity was relatively low from the RT, although a high percentage of the men receiving the antiandrogen did develop breast tenderness.

**The Bottom Line:** Salvage RT plus an antiandrogen offers a small survival benefit for men with a rising PSA after RP.

**P1 "Long-term ADT..."** The role of androgen deprivation therapy (ADT) was the focus of another study in this issue of the *Hot SHEET*. Long-term results of RTOG 9202 were reported. This was a randomized study of four months vs. 28 months of ADT in men with T2c to T4 prostate can-

cer treated with RT to the prostate (65-70 Gy) with RT also given to the pelvic lymph nodes. The impact on survival was not very large, increasing from 27% to 30% at 12 years. This means that one out of every 10 men receiving the combination will avoid dying from the disease. One out of every nine men avoided metastatic disease during that time.

The duration of ADT should be a focus for men with locally advanced disease or high risk localized disease. During my years in practice, I observed many doctors prescribing ADT for longer than a year, a duration not supported by the randomized studies using six to 12 months of ADT. Another study showed longer survival using 36 months of ADT, but preliminary results of yet another ongoing study suggested that 18 months may achieve similar results.

**The Bottom Line:** Men with locally advanced or high risk prostate cancer should be informed of the benefits of longer-term ADT in combination with external beam RT, although the optimal ADT duration is not yet resolved.

**P1 "FDA Approves First..."** In an interesting, but somewhat concerning outcome, FDA approved HIFU for ablating prostate tissue. That may open the flood gates to treating men with prostate cancer even though no data was presented showing how well it works for men with the disease or how it might compare to other standard therapies.

HIFU has been used extensively in other countries and by US doctors performing the procedure outside the US for a considerable cash fee. How-

ever, the data continue to show it to be an inferior treatment for prostate cancer (<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3235211/>). In 2014, an FDA advisory panel voted against approving HIFU for low-risk prostate cancer because the data presented did not show substantially equivalent effectiveness (<http://www.medscape.com/viewarticle/829179>).

It now seems that the company has found a way around that review. Any man advised to undergo this treatment instead of other established therapies should ask careful questions to his doctor about the high rate of positive biopsies and the absence of comparable long-term survival data. Hopefully better information is forthcoming, but one has to question why the FDA approved HIFU today without any more convincing evidence proving substantially equivalent effectiveness.

**The Bottom Line:** Although the FDA has approved HIFU for tissue ablation that does not mean it will provide comparable cancer control that is achieved with RP or RT.

**P2 "5-point Likert..."** Should MRI become the gold standard for evaluating men with a high PSA instead of transrectal ultrasound? Proponents of the procedure are making that claim and data is accumulating that may support it. A lack of standardized reporting is just one obstacle. Harada and co-workers now report on a five-point Likert system for evaluating lesions seen on MRI. They studied 44 men who underwent RP.

The first problem is that 56 men actually had a MRI but 12 (21%) scans could not be

used due to technical problems. Secondly, the RP revealed 102 tumor foci, but, the radiologists only identified 55 of them, meaning that 57/102 (56%) of the cancers were missed by MRI. Of the lesions recognized by the radiologists, the positive predictive values were best for Likert scores four (PPV 95%) and five (PPV 82%), but PPVs were <25% for scores of one or two. Although the sensitivity was 87% for lesions larger than 0.5 cc, only 57/102 (56%) lesion were of that tumor volume.

Taken together, MRI will miss a significant percentage of cancers. Furthermore, in this study the radiologists were not blinded to the diagnosis of cancer; they knew cancer was present in each case they reviewed and they had to identify the location of those lesions. One wonders, how many more lesions might be missed if the radiologists did not know cancer was present.

**The Bottom Line:** The value of MRI as the method of choice for evaluating an elevated PSA remains unclear and there is a concern that it will miss many cancers.

**P2 "MRI on Disease..."** Another article on the potential use of MRI was reported by Guo et al. They conducted a meta-analysis of studies reporting MRI results in men on active surveillance (AS) to determine the odds of finding more aggressive disease that may warrant treatment. Although they found a small percentage of men with more aggressive disease, the sensitivity, specificity, and positive and negative predictive values were poor. This

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## Doctor Chodak's Bottom Line *(Continued from page 7)*

means that relying on MRI to make a decision will miss some potentially aggressive tumors and also incorrectly label others as aggressive.

**The Bottom Line:** Better data are needed to support the routine use of MRI as a means to determine if more aggressive cancers are present in men on AS.

### P5 "Liquid Biopsy Assay..."

Abiraterone has been in use now for several years in men who progress on ADT. It improves survival in men receiving it either before or after docetaxel chemotherapy. Unfortunately, the drug does not work in all men and a desirable goal is to identify those men that will benefit.

Preliminary work suggests that the presence of a mutation in the androgen receptor (AR) gene is a marker for those cancers unlikely to respond to the drug. Researchers at the Institute of Cancer Research in London reported on nearly 100 men

and again found a good correlation. Men with the mutation had a poor response to abiraterone. Another large study is underway to assess the test's value and it could help make the drug more cost effective by avoiding treatment in the men who will not respond.

**The Bottom Line:** A genetic test for an AR mutation could help identify men unlikely to benefit from abiraterone.

**P6 "Cost of Treating..."** Everyone sees that medical costs are rising. Since prostate cancer can be treated by so many different options, one might question how variable are the costs of treatment. Laviana and co-workers conducted an analysis of the cost of treating localized prostate cancer at the University of California Los Angeles (UCLA).

They attempted to identify a cost associated with each step of the management process. Unfortunately, it appears they did not include

the patient-related expenses such as time lost from work, traveling, etc. It is also unclear if they included the cost of treating side effects or recurrent disease. Nevertheless they did find a wide variation with AS actually the least expensive option and IMRT the most expensive. Now the question is what to do with this information. It seems highly unlikely that insurance companies will ever force men to choose a therapy based on expense. Information could be used to identify potential ways to lower some of those costs. Another consideration for insurance companies is that they could make a case that if different forms of RT are available, why reimburse for a more expensive form unless it clearly shows benefits.

**The Bottom Line:** Cost of treating localized prostate cancer varies considerably depending on the option selected, with AS the lowest.

## Olaparib

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evaluated (33%). Of these 16 men, 14 (88%) responded to olaparib, including all seven men with BRCA2 loss (four with biallelic somatic loss, and three with germline mutations) and four of five with ATM aberrations. The specificity of the biomarker suite was 94%. Anemia (in 10/50 [20%]) and fatigue (in 6/50 [12%]) were the most common grade 3 or 4 adverse events, findings that are consistent with previous studies of olaparib.

**Conclusions:** Treatment with olaparib in men whose prostate cancers were no longer responding to standard treatments and who had defects in DNA-repair genes led to a high response rate.

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