Informed Prostate Cancer Support Group Inc.
"A 501 C 3 CORPORATION ID # 54-2141691"

JULY 2021 NEWSLETTER

P.O. Box 420142 San Diego, CA 92142
Phone: 619-890-8447 Web: http://ipcsg.org

Wednesday, August 18,

Volume 14 Issue 08

- **Saturday, August 28, 2021 IPCSG - Live-Stream Event, 10:00pm PT**

Jane Shellhouse - Improve nutrition & improve health

- Jane Shellhouse CN, CNM Clinical Nutrition consultant; http://dietnutritionsupport.com/about-us/
- Improve nutrition & improve health https://youtu.be/qCraEelltV8
- Due to COVID-19, no in-person meetings at the Sanford Burnham Prebys Medical Discovery Institute will take place until further notice. This meeting will be live-streamed and will also be available on DVD.
- **For further Reading: https://ipcsg.blogspot.com/**
- **For Comments, Ideas and Questions,** email to Newsletter@ipcsg.org

July 2021 Informed Prostate Cancer Support Group Meeting

Summary by Bill Lewis

Modern Advances in Men's Sexual Health -- Men's Health, Pre & Post Prostate Cancer Treatment

Dr. Justin J. Houman is a urologist (at Tower Urology in Los Angeles) and fellowship-trained Male Reproductive Medicine and Surgery specialist, whose practice is focused on men's health, including male hormone management, sexual and ejaculatory dysfunction, male fertility, male incontinence, and Peyronie's disease. In this talk, Dr. Houman discusses men's health with respect to pre and post prostate cancer treatments.

Sexual Health includes the following:

Erectile Dysfunction (ED)

Ejaculatory Dysfunction

Sexual Dysfunction

Decreased Libido/Sex Drive

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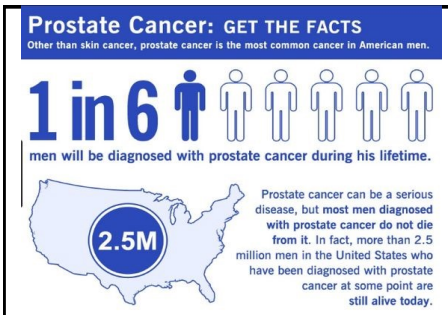

Organization

a 501c3 non-profit organization - all positions are performed gratis

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NEWSLETTER

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PROSTATE CANCER—*2 WORDS, NOT A SENTENCE*

What We Are About

Our Group offers the complete spectrum of information on prevention and treatment. We provide a forum where you can get all your questions answered in one place by men that have lived through the experience. Prostate cancer is very personal. Our goal is to make you more aware of your options before you begin a treatment that has serious side effects that were not properly explained. Impotence, incontinence, and a high rate of recurrence are very common side effects and may be for life. Men who are newly diagnosed with PCa are often overwhelmed by the frightening magnitude of their condition. Networking with our members will help identify what options are best suited for your life style.

Meeting Video DVD's

DVD's of our meetings are available for purchase on our website at https://ipcsg.org/purchase-dvds and are generally available by the next meeting date.

Join the IPCSG TEAM

If you consider the IPCSG to be valuable in your cancer journey, realize that we need people to step up and HELP. Call **President** Bill Lewis @ (619) 591-8670 ; or **Director** Gene Van Vleet @ 619-890-8447.

From the Editor

Due to COVID-19, no in-person meetings will be held until further notice. We will continue to post and distribute the newsletter in the interim. Our speaker this month will be broadcast via the IPCSG website at https://ipcsg.org/live-stream and can be watched by scrolling down and clicking on the "WATCH THE PRESENTATION" button. The broadcast will begin approximately 10 minutes before to the listed start time.

In this issue:

First, we have Bill Lewis's great summary of the last talk, followed by Articles of Interest

Daryl Halencak describes how he had to push to get his cancer detected and treated in "Prostate Cancer: Why Early Detection Matters". Nick Mulcahy says that men will soon be given more alternative treatments besides radical prostatectomy in "'Routine' Use of Focal Therapy for Prostate Cancer in Next 5 Years". Marilynn Larkin then shows that older men in their 80's are now benefiting from newer medications with increased survival in "Androgen Blockers Likely Boost Survival in Older Men With Nonmetastatic CR Prostate Cancer". The article "PROMISE: a real-world clinical-genomic database to address knowledge gaps in prostate cancer" describes the database being developed to improve genomic treatment of cancer. The article "Prospective Evaluation of Health Care Provider and Patient Assessments in Chemotherapy-Induced Peripheral Neurotoxicity" describes peripheral neuropathy as a side effect of chemotherapy. "Death of Spouse Could Raise Odds for Prostate Cancer" describes a Canadian study on Prostate Cancer frequency in widowers.

(Continued on page 11)

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Low Testosterone/Hypogonadism

Peyronie's Disease (a bend in the penis)

Post-Pelvic Surgery ED & Penile Rehabilitation

Sexual health is important for men of all ages. Dr. Houman noted that 90% of men want to talk about sex with their doctors, but only 20% of doctors feel comfortable about it.

I. Testosterone – the male hormone that makes us men. It declines 1-2% per year on average after age 30, but the rate of decline varies between individuals. Low testosterone leads to low sex drive, fatigue, reduced lean muscle mass, irritability, ED (erectile dysfunction), depression, sleep or appetite disturbances, reduced endurance / physical strength, poor memory, poor focus (brain fog), and/or not being able to exercise or perform at work the way you used to. "Normal" testosterone levels vary from one individual to another, from about 300 to about 1000. So, the symptoms, rather than the blood level, is what should be treated. In addition to normal aging, testosterone levels decrease because of weight gain, poor sleep, stress, and lifestyle factors (such as drug or alcohol use). There are various ways of supplementing testosterone – see the video for details. Particularly low testosterone levels lead to greater risks of heart attacks, strokes, and shortened lifespan. It has now been shown that testosterone levels in the normal range are not a risk factor for heart attacks, and that they do not cause increases in the growth of prostate cancer. High weekly or monthly doses of testosterone have actually been helpful to boost the immune system and fight metastatic prostate cancer, in a study at MD Anderson that has not been published yet.

II. Erectile Dysfunction is very common – it affects about 40% of men at age 40, about 50% of men at age 50, and so forth. It correlates with poor overall health, and often is an indicator of heart disease. The top 4 causes are vascular, hormonal, neurologic and mental issues. Treatment options include oral medications, injections, penile implants (95% satisfaction rate!), vacuum erection devices, and urethral suppositories. Another new option is shockwave therapy. High-energy sound waves release growth factors that promote new blood vessel growth. The $2-4,000 cost is not yet covered by insurance, but it "works great," over a few months. "P-shots" involve collecting platelet-rich plasma and injecting activated platelets, which cause the release of growth factors to increase the number of reparative cells produced by the body. It works great for some, but so far, on average, not quite as well as shockwave therapy.

III. Enlarged Prostate/BPH – Symptoms include waking up at night to urinate, incomplete bladder emptying, involuntary urination, urgency and frequency. Oral therapies include Flomax or the like, Finasteride or Dutasteride (which shrink the prostate and also can treat male-pattern baldness but have a libido side effect). Surgery, i.e., TURP (transurethral resection of prostate), can "core out" the prostate to allow better urine flow. It's straightforward and usually highly beneficial. In the Rezum (in-office) system, steam is injected into the prostate, and the tissue dies off over a few days, opening up the channel. Urolift is a procedure in which staples are placed to hold the prostate channel open. Prostate artery embolization (PAE) is a less-used option in which the blood flow to the prostate is mostly blocked, and tissue dies off over several months.

IV. Peyronie's Disease – About 10% of men have some form of it, in which the penis has some kind of bend. A plaque of collagen forms and prevents that side of the penis from expanding. Oral therapies are used to try to dissolve or soften the plaque. There are also injections with CCH (collagenase clostridium histolyticum, brand name Xiaflex) – which are FDA approved and effective by using a series of injections.

Questions:

Does ADT (androgen deprivation therapy) cause ED? Yes, so many men elect the penile prosthesis.

Tell more about the correlation between Testosterone level and prostate cancer growth. Below 250 ng/dL, there is a correlation, but above that, there is none.

(Continued on page 4)

(Continued from page 3)

Therapies for men with poor/no orgasm, that don't have classic ED? Often, increasing the strength of the erection will better allow the nerve stimulation that leads to orgasm. Therapies are available.

What about having on hand the antidote, for excessively persistent erections after an injection? It's best to then go to an emergency room, because the antidote can cause heart issues, so careful monitoring is needed.

What about the use of Cialis after radical prostatectomy, to rebuild the ability to have an erection? Dr. Houman goes further and starts the Cialis even before the surgery. The dose he gives causes daily mild erections (including normal, multiple nightly), to maintain blood flow, to prevent the penis from scarring and shrinking.

Do you need to have Testosterone, for Cialis to work? Yes, it doesn't work well for men on ADT.

What about pelvic physical therapy? It seems to only help mild ED, and urinary incontinence after radical prostatectomy. He does recommend Kegel exercises before RP as a first option, and PPT as the backup option. Dr. Houman noted that with robotic RP, urinary incontinence is much less a problem than in the past, because of the better, close-up visualization of the sphincter muscles.

What is the best therapy for PCa, vis-à-vis sexual effects? He prefers RP, as being more exact. The chance of collateral damage to the nerves is higher with external radiation or brachytherapy.

What about penile shortening from RP? It's actually minimal from the surgery. The scarring and shortening from lack of frequent erections is much more the cause.

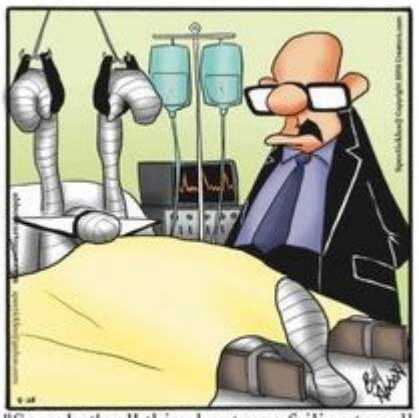
How to prevent bone density loss on ADT? Vitamin D and calcium – but get a calcification scan first.

Contact info: Dr. Justin J. Houman, Cedars-Sinai Office Towers, 8635 West 3rd Street, Suite 1 West, L. A., CA 90048 Phone: 310-854-9898

We recommend that you watch the video online for more definitive information about the talk and slides: https://www.youtube.com/watch?v=mttLEr3wv7M

A DVD of the talk and Dr. Houman's slides will be available for purchase from the IPCSG about one month after the meeting.

On the Lighter Side



"So, what's all this about you failing to call in sick per company policy?"

Articles of Interest

Prostate Cancer: Why Early Detection Matters

webmd.com

By Daryl Halencak

From the WebMD Archives Medically Reviewed by Laura J. Martin, MD on July 13, 2021

My father died at 54 from prostate cancer, and his brother had prostate cancer at the same time. I have several cousins who also have this problem, so I knew that I needed to get screened since prostate cancer runs in my family. I was also having certain symptoms: incontinence, pain in my groin, and ED [erectile dysfunction].

I had a PSA test, and it came out negative. My doctor thought the symptoms might be stress, as I had many jobs, including taking care of my mother's farm. But even though the doctors could not find anything, I knew something was wrong. I was 55, and there was no reason to have ED or problems going to the bathroom.
I was sent to another doctor, and he did 10 biopsies and found the cancer. In 2008, I had surgery, a radical prostatectomy. The surgeon removed my prostate, fatty tissue surrounding it that might be cancerous, and several lymph nodes.

The road to recovery after surgery was very hard. The incontinence was still there for a bit but then it abated. I was worried before the surgery about sexual issues, but even though I had a radical procedure, my surgeon saved my nerves, and eventually I didn't have ED problems any more.
After my cancer, I changed my ways. I was just a regular guy in rural Texas. We eat a lot of meat, go to a lot of parties, drink a lot of beer, and that's what I was doing. I wasn't exercising. After my surgery, I quit smoking, and I cut back on drinking. I started going to the track to exercise for at least 35 to 40 minutes a day, even in bad weather. I started eating lots of vegetables and salads. Now I rarely eat meat, except occasionally at family barbecues.

Having cancer also made me rethink my life. I started working less and spending more time with my family. I'm a prose poet and wrote a book about my journey, talking about my fears and experience.

Today, I feel great. I still go every 6 months for checkups. Early detection saved my life. I feel very blessed.

Daryl's Life Lessons

"Be an advocate for your own health. If you feel something is wrong and your doctor doesn't find anything, get another opinion."

"If you have symptoms, run, do not walk, to your doctor."

"I believe that men should get screened for prostate cancer, especially if they have a family history."

Find more articles, browse back issues, and read the current issue of "WebMD Magazine."

'Routine' Use of Focal Therapy for Prostate Cancer in Next 5 Years

medscape.com

Nick Mulcahy

There will be "routine application" and "broader acceptance" of minimally invasive focal therapies for early-stage

prostate cancer within the next 5 years in the United States, predict a trio of clinicians in a new essay published online July 28 in *JAMA Surgery*.

They maintain that focal therapy (FT) offers a "middle ground" between two extremes: treating the whole gland with radical prostatectomy or radiotherapy, and not treating immediately via active surveillance or watchful waiting.

Focal therapy typically treats the primary lesion within the prostate, while leaving the rest of the gland intact. Most often performed with cryoablation or high-intensity focused ultrasound (HIFU), it can also be carried out with a variety of technologies, including transurethral ultrasound ablation and focal laser ablation.

The shift to focal therapy will coincide with maturing, long-term data from studies with various technologies, predict the authors, led by Amir Lebastchi, MD, a urologist at the University of Southern California.

"Standard adoption of focal therapy is ultimately dependent on the availability of robust level I evidence, which in turn will drive medical societies and payees," the authors also write.

But payees are already making changes, even without such data, they add.

For example, the American Medical Association announced in January a new code for high-intensity focal ultrasound (HIFU): this approach now has a Current Procedural Terminology (CPT) code from the US Centers for Medicare & Medicaid Services

Medscape Medical News reached out to Matthew Cooperberg, MD, MPH, a urologist at the University of California San Francisco (UCSF), for comments about the essay's optimism; he has questioned focal therapy in the past because of a lack of strong supporting evidence.

I do expect its use will in fact increase in the next 5 years. Dr Matthew Cooperberg, on high-intensity focal ultrasound

"While 'routine' is a bit of a vague term, now that HIFU has a CPT code, I do expect its use will in fact increase in the next 5 years," Cooperberg wrote in an email. "The question is whether its use will increase *appropriately*."

The challenge with focal therapy — regardless of energy modality — remains patient selection and accurate ablation zone definition, he added.

Notably, UCSF has launched a new HIFU program — and Cooperberg has referred selected patients. "I'm both enthusiastic and cautious about the future, and we need to track our outcomes very closely across various practice settings," he said.

While Waiting for CHRONOS, Select Wisely

The goal of focal therapy is to treat only the area with the most aggressive tumor, known as the index tumor, while leaving the remaining gland and its surrounding structures alone, according to Derek Lomas, MD, PharmD, a urologist at the Mayo Clinic in Rochester, Minnesota, in an explanatory article. "This approach is widely accepted in other types of cancer. For example, we commonly treat kidney cancers by removing or ablating only the tumor while leaving the rest of the kidney intact."

Androgen Blockers Likely Boost Survival in Older Men With Nonmetastatic CR Prostate Cancer

By Marilynn Larkin

medscape.com

NEW YORK (Reuters Health) - Androgen receptor inhibitors improved survival in men ages 80 and older with non-metastatic, castration-resistant prostate cancer in a pooled analysis by the US Food and Drug Administration.

"Older adults remain dismally underrepresented in most cancer clinical trials, due to a variety of factors, including restrictive eligibility criteria," Dr. Jaleh Fallah of the FDA's Center for Drug Evaluation and Research told Reuters Health by email. "There is biologic rationale to include older adults in all stages of cancer drug development, given the physiologic changes that naturally occur with aging."

"Treatment decisions should be based on the patient's overall clinical condition and not merely on the patient's age," she said. "Use of geriatric assessment tools can be helpful in assessing the potential risk of treatment-related adverse events and to implement appropriate risk-mitigation strategies to prevent such events as possible."

As reported in The Lancet Oncology, Dr. Fallah and colleagues searched the literature through August 2020 and identified three randomized controlled trials that met the selection criteria. All patients had an Eastern Cooperative Oncology Group performance status of 0-1, castration-resistant prostate cancer, prostate-specific antigen 2.0 mcg/L or greater, PSA doubling time of 10 months or less, and no evidence of distant metastatic disease.

Younger patients in the intervention and placebo groups had a median age of 71 and 74% were white; older patients had a median age of 83 and 69% were white. The effects of age on metastasis-free and overall survival were assessed in the intention-to-treat population. Safety analyses were done in patients who received at least one dose of study treatment.

Between 2013 - 2018, across the three trials, 2,694 patients were assigned to an androgen receptor inhibitor (apalutamide, enzalutamide, or daralutamide) and 1,423 to placebo.

In older patients, the estimated median metastasis-free survival was 40 months in the androgen receptor inhibitor groups and 22 months in the placebo groups (adjusted hazard ratio, 0.37); median overall survival was 54 months versus 49 months, respectively (adjusted HR, 0.79).

In younger patients, the estimated median metastasis-free survival was 41 months in the androgen receptor inhibitor groups and 16 months in the placebo groups (adjusted HR, 0.31); median overall survival was 74 months versus 61 months (adjusted HR, 0.69).

Grade 3 or worse adverse events were reported in 55% of older patients in the intervention group and 41% of those on placebo.

In younger patients, 44% in the androgen receptor inhibitor groups and 30% of those on placebo experienced grade 3 or worse adverse events.

The most common grade 3-4 adverse events were hypertension (8% of both older and younger patients on androgen receptor inhibitors vs. 6% of older placebo patients and 5% of younger) and fracture (5% of older patients on androgen receptor inhibitors vs. 3% on placebo, and 3% vs. 1%, respectively, of those on placebo).

Dr. Ali Zhumkhawala, a urologic oncology surgeon at City of Hope in Duarte, California, called the findings "clinically helpful," noting, "the caveat is that patients who received the second-generation androgen receptor inhibitors did show higher rates of severe adverse events. While the quality-of-life questionnaire did not show a downside to treatment with these medications, the higher risk of side effects needs to be taken into account and treatment should be personalized per patient."

"I would like to see this study, or a similar study, stratify these outcomes based on the specific medication used," he said. "There are concerns about the use of enzalutamide in the elderly. I would like to see the adverse events, survival and questionnaire data broken down by which medication the patient received so that we can further assess which specific medicine works best in which age group."

"My take-home message is that clinicians should strongly consider the use of second-generation androgen receptor inhibitors in patients with castrate-resistant prostate cancer that has not metastasized. This seems to hold true in both younger and elderly patients," Dr. Zhumkhawala concluded.

Dr. Fallah noted, "The FDA encourages broader inclusion of older adults in cancer clinical trials and has issued a guidance for industry providing advice on the inclusion of older patients in early-phase and pivotal clinical trials, as well as in the post-market setting. Additionally, the FDA includes information on the use of drugs in older patients on drug labels," as applicable.

SOURCE: https://bit.ly/3AgP8U4 The Lancet Oncology, online July 23, 2021.

PROMISE: a real-world clinical-genomic database to address knowledge gaps in prostate cancer

Vadim S. Koshkin, Vaibhav G. Patel, Rana McKay

Prostate Cancer and Prostatic Diseases (2021)Cite this article

Abstract

Purpose

Prostate cancer is a heterogeneous disease with variable clinical outcomes. Despite numerous recent approvals of novel therapies, castration-resistant prostate cancer remains lethal. A "real-world" clinical-genomic database is urgently needed to enhance our characterization of advanced prostate cancer and further enable precision oncology.

Methods

The Prostate Cancer Precision Medicine Multi-Institutional Collaborative Effort (PROMISE) is a consortium whose aims are to establish a repository of de-identified clinical and genomic patient data that are linked to patient outcomes. The consortium structure includes a (1) bio-informatics committee to standardize genomic data and provide quality control, (2) biostatistics committee to independently perform statistical analyses, (3) executive committee to review and select proposals of relevant questions for the consortium to address, (4) diversity/inclusion committee to address important clinical questions pertaining to racial disparities, and (5) patient advocacy committee to understand patient perspectives to improve patients' quality of care.

Results

The PROMISE consortium was formed by 16 academic institutions in early 2020 and a secure RedCap database was created. The first patient record was entered into the database in April 2020 and over 1000 records have been entered as of early 2021. Data entry is proceeding as planned with the goal to have over 2500 patient records by the end of 2021.

Conclusions

The PROMISE consortium provides a powerful clinical-genomic platform to interrogate and address data gaps that have arisen with increased genomic testing in the clinical management of prostate cancer. The dataset incorporates data from patient populations that are often underrepresented in clinical trials, generates new hypotheses to direct further research, and addresses important clinical questions that are otherwise difficult to investigate in prospective studies.

Prospective Evaluation of Health Care Provider and Patient Assessments in Chemotherapy-Induced Peripheral Neuro-

toxicity

Paola Alberti, Davide P. Bernasconi, David R. Cornblath, Ingemar S.J. Merkies, Susanna B. Park, View ORCID ProfileRoser Velasco, Jordi Bruna, Dimitri Psimaras, Susanne Koeppen, Andrea Pace, Susan G. Dorsey, View ORCID ProfileAndreas A. Argyriou, Haralabos P. Kalofonos, Chiara Briani, Angelo Schenone, Catharina G. Faber, Anna Mazzeo, Wolfgang Grisold, MariaGrazia Valsecchi, View ORCID ProfileGuido Cavaletti, on behalf of the CI-PeriNomS group

First published June 2, 2021, DOI: https://doi.org/10.1212/WNL.0000000000012300

Abstract

Background and Objective There is no agreement on the gold standard for detection and grading of chemotherapy-induced peripheral neurotoxicity (CIPN) in clinical trials. The objective is to perform an observational prospective study to assess and compare patient-based and physician-based methods for detection and grading of CIPN.

Methods Consecutive patients, aged 18 years or older, candidates for neurotoxic chemotherapy, were enrolled in the United States, European Union, or Australia. A trained investigator performed physician-based scales (Total Neuropathy Score–clinical [TNSc], used to calculate Total Neuropathy Score–nurse [TNSn]) and supervised the patient-completed questionnaire (Functional Assessment of Cancer Treatment/Gynecologic Oncology Group–Neurotoxicity [FACT/GOG-NTX]). Evaluations were performed before and at the end of chemotherapy. On participants without neuropathy at baseline, we assessed the association between TNSc, TNSn, and FACT/GOG-NTX. Considering a previously established minimal clinically important difference (MCID) for FACT/GOG-NTX, we identified participants with and without a clinically important deterioration according to this scale. Then, we calculated the MCID for TNSc and TNSn as the difference in the mean change score of these scales between the 2 groups.

Results Data from 254 participants were available: 180 (71%) had normal neurologic status at baseline. At the end of the study, 88% of participants developed any grade of neuropathy. TNSc, TNSn, and FACT/GOG-NTX showed good responsiveness (standardized mean change from baseline to end of chemotherapy >1 for all scales). On the 153 participants without neuropathy at baseline and treated with a known neurotoxic chemotherapy regimen, we verified a moderate correlation in both TNSc and TNSn scores with FACT/GOG-NTX (Spearman correlation index $r = 0.6$). On the same sample, considering as clinically important a change in the FACT/GOG-NTX score of at least 3.3 points, the MCID was 3.7 for TNSc and 2.8 for the TNSn.

Conclusions MCID for TNSc and TNSn were calculated and the TNSn can be considered a reliable alternative objective clinical assessment if a more extended neurologic examination is not possible. The FACT/GOG-NTX score can be reduced to 7 items and these items correlate well with the TNSc and TNSn.

Classification of Evidence This study provides Class III evidence that a patient-completed questionnaire and nurse-assessed scale correlate with a physician-assessed scale.

Death of Spouse Could Raise Odds for Prostate Cancer

By Robert Preidt

HealthDay Reporter

FRIDAY, Aug. 13, 2021 (HealthDay News) -- Widowers have a higher risk for advanced prostate cancer than men who are part of a couple, Canadian researchers say.

The new findings are from an analysis of 12 studies comparing 14,000 men newly diagnosed with prostate cancer and 12,000 healthy men.

The study — recently published in the *European Journal of Epidemiology* — suggests that social environment is an important factor in men's risk of advanced prostate cancer.

NETWORKING

Please help us in our outreach efforts. Our speakers bureau consisting of Gene Van Vleet is available to speak to organizations of which you might be a member. Contact Gene 619-890-8447 or gene@ipcsg.org to coordinate.

Member John Tassi is the webmaster of our website and welcomes any suggestions to make our website simple and easy to navigate. Check out the Personal Experiences page and send us your story. Go to: https://ipcsg.org/personal-experience

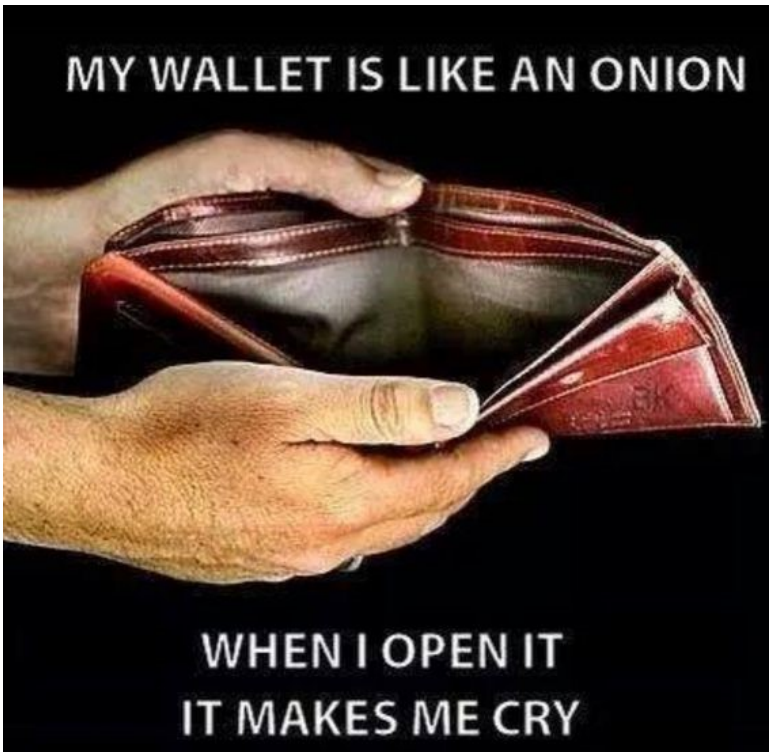
Our brochure provides the group philosophy and explains our goals. Copies may be obtained by mail or email on request. Please pass them along to friends and contacts.

Ads about our Group may be in the Union Tribune the week prior to a meeting. Watch for them.

FINANCES

We want to thank those of you who have made special donations to IPCSG. Remember that your gifts are tax deductible because we are a 501(c)(3) non-profit organization.

We again are reminding our members and friends to consider giving a large financial contribution to the IPCSG. This can include estate giving as well as giving in memory of a loved one. You can also have a distribution from your IRA made to our account. We need your support. We will, in turn, make contributions from our group to Prostate Cancer researchers and other groups as appropriate for a non-profit organization. Our group ID number is 54-2141691. Corporate donors are welcome!



While our monthly meetings are suspended, we still have continuing needs, but no monthly collection. If you have the internet you can contribute easily by going to our website, http://ipcsg.org and clicking on "Donate" Follow the instructions on that page. OR just mail a check to: IPCSG, P. O. Box 420142, San Diego CA 92142

Continued Editors Notes:

Good pathology evaluation of mpMRI imagery is important in detection of PCa, and the article "Convolutional Neural Networks for Automated Classification of Prostate Multiparametric Magnetic Resonance Imaging Based on Image Quality" describes how computers are performing this task. The article "Natural history of an immediately detectable PSA following radical prostatectomy in a contemporary cohort" shows how important PSA history after radical surgery is to determining prognosis. For those on active surveillance, Swedish researchers show a new blood test combined with MRI reduces the frequency of imagery needed for accurate detection in "New blood test improves prostate cancer screening" and "Novel Blood-Based Test Could Bolster MRI-Based Prostate Cancer Screening". The mechanism for PARP inhibitors to counter BRCA cancer is revealed in "Researchers pinpoint how PARP inhibitors combat BRCA1 and BRCA2 tumor cells". "Timing of initiation of ADT for men with biochemical progression after first-line surgery" describes considerations for when to start ADT after recurrence following surgery. Also, for those on AS, the article "Rethinking risk stratification for radiation therapy" describes considerations for determining your odds of survival with RT.

"This large group of subjects showed us that widowers were at risk of being diagnosed later than married men or men in relationships," said study author Charlotte Salmon, a doctoral student at the National Institute of Scientific Research in Quebec City, Canada.

Salmon's thesis focused on social isolation and the incidence of prostate cancer.

A number of previous studies have linked living with a partner to a healthier lifestyle.

"Without a spouse's encouragement to see a doctor or get screened if there are symptoms, cancers remain undetected longer and may be diagnosed at a more advanced stage," Salmon said in an institute news release. "This makes the prognosis bleaker."

To stay healthy, widowers should get support from family and friends and have regular medical follow-up, the study authors recommended.

Other possible reasons for the increased risk of advanced prostate cancer in widowers include lifestyle factors such as alcohol use and the emotional impact of bereavement, the researchers suggested.

Diet could also be a risk factor, they said.

The researchers plan further studies to investigate reasons for the risk and to identify appropriate public health strategies to reduce it.

Along with examining men's marital status, Salmon plans to also look at the number of family members living with them, family structure, neighborhood characteristics and other social factors.

More information

The American Cancer Society has more on prostate cancer.

SOURCE: National Institute of Scientific Research, news release, Aug. 12, 2021

Convolutional Neural Networks for Automated Classification of Prostate Multiparametric Magnetic Resonance Imaging Based on Image Quality

Stefano Cipollari MD, Valerio Guarrasi MS, Martina Pecoraro MD, Marco Bicchetti MD, Emanuele Messina MD, Lorenzo Farina PhD, Paola Paci PhD, Carlo Catalano MD, Valeria Panebianco MD

First published: 09 August 2021

https://doi.org/10.1002/jmri.27879

Sections

Abstract

Background

Prostate magnetic resonance imaging (MRI) is technically demanding, requiring high image quality to reach its full diagnostic potential. An automated method to identify diagnostically inadequate images could help optimize image quality.

Purpose

To develop a convolutional neural networks (CNNs) based analysis pipeline for the classification of prostate MRI image quality.

Study Type

Retrospective.

Subjects

Three hundred sixteen prostate mpMRI scans and 312 men (median age 67).

Field Strength/Sequence

A 3 T; fast spin echo T2WI, echo planar imaging DWI, ADC, gradient-echo dynamic contrast enhanced (DCE).

Assessment

MRI scans were reviewed by three genitourinary radiologists (V.P., M.D.M., S.C.) with 21, 12, and 5 years of experience, respectively. Sequences were labeled as high quality (Q1) or low quality (Q0) and used as the reference standard for all analyses.

Statistical Tests

Sequences were split into training, validation, and testing sets (869, 250, and 120 sequences, respectively). Inter-reader agreement was assessed with the Fleiss kappa. Following preprocessing and data augmentation, 28 CNNs were trained on MRI slices for each sequence. Model performance was assessed on both a per-slice and a per-sequence basis. A pairwise *t*-test was performed to compare performances of the classifiers.

Results

The number of sequences labeled as Q0 or Q1 was 38 vs. 278 for T2WI, 43 vs. 273 for DWI, 41 vs. 275 for ADC, and 38 vs. 253 for DCE. Inter-reader agreement was almost perfect for T2WI and DCE and substantial for DWI and ADC. On the per-slice analysis, accuracy was 89.95% ± 0.02% for T2WI, 79.83% ± 0.04% for DWI, 76.64% ± 0.04% for ADC, 96.62% ± 0.01% for DCE. On the per-sequence analysis, accuracy was 100% ± 0.00% for T2WI, DWI, and DCE, and 92.31% ± 0.00% for ADC. The three best algorithms performed significantly better than the remaining ones on every sequence (*P*-value < 0.05).

Data Conclusion

CNNs achieved high accuracy in classifying prostate MRI image quality on an individual-slice basis and almost perfect accuracy when classifying the entire sequences.

Natural history of an immediately detectable PSA following radical prostatectomy in a contemporary cohort

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Read the full text

Abstract

Background

A detectable prostate-specific antigen (PSA) following radical prostatectomy (RP) is an unfavorable prognostic factor. However, not all men with a detectable PSA experience recurrence. We describe the natural history and outcomes in men with a detectable PSA following RP in a contemporary cohort.

Methods

A retrospective analysis of men who underwent RP for non-metastatic prostate cancer at the University of California, San Francisco from 2000 to 2020 was performed. A detectable PSA was defined as PSA ≥ 0.03 ng/ml within 6 months of RP. Cox regression models tested the effect of detectable PSA on the development of metastasis, prostate cancer-specific mortality, and overall survival.

Results

We identified 2941 men who had RP with 408 (13.9%) with a detectable PSA within the first 6 months. The median follow-up was 4.42 years (interquartile range [IQR], 2.58–8.00). In total, 296 (72.5%) men with a detectable PSA had salvage treatment at a median of 6 months (IQR, 4–11). One hundred sixteen of these men had PSA failure after salvage treatment at a median of 2.0 years (IQR, 0.7–3.8). On multivariable Cox regression, the risk of development of metastasis (hazard ratio [HR], 1.05; 95% confidence interval [CI], 1.01–1.09; p = .01), prostate cancer-specific mortality (HR, 1.13; 95% CI, 1.05–1.21; p = .0005), and overall mortality (HR, 1.07; 95% CI, 1.03–1.12; p = .002) was associated with PSA velocity after salvage treatment in men with a detectable PSA.

Conclusions

Men with a detectable PSA after RP may have excellent long-term outcomes. PSA velocity after salvage treatment may be an important predictor for the development of metastasis, prostate cancer-specific mortality, and overall mortality.

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New blood test improves prostate cancer screening

Researchers at Karolinska Institutet in Sweden recently reported that magnetic resonance imaging (MRI) could reduce overdiagnoses and thereby improve prostate cancer screening. Now, the same research group has published a study in *The Lancet Oncology,* which shows that the addition of a novel blood test, the Stockholm3 test, can reduce the number of MRIs performed by a third while further preventing the detection of minor, low-risk tumours.

"Overall, our studies show that we have identified the tools needed to be able to carry out effective and safe screening for prostate cancer. After many years of debate and research, it feels fantastic to be able to present knowledge that can improve healthcare for men," says Tobias Nordström, associate professor of urology at the Department of Clinical Sciences, Danderyd Hospital at Karolinska Institutet, who is responsible for the STHLM3MRI study.

Current screening methods -- PSA (prostate-specific antigen) tests combined with traditional biopsies -- result in unnecessary biopsies and the detection of numerous minor, low-risk tumours (overdiagnosis). Consequently, no country except Lithuania has chosen to introduce a nationwide prostate cancer screening programme, as the benefits do not outweigh the disadvantages.

On July 9 2021, results from the STHLM3MRI study were presented in *The New England Journal of Medicine*, indicating that overdiagnosis could be reduced by substituting traditional prostate biopsies with magnetic resonance imaging (MRI) and targeted biopsies. The new results, now published in *The Lancet Oncology*, show that the addition of the Stockholm3 test, which was developed by researchers at Karolinska Institutet, can be an important complement. It is a blood test that uses an algorithm to analyse a combination of protein markers, genetic markers and clinical data.

"The availability of MRI in healthcare will be a limiting factor. We now show that a novel blood test as adjunct to MRI can reduce the number of MRIs performed by a third. Compared with traditional screening, overdiagnosis is reduced by as much as 69 percent. At the same time, the number of biopsies is halved, while we can find just as many clinically significant tumours," says Martin Eklund, associate professor at the Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, with joint responsibility for the STHLM3MRI study.

STHLM3MRI is a randomised study that was conducted between 2018 and 2021 with 12,750 male participants from Stockholm County. The participants provided an initial blood sample for PSA analysis and analysis using the new Stockholm3 test. Men with test results showing elevated PSA levels were then randomly selected for traditional biopsies or MRI. In the MRI group, biopsies were conducted strictly on suspected tumours identified by MRI.

"Separate use of the Stockholm3 test and MRI has previously been shown to be cost-effective. We have now analysed the cost-effectiveness when these tools are combined and will shortly report exciting results from that analysis," Tobias Nordström concludes.

The research was financed by the Swedish Cancer Society, the Swedish Research Council, the Swedish Research Council for Health, Working Life and Welfare, Karolinska Institutet, Hagstrandska Minnesfonden, Region Stockholm, the Swedish Order of Druids, the Åke Wiberg Foundation, the Swedish e-Science Research Center (SeRC) and Prostatacancerförbundet (the Prostate Cancer Association). Early validation was financed by EIT Health.

Henrik Grönberg, Martin Eklund and Tobias Nordström are partners of the company A3P Biomedical AB, which holds the development rights of the Stockholm3 test.

Story Source:

Materials provided by **Karolinska Institutet**. *Note: Content may be edited for style and length.*

medpagetoday.com

Novel Blood-Based Test Could Bolster MRI-Based Prostate Cancer Screening

by Mike Bassett, Staff Writer, MedPage Today August 13, 2021

Urology > Prostate Cancer

— Combination reduced over-detection, but still found clinically significant tumors in Swedish study

Addition of a novel blood test to MRI-targeted biopsy in prostate cancer screening decreased over-

detection while maintaining the ability to detect clinically significant cancer, Swedish researchers reported.

They found that use of the test -- called Stockholm3 -- in a screening setting where MRI and targeted biopsies were used, performed at least as well as a traditional strategy of using prostate-specific antigen (PSA) measurements and systematic biopsies. The number of MRI procedures was reduced by 36% and the number of men referred for biopsy was reduced by 8%, reported Tobias Nordström, MD, PhD, of Karolinska Institutet in Stockholm, and colleagues.

"The ultimate aim of any screening program is to decrease mortality and harm among participants. Although our study does not include prostate cancer mortality endpoints, we argue that, based on previous evidence of a mortality benefit from prostate cancer screening using PSA and systematic biopsies, it is plausible that maintained detection of significant cancer will translate to future mortality benefits," the researchers wrote in the study online in *Lancet Oncology*.

They also found that when compared with a screening approach of PSA combined with standard transrectal ultrasound-guided biopsies, Stockholm3 testing followed by MRI-targeted biopsy improved the detection of clinically significant prostate cancers and reduced the detection of low-grade cancers.

While the availability of MRI will be a limiting factor, "we now show that a novel blood test as adjunct to MRI can reduce the number of MRIs performed by a third," said co-author Martin Eklund, PhD, also of the Karolinska Institute, in a statement.

"Compared with the traditional PSA-based diagnostic strategy, we show that the novel strategy of combining the Stockholm3 test and an MRI-targeted biopsy approach is associated with a 69% reduction in the rate of overdetection, while maintaining the sensitivity to detect clinically significant prostate cancer," the researchers wrote. "This finding provides a viable option for prostate cancer screening, in which the mortality benefit of prostate cancer screening is maintained and the overdetection decreased compared with a traditional screening strategy (using PSA and systematic biopsies)."

In an accompanying commentary, Caroline Moore, MD, of University College London, called the study "an important step towards smarter screening for prostate cancer."

The blood-based Stockholm3 test uses an algorithm to analyze clinical data (age and previous biopsy status), and a combination of genetic and protein markers (including PSA) to yield a percentage risk of clinically significant prostate cancer.

In a prior study, the test was shown to reduce benign biopsies by 44% and the detection of clinically insignificant cancers by 17%. At the same time, Nordström and colleagues pointed out, studies (such as PRECISION) have shown that using MRI before biopsy can reduce overdetection and increase detection of clinically significant prostate cancers.

The new study was a prospective, population-based, randomized, open-label non-inferiority trial that included 12,750 men ages 50 to 74. Of these, 2,293 were considered to have an elevated risk of prostate cancer (i.e., a PSA level ≥3 ng/mL or a Stockholm3 score ≥11) were randomized 2:3 to either the standard group (systematic prostate biopsies) or the experimental group (biparametric MRI followed by MRI-targeted and systematic biopsy in MRI-positive men).

The primary outcome was detection of clinically significant cancer (Gleason score of 3+4 or higher). Secondary outcomes included the proportion of men with clinically insignificant prostate cancer (defined as a Gleason score of 3+3), and the number of any prostate MRI and biopsy procedures performed.

In the intention-to-treat analysis, Stockholm3 score ≥11 detected more clinically significant prostate cancers than did PSA (227 vs 192; relative proportion [RP] 1.18, 95% CI 1.09-1.28). However, compared with a PSA of 3 ng/mL or higher, Stockholm3 ≥11 was also associated with detection of a similar number of low-grade prostate cancers (50 vs 41; RP 1.22, 95% CI 0.96-1.55) and a greater number of MRIs and biopsy procedures.

Use of Stockholm3 ≥15 resulted in fewer MRI procedures performed compared with PSA (545 vs 846; RP 0.64, 95% CI 0.55-0.82), the researchers reported, adding that the number of biopsy procedures performed was also lower, although not significantly different (311 vs 338, respectively).

The investigators also compared the performance of two diagnostic workflows for the entire cohort of 12,750 men, and found that Stockholm3 combined with MRI-targeted and systematic biopsy (7,609 men) detected clinically significant cancers in 3% of that group compared with 2.1% of the men tested with PSA plus standard biopsy (RP 1.44, 95% CI 1.15-1.81).

Stockholm3 ≥11 plus MRI also detected fewer low-grade cancers (0.7% vs 1.4%, RP 0.46, 95% CI 0.32-0.66),

and led to fewer biopsy procedures than did the PSA plus standard biopsy workflow.

Study limitations, the researchers said, included that as with all prostate cancer research, there is no universal definition of clinically significant prostate cancer; that there were no subsequent screening rounds; that not all invited men participated in the trial and some participants did not undergo the assigned intervention; and that despite the use of prostate biopsy procedures, the true disease status of participants was unknown.

Moore pointed out in her commentary that in screening programs in general, getting high enough uptake of the invitation to participate can be problematic. Nordström and colleagues reported a 26% uptake of the screening invitation, compared with 32% in the European Randomized Study of Screening for Prostate Cancer in The Netherlands (which eventually increased to 42%).

She suggested that a combination of interventions may help increase participation, particularly if the need for digital rectal examination is eliminated.

Another challenge is implementing high-quality MRI during screening: "This diagnostic strategy is markedly more challenging than standard transrectal ultrasound-guided biopsy," Moore wrote. "Implementation requires a coordinated approach across multiple departments, including imaging, urology, and histopathology, and might include a formal quality assurance and quality control program, with accreditation by professional bodies."

Disclosures

The study was funded by the Swedish Cancer Society (Cancerfonden), the Swedish Research Council (Vetenskapsrådet), the Swedish Research Council for Health Working Life and Welfare (FORTE), the Strategic Research Programme on Cancer (StratCan), Hagstrandska Minnesfonden, Region Stockholm, Svenska Druidorden, Åke Wibergs Stiftelse, the Swedish e-Science Research Center, the Karolinska Institutet, and Prostatacancerförbundet.

Eklund, Nordström, and another co-author, Henrik Grönberg, are partners in A3P Biomedical AB, which holds the development rights for the Stockholm3 test. Eklund and Grönberg have four pending prostate cancer diagnostic-related patents. The Karolinska Institutet collaborates with A3P Biomedical in developing the technology for the Stockholm3 test.

Moore reports grants from SpectraCure, the Medical Research Council, Movember, Prostate Cancer UK, the National Institute for Health Research, Cancer Research UK, and the EAU Research Foundation, and financial relationships with Sonablate, Astellas, and Janssen.

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Researchers pinpoint how PARP inhibitors combat BRCA1 and BRCA2 tumor cells

A team of Massachusetts General Hospital (MGH) researchers has discovered how an important class of anti-cancer drugs called PARP inhibitors works, a finding that could help improve treatment and prolong survival for patients with breast cancer and other malignancies.

PARP (poly[ADP-ribose] polymerase) inhibitors such as olaparib (Lynparza), rucaparib (Rubraca) and niraparib (Zejula) are used to treat patients with cancers of the breast, ovaries, prostate and pancreas, and are particularly effective against tumors carrying mutations in the *BRCA1* and *BRCA2* tumor suppressor genes.

PARP inhibitors, like many other classes of anti-cancer drugs, are known to work by interfering with the ability of cancer cells to repair themselves after experiencing damage to their DNA, but exactly how PARP inhibitors selectively kill cancer cells was poorly understood.

But as Zou Lee, PhD, and colleagues found, PARP inhibitors work by creating gaps in tumor-cell DNA that remain present through multiple cell cycles (the process by which cells replicate: grow, divide, repeat). They also found that *BRCA1/2* mutant cancer cells cannot respond to these gaps and therefore fail to repair properly, leading to the death of tumor cells.

"These findings provide a mechanistic explanation of the selectivity of PARP inhibitors toward cancer cells, and they also offer new opportunities to improve the use of PARP inhibitors in the clinic," says Zou, scientific co-director of the Mass General Cancer Center and the Center for Cancer Research, and professor of Pathology at Harvard Medical School.

"This work finally explains why PARP inhibitors kill BRCA-mutant cells selectively," he adds.

The research findings by Zou and colleagues Antoine Simoneau, PhD, and Rosalinda Xiong, both from the MGH Department of Pathology, are published in the journal *Genes and Development*.

The discovery has the potential to help clinical researchers better identify cells that are sensitive to PARP inhibitors, and to identify potential mechanisms by which cancer cells may develop resistance to PARP inhibitors, Zou says.

"We can actually monitor BRCA-mutant cells during PARP inhibitor therapy, and then watch them if they change during the therapy, and then we can predict when they will become resistant to the drugs," he explains.

Zou and colleagues propose development of a clinical test to determine whether BRCA-mutant cells are slowing in growth in the second cell cycle during PARP inhibitor treatment.

"We think that this slowdown is the reason for the development of resistance to PARP inhibitors. If the cells don't slow down, they should be sensitive to the drugs, but if they do slow down they may be developing resistance," he says.

Because the ability of BRCA-mutant cells to slow down and thus develop resistance to PARP inhibitors is dependent on a master checkpoint protein (kinase) labeled ATR, it should be possible to combine PARP inhibitors with another class of drugs in development that are designed to inhibit ATR, thereby preventing resistance to PARP inhibitors.

The work is supported by grants to Zou from the National Institutes of Health.

Story Source:

Materials provided by **Massachusetts General Hospital**. *Note: Content may be edited for style and length.*

Timing of initiation of ADT for men with biochemical progression after first-line surgery

prostatecancerinfolink.net

Early use of androgen deprivation therapy (ADT) in many men with progressive prostate cancer is ***not*** necessarily the best decision (for a number of possible reasons). The benefits of such early ADT — in terms of metastasis-free survival (MFS) and/or overall survival (OS) — have never been categorically proven to outweigh the risks of the well-understood side effects.

A newly published paper by Marshall et al. — from Johns Hopkins (in Baltimore, MD) and the Center for Prostate Disease Research at the Uniformed Services University of Health Sciences (in Washington, DC) has now provided additional data supporting this premise for definable subsets of patients with a rising PSA after initial treatment.

What Marshall and her colleagues did was to conduct a retrospective analysis of prospectively collected data from 806 patients initially diagnosed with localized prostate cancer and treated with first-line surgery (a radical prostatectomy) at either Johns Hopkins or at Walter Read National Military Medical Center between 1983 and 2014. All 806 of these patients met the following additional criteria:

They developed biochemically recurrent prostate cancer post-surgery with a PSA doubling time of < 10 months.

They could also have been treated with salvage radiotherapy ***alone*** (but not salvage radiotherapy together with ADT).

They received no other prostate cancer-specific treatment until they showed clear evidence of metastatic disease.

The following information is also relevant:

Average (median) age of the patients was 61 years at time of initial surgery.

Of the 806 patients

132 (16 percent) were African American

639 (79 percent) were Caucasian

35 (5 percent) were of other or of unknown ethnicity

Pathological (post-surgical) Gleason scores for 746 of the 806 patients were

Gleason 6 or less in 124/746 (17 percent)

Gleason 7 in 403/746 (54 percent)

Gleason 8, 9 or 10 in 219/746 (29 percent)

Pathological T stages for 786 of the 806 patients were

T2 for 247/786 (31 percent)

T3/4 for 539/786 (66 percent)

Positive surgical margins were evident among 304/799 (38 percent) of the 806 patients.

Negative surgical margins were observed among 495/799 (62 percent) of the 806 patients.

304/ 806 patients (38 percent) had died by the time of data analysis (which is assumed to have been in about 2018 or 2019, but this is not explicitly stated in the paper)

At time of initial onset of metastatic disease, all patients received initial systemic treatment with ADT alone.

Based on these data, Marshall et al. were able to make the following determinations:

Average (median) time to onset of metastatic disease from time of initial surgery (metastasis-free survival or MFS) was

192 months (16 years) in men with a PSA doubling time of < 10 months

144 months (12 years) in men with a PSA doubling time of < 6 months

Average (median) overall survival (OS) from time of surgery was

204 months (17 years) in men with a PSA doubling time of < 10 months

166 months (nearly 14 years) in men with a PSA doubling time of < 6 months

In other words, a man of 65 years of age initially treated by radical prostatectomy who had a biochemical recurrence post-surgery with a PSA doubling time of < 10 months would — on average — reach 81 years of age before showing any sign of metastasis.

Other findings included the following:

African America patients were significantly less likely to exhibit metastatic disease than Caucasian patients (hazard ratio [HR] = 0.5).

Time from initial surgery to biochemical recurrence correlated with risk for metastatic disease (HR = 0.5).

A PSA doubling time of < 0.6 months was significantly associated with greater risk for development of metastatic disease than a PSA doubling time of < 10 months (HR =3.2).

We would point out the following additional facts:

All of the patients in this cohort can be classified as high risk for one or more reasons.

All of the patients in this cohort were treated exclusively with systemic ADT as their first-line therapy once there was evidence of metastatic disease.

Assessment of evidence of metastatic disease in this patient cohort was limited to data from bonce scans and CT scans.

Few of these patients are likely to have received drugs like abiraterone acetate or enzalutamide after progressing on ADT, which may well have affected their overall survival.

Marshall et al. conclude as follows:

Men with biochemically recurrent prostate cancer, who defer hormone therapy until metastasis have overall survival that is quite long and the early initiation of continuous androgen deprivation for biochemical relapse, may not meaningfully improve overall survival.

An associated editorial commentary on this article (by David VanderWeele, MD, and Maha Hussain, MD) come to very similar conclusions.

Now we should be clear that there certainly are some patients who should ***not*** be advised to defer ADT until time of metastasis (probably including those with a PSA doubling time of < 3 months at time of recurrence). On the other hand, it is becoming increasingly evident that many men may be well advised to defer initiation of ADT for a considerable period of time if this seems reasonable, given the well-established side effects of ADT. The problem is that we still don't really know what is the "best" scenario for each definable subset of men who progress after first-line treatment for localized and locally advanced, clinically significant prostate cancer. Future data and the continuing evolution of "precision medicine" may be able to assist us in this arena.

Editorial note: *We would like to thank Catherine Handy Marshall, MD, for promptly providing us with a full-text copy of this article.*

Rethinking risk stratification for radiation therapy

prostatecancerinfolink.net

In 2016, we looked at the Candiolo risk stratification system for radiation therapy. To our knowledge, it

has not been prospectively validated or widely adopted. In the intervening 5 years, a number of things have changed:

Active surveillance (AS) has become the treatment of choice for many patients with low-risk prostate cancer, and for some with favorable intermediate-risk disease.

We have data from the first large randomized trial (ProtecT) of external beam radiation vs. surgery vs "active monitoring" — demonstrating 10-year oncological equivalence for favorable-risk patients.

Multiparametric MRI is increasingly used to find higher grade cancer. (We won't discuss whether this has been a net benefit, as Vickers et al. doubt.)

Multiparametric MRI has also been used for staging by some doctors.

Multiparametric MRI has been used to detect local recurrence.

Decipher and other genomic tests of biopsy tissue have been used to independently assess risk.

PSMA PET scans have recently been FDA approved by the FDA for unfavorable risk patients to rule out distant metastases.

PSMA PET and Axumin PET scans have been approved by the FDA to determine radiographic recurrence.

NCCN has added the distinction between favorable and unfavorable intermediate-risk disease, as described by Zumsteg et al.

The use of brachytherapy has declined.

Several new hormone therapies (abiraterone, enzalutamide, apalutamide, and darolutamide) have been approved for metastatic patients.

Prognostic vs Predictive Risk Stratification

There is a new staging system called "STAR CAP." It shows a patient's prognosis of dying in 5 years or 10 years from prostate cancer (prostate cancer-specific mortality or PCSM) after availing himself of whatever standard therapies he may have chosen. This was an enormous undertaking. The researchers looked at the records of 19,684 men with non-metastatic prostate cancer (those with positive pelvic lymph nodes were included) who were treated at 55 sites in the US, Canada, and Europe between January 1992 and December 2013. Treatment may have consisted of radiation of any kind (7,263 patients) or prostatectomy (12,421 patients). Any one patient may have also have had ADT and salvage therapy. He may have also had docetaxel (2004) and Provenge (2010) therapy; Xofigo was approved in May 2013, so some few may even have had this form of therapy too. Follow-up ended in December 2017. The patients were split equally into "training" and "validation" cohorts. Secondarily, they validated it using 125,575 men in the SEER database. It has also been independently validated in Europe for prostatectomy patients.

The research team used five risk factors (except for pelvic lymph nodes [N stage]) to assign points (similar to CAPRA and Candiolo, in the following groupings:

Age: ≤ 50, 51-70, 71+

T stage: T1, T2a,b, T2c/T3a, T3b/T4 (based on physical examination, not imaging)

N stage: N0. N1 (based on CT)- *note: only 22 patients were N1 in the training cohort*

Gleason score: 6, 3 + 4, 4 + 3, 4 + 4/3 + 5, 4 + 5, 5 + 3/5 + 4/5 + 5

Percent positive cores: ≤ 50 percent, 51-75 percent, 76-100 percent

PSA: ≤ 6, > 6-10, >10-20, > 20-50, > 50-200 ng/ml

It divides patients into nine risk groups (three low (IA-C), three intermediate (IIA-C), and three high (IIIA-C)) based on how likely they are to die of their prostate cancer after their therapies. Interested patients can use this handy nomogram.

Their system outperforms the AJCC prognostic stage groups (8th edition) or the NCCN system if they were used to predict prostate cancer mortality.

Their system is necessarily limited by the risk factors available in the large databases they used to train and validate their model. That means that there may be risk factors that are not accounted for, including:

Genomic risk

Percentage of Gleason pattern 4 in Gleason 3 + 4 = 7 (this may be important in determining prostatectomy risk and risk of staying on AS; it is often not reported on biopsies)

Multiparametric MRI for staging and tumor volume

PSA density and perineural invasion

Use of 5-ARIs (Proscar or Avodart)

Use of PSMA PET scans to better select patients for local therapy

The STAR CAP system is also limited by how prostate cancer mortality is ascertained. For example, if a man dies of a blood clot in his lungs, heart, or brain, was that because the cancer increases blood clots, or was that a competing cause of death?

Decision-making

For most patients with localized prostate cancer, their cancer is not likely to be lethal after well-done therapies, at least not for a long time. Patients who are correctly diagnosed with localized PCa and treated for it will usually die of something else — their prognosis is excellent. What patients want to know is which therapy gives them the best chance of a cure and what side effects they can reasonably expect — their ***predicted*** outcomes are more important than their ***prognosis***.

The wise advocate often counsels patients to try to stay in the present moment, and not be concerned with what may or may not happen down the line. The patient is rightly concerned with making the best treatment decision he can make given what he currently knows about his cancer. If his cancer progresses, there are potentially curative salvage therapies for both surgery and radiation. If his cancer progresses after salvage therapy, his cancer can often be managed with a variety of systemic therapies for many years. The list of systemic therapies is growing rapidly. It doesn't help the patient to know the percentage of patients who died in the past, given the therapies that were available then. (The STAR CAP cohort goes back to 1992!) The patient wants to know his odds of a given therapy working for him ***now*** — a predictive model.

A good example of such a predictive model is the Memorial Sloan-Kettering (MSK) nomogram for predicting prostatectomy outcomes. It is based on the outcomes of over 10,000 men and is continually updated. Like STAR CAP, CAPRA, and Candiolo, it includes patient age and percentage of positive cores, as risk factors. While it also provides 10-year and 15-year prostate cancer survival estimates (also, see this MSK nomogram that uses comorbidities and actuarial survival tables to calculate 10- and 15-year survival probabilities), it tells the patient what his probability for progression-free survival (PFS) is if he is like the average man with his risk characteristics who chooses prostatectomy as his treatment. They define "progression-free survival (PFS)" as a PSA of less than 0.05 ng/ml and no evidence of clinical recurrence. It also shows the probability of adverse pathology after prostatectomy.

I know of no such comparable nomogram for radiation therapies. What is needed is a large predictive model for each of the major types of radiation therapies: external beam radiation, brachytherapy monotherapy, and the combination of external beam radiation and brachytherapy. It also needs to include whether whole pelvic treatment and androgen deprivation therapy (and its duration) are used with the radiation to the prostate itself.

Building such a database is an enormous undertaking. No one institution has enough primary radiotherapy patients to create a reliable sample for all risk strata and for modern best practice. Unlike surgery, which has changed little in its effectiveness over time (even nerve-sparing surgery didn't change that), the effectiveness of radiation therapy changed a lot with dose escalation. Perhaps ASTRO or a multi-institutional consortium can create a registry to hold the data.

While patients making a treatment decision want to compare predictive outcomes across the treatments available to them, there are many reasons why such comparisons are difficult. The only valid way of comparing treatments is via a prospective randomized trial, like ProtecT. As we saw in the MSK nomogram, PFS or biochemical recurrence-free survival (bRFS) depends on the definition of PSA recurrence. MSK uses a PSA of 0.05 ng/ml as their definition of PSA progression after prostatectomy. Radiation therapies define biochemical recurrence as "nadir + 2.0 ng/ml." It is impossible to say if these are comparable benchmarks. Perhaps future definitions of local recurrence after radiotherapy will include detection by mpMRI or one of the PSMA radioindicators that are not urinarily excreted that are in trials now.

The patient also needs to understand his likelihood of incurring the side effects associated with each treatment. ProtecT again provides the only direct comparison, but that is limited to prostatectomy, external beam radiation, and active monitoring. We know that side effects may increase with brachy boost therapy, use of ADT, and whole pelvic treatment.

Case Examples

(1) ***A 65-year-old man in good health***, recently diagnosed with

Gleason 4+3, 7 cores out of 12 were positive

Clinical stage T1c (nothing felt by DRE)

Bone scan/CT negative

PSA of 7.5 ng/ml

Here's how the various staging systems categorize him:

STAR CAP: Stage IIB (IIA-C is intermediate risk)

5-year PCS =1.1 percent; 10-year PCSM = 4.4 percent

CAPRA Score: 6 — high risk (6-10 is high risk)

AJCC Prognostic Stage Group: IIC (IIA-C is intermediate risk)

NCCN: Unfavorable intermediate risk

Recommended treatment options: RP + PLND, EBRT + ADT (4-6 months), brachy boost therapy ± ADT (4-6 months)

Candiolo score: 162 (intermediate range is 117-193)

5-year bPFS= 80 percent; 10-year bPFS=60%

MSK pre-op nomogram:

10-year and 15-year PCSM = 1 percent

5-year PFS = 5 8 percent; 10-year PFS = 42 percent

Organ confined = 34 percent; EPE=63 percent; N1=14 percent; SVI=16 percent

Multi-institutional SBRT consortium (Kishan et al.) reported 7-year bRFS of 85 percent for unfavorable intermediate-risk (NCCN)

10-year bRFS was reported (Abugharib et al.) to be 92 percent for brachy boost therapy among unfavorable intermediate-risk (NCCN) with relatively high late-term urinary toxicity

5-year bRFS was reported (Kittel et al.) to be 81 percent for low dose rate brachytherapy monotherapy among unfavorable intermediate-risk (NCCN)

So brachy boost therapy is far more successful than surgery for unfavorable intermediate-risk patients. SBRT monotherapy may be better than either EBRT or LDR brachytherapy monotherapy because of the higher biologically effective dose.

(2) ***A 55-year-old man in good health***, diagnosed with

Gleason score 3 + 4 = 7 (10 percent pattern 4)

3/12 positive biopsy cores

Perineural invasion

Clinical stage T1c

PSA 4.5 ng/ml

Here's how the various staging systems categorize him:

STAR CAP: Stage IC (1A-C is low risk)

5-year PCSM = 0.5 percent; 10-year PCSM = 2 percent

CAPRA score: 2 (0-2 is low risk)

AJCC Prognostic Stage Group: IIB (IIA-C is intermediate risk)

NCCN: favorable intermediate risk

Recommended management options: AS, EBRT, brachytherapy monotherapy, RP ± PLND

Candiolo score: 86 (low risk 57-116)

5-year bPFS = 85 percent; 10-year bPFS =74 percent

MSK pre-op nomogram: 10-year and 15-year PCSM = 1 percent

5-year PFS = 90 percent; 10-year PFS = 83 percent

Organ confined= 77 percent, EPE=21 percent, N1=2 percent, SVI=2 percent

Multi-institutional SBRT consortium (Kishan et al.) reported 7-year bRFS of 91 percent for favorable intermediate-risk (NCCN)

5-year bRFS was reported (Kittel et al.) to be 90 percent for low dose rate brachytherapy

monotherapy among favorable intermediate-risk (NCCN)

So, all therapies for favorable intermediate-risk patients have "success" rates in the same range (85-91 percent at ~ 5 years), independent of the chosen therapy. This is consistent with what we saw in the ProtecT trial. However, he isn't a good candidate for AS because of his biopsy-detected perineural invasion (see this link).

(3) ***A 72-year-old man with a heart stent but otherwise healthy***, diagnosed with

Gleason score 4 + 5 = 9

8/12 positive biopsy cores

Clinical stage T3a (felt bulge)

PSA 15 ng/ml, neg. bone scan/CT

Here's how the various staging systems categorize this patient:

STAR CAP: Stage IIIB (IIIA-C is high risk)

5-year PCSM = 6 percent; 10-year PCSM = 21.2 percent

CAPRA score: 8 (6-10 is high risk)

AJCC Prognostic Stage Group: IIIC (IIIA-C is high risk)

NCCN: high/very-high risk (two high-risk features)

Recommended treatment options: EBRT + ADT (1.5-3 yrs), brachy boost therapy + ADT (1-3 yrs), RP + PLND

Candiolo score: 256 (high risk 57-116)

5-year bPFS= 67 percent; 10-year bPFS= 43 percent

MSK pre-op nomogram: 10-year PCSM = 4 percent; 15-year PCSM = 10 percent

5-year PFS =12 percent; 10-year PFS = 7 percent

Organ confined= 1 percent, EPE=99 percent, N1 = 71 percent, SVI = 79 percent

Kishan et al. reported that for Gleason 9/10 patients at UCLA and Fox Chase, 10-year bRFS was 70 percent for brachy boost therapy, 60 percent for EBRT, and 16 percent for prostatectomy. While surgery by itself is inferior to radiation therapies for these very high-risk patients, surgery+ ***salvage*** RT has success rates that seem to be closer.

In this case, age and the heart stent probably rule out surgery. His expected lifespan argues against watchful waiting. Brachy boost therapy and 18 months of adjuvant ADT (with cardiologist agreement) is a preferred option. Pelvic lymph nodes should be treated because of the high risk of pelvic lymph node invasion. If possible, a PSMA PET scan should be used to rule out distant metastases.

For patient decision-making, prognostic risk groups like STAR CAP, AJCC, and CAPRA are useless. The NCCN risk groups were based on prostatectomy bRFS. Counts of positive cores already used in the NCCN schema help differentiate very low-risk from low-risk, favorable intermediate-risk from unfavorable intermediate-risk, and high-risk from very high-risk patients. It is not clear that age is a risk factor that determines the oncological success of any therapy (although it undoubtedly affects toxicity). As we can see from these prototype cases, we are more needful of a risk stratification system/nomograms for the various radiation therapies similar to the MSK pre-op nomogram.

Editorial note: *This commentary was written by Allen Edel for The "New" Prostate Cancer InfoLink.*

Filed under: Diagnosis, Management, Risk, Treatment | Tagged: nomogram. radiation, predictive, prognosis, risk, stratification, therapy |

On the Lighter Side