Informed Prostate Cancer Support Group Inc.
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February 2021 NEWSLETTER

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Friday, February 19,

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Saturday, February 20th, 2021 IPCSG - Live-Stream Event, 10:00am PT

Active Surveillance 2021 - Have we come a long way Baby? Dr. Paul Dato is a urologist and currently serves as Director for Medical Quality and Director of the Prostate Cancer Center for Genesis healthcare. Dr. Dato will be discussing Active Surveillance, what it is and where we are at today with utilizing this form of Prostate Cancer monitoring.

- 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

January 2021 Informed Prostate Cancer Support Group Meeting

Summary by Bill Lewis

1. Introduction to Radiation Therapy in Prostate Cancer – Terminology and Approaches.
Dr. A.J. Mundt, UCSD.

Dr. Mundt began with an overview of prostate cancer (PCa) treatments. Surgery is now often done by robotic assistance. Hormone therapy includes ADT (androgen deprivation therapy) and chemotherapies. Radiation treatments can be given externally by photon or proton beams, or internally by "brachytherapy" – permanent or temporary introduction of radioactive "seeds" into the prostate. When radiation is given without surgery, it is called definitive treatment. It is called adjuvant treatment if it follows surgery.

When definitive external beam radiation treatment (EBRT) is given – either by photons (X-rays) or protons – it can be given in different numbers of doses, referred to as fractionation. Conventional fractionation involves small daily doses over about 8 weeks. Beginning about 5 years ago, "hypofractionation" accelerates the treatment with moderate daily doses over 5-6 weeks. And SBRT (stereotactic body radiation therapy) gives high doses daily over one week or less. The choice is tailored to the patient.

In some cases, EBRT (protons or photons, with conventional fractionation) is combined with brachytherapy (permanent or temporary seeds), giving better cancer control or cure. Definitive radiation therapy is also often combined with a period of hormone therapy to good effect.

Adjuvant radiation therapy is always given by EBRT (photons or protons, with only conventional fractionation used up until now). Brachytherapy cannot be used, since there is no longer a prostate present in which to intro-

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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.

From the Editor

Due to COVID-19, no in-person meetings will be held until further notice. 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.

We will continue to post and distribute the newsletter in the interim. In order to include more articles of interest in this issue, we have included extra pages in the web distributed version of the newsletter. The mail version is limited to ten pages.. The January edition of the newsletter is a little different. Since there was no meeting last month, we provide a review of what was covered in all 11 meetings last year to help new members in particular in finding issues which are of interest.

Articles of Interest

- Oncologic outcome of radical prostatectomy versus radiotherapy as primary treatment for high and very high risk localized prostate cancer - Emam - 2021 - The Prostate - Wiley Online Library
- CCR Score Can Guide Treatment After Radiation in Prostate Cancer
- Another new urine test for risk of prostate cancer | THE "NEW" PROSTATE CANCER INFOLINK
- AI tool shows promise in predicting biochemical recurrence in prostate cancer | Urology Times
- Improving PET scans are good news for doctors and patients alike - Harvard Health Blog - Harvard Health Publishing

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** Lyle LaRosh @ 619-892-3888; or **Director** Gene Van Vleet @ 619-890-8447.

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duce seeds.

Salvage RT (radiation therapy) is adjuvant RT given to patients with a rising PSA (which indicates that not all of the cancer was removed by the surgery). Salvage RT may be combined with hormone therapy.

Dr. Mundt also provided information about an improved machine for delivering radiation treatments, called ETHOS, from Varian. It is able to not only scan for daily variation in the position of the prostate (due to gas in the rectum or urine in the bladder) during a series of treatments, it can also adjust for variations in the shape of the prostate and seminal vesicles. Whereas current machines can adjust for position, they can't routinely adjust to changes in shape. Current EBRT has to add "margins" to ensure treatment despite these changes. This increases the dose that the bladder and rectum receive, leading to side effects. The new ETHOS machine, which will be installed at UCSD in February 2021, will be able to do rapid adaptive RT calculations in 3-5 minutes, with total treatment time under ten minutes. Another advancement is the use of artificial intelligence (AI) to generate treatment plans in a few minutes versus over several days, which will significantly reduce the time interval between planning and first treatment – theoretically allowing next-day start dates.

2. Radiation therapy for Oligometastatic Cancer: A new paradigm and opportunities to combine with Immunotherapy. Dr. Andrew Sharabi.

-- Overview and Definitions of Oligometastatic Disease and Stereotactic Body Radiation therapy (SBRT)

-- Review of randomized trials demonstrating improved Overall Survival with SBRT

-- Highlight of Research and Clinical Trials with Immunotherapy at UCSD – there are open trials at UCSD using immunotherapy with SBRT in patients with oligometastatic or widely metastatic disease.

-- See the video for additional details.

3. Tracking prostate cancer response to radiation and ADT with quantitative diffusion MRI (a new clinical trial at UC San Diego). Dr. Tyler M. Seibert.

-- Focus of a current trial is on high-risk, localized prostate cancer, and on answering patient questions as to whether their treatment (typically RT + ADT) is working, and physician questions as to which patients might benefit from a higher radiation dose, or a second-tier hormone therapy drug (despite more side effects than standard ADT).

-- Apparent diffusion coefficient (ADC) of water in tumors is lower than elsewhere, but it isn't a sufficiently reliable indicator after treatment(s), because extracellular diffusion ("hindered diffusion") typically goes down due to scarring and atrophy, counterbalancing the rise in "restricted diffusion" within cells as those cells die due to treatment.

-- Restriction Spectrum Imaging (RSI) developed at UCSD is able to "look at" the "restricted" intracellular water, and has been correlated with tissue cellularity and cancer grade. This advantage over ADC applies both before and after treatment of prostate cancer.

-- A clinical trial has just opened for high risk, localized prostate cancer for which RT and ADT are planned.

-- UCSD has also developed a genetic test called the Polygenic Hazard Score (PHS), which is predictive of the age of onset of aggressive prostate cancer. It may guide decisions as to who should be screened (e.g., PSA test) and starting at what age. Based on 100,000 men, the test shows a 20-year difference in the need for PSA or other screening tests, depending on the individual's genetic makeup. A subsequent validation in 80,000 men showed great value in prediction for European and Asian men, but less in African men – until the parameters were adjusted. More data is needed, so data is being collected locally, using a spit sample, of men who have participated in any UCSD imaging trial, or who are of non-European ancestry. Contact kcuervo or croneil @health.ucsd.edu if you are willing to participate.

4. Adaptive Radiotherapy for Prostate Cancer. Dr. Brent Rose.

Recent advances in technology now allow much more precise targeting of the prostate vs. the past. Now we are about to be able to adjust the radiation targeting plan every day (to account for shifting of the prostate due to changes in the fullness of the rectum and/or bladder) using artificial intelligence and machine learning in the ETHOS platform. This is Varian technology that UCSD and other groups helped to develop. The machine is being installed here in February, one of the first few centers to have it. It also helps to precisely target nearby lymph nodes.

5. Introduction to Intensity-Modulated Proton Therapy - 2021 Update -- Carl J. Rossi, Jr., MD Medical Director, California Protons Cancer Treatment Center, San Diego, CA

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A brief history of proton therapy and X-ray therapy was given. They have followed a similar development path. X-rays and naturally occurring radioactivity were discovered in 1895-96. The first patients were treated with X-rays in 1896! MD's observed that these new rays caused skin redness/breakdown, and theorized that they could do the same to cancer. Knowing nothing of the dangers of radiation, hundreds of physicians died from the effects of administering radiotherapy in the "Early Days."

All radiation kills cells by damaging DNA; this damage prevents cellular replication and results in cell death. In most cases death is NOT immediate – it can take months to years! (That's why PSA does not drop to zero immediately following radiotherapy). All cells can be killed by radiation, but the needed dose varies. In general, malignant cells are less able to repair DNA damage -- which means they can be killed by radiation doses which will not kill their healthy, normal counterparts. Although controversial, at this time international regulatory agencies feel that there is no "Threshold Dose" below which damage cannot and does not occur, hence the "ALARA" principle (as low as reasonably achievable) when using radiation as a diagnostic and therapeutic modality.

All advances in radiation therapy technology since 1896 have been stimulated by the desire to LIMIT radiation dose to normal tissue while INCREASING dose to the target. This is true of:

IMRT and other forms of external beam therapy with photons (X-rays or Gamma rays)

Protons

Brachytherapy (temporary use or permanent implants of radioactive "seeds")

Radioimmunotherapy (a radioactive element carried by a protein or other molecule)

We understand the physics of radiation therapy far better than we understand the basic radiation biology; hence R & D has been focused on methods which exploit physics as opposed to radiation biology.

IMRT is a version of X-Ray therapy in which the radiation dose delivery's intensity is modulated to spare normal tissue while increasing the dose to the target. It requires a 3-D reconstruction of the target area (typically based on CT) and massive computer support to plan and deliver treatment. "Cyberknife," "Tru-Beam," "VMAT" (volumetric arc treatment) and "TomoTherapy" are all variations of IMRT and all employ x-rays to deliver treatment. IMRT was introduced into clinical radiation oncology in the early 2000's, largely as a modification of existing x-ray therapy devices. IMRT was NOT tested in any Phase III Randomized Trial before widespread implementation; it was embraced because of superior physics.

The dose bath received by surrounding tissues is substantial, but has been decreased over time, by 3DCRT (conformal radiation therapy), by IMRT, and even more by VMAT. IMRT has become the de facto standard of care for external beam treatment of prostate cancer -- not based on Phase III data (there is none) but because of a) physics vs. non-modulated protocols and b) widespread availability. Proton therapy can be given with less dose to surrounding tissues vs IMRT, especially when the target area is large and irregular in shape.

Protons have superior physics (because they stop instead of passing all the way through), but far inferior availability, largely due to cost and complexity of facilities. Protons will continue to fall under intense scrutiny and restricted applicability until it is shown that there is a demonstrable clinical benefit to justify the increased cost and/or the cost of proton therapy can approximate IMRT.

A key property of protons was discovered in 1903 by William H. Bragg, who shot helium ions (pairs of protons) into a tank of water, finding that that they gave up most of their energy as they stopped at a certain point in traveling through this somewhat-resistant medium. The so-called "Bragg Peak" is a burst of energy released into the water (as the ions stop) at a distance from the source determined by the experimental setup. Robert R. Wilson proposed in 1946 that "fast protons" could be used for therapy, and the first patient was treated in 1954 (using a research cyclotron to accelerate the protons), followed by many others likewise, and finally leading to the first purpose-built "clinical proton treatment center" in 1988, at Loma Linda.

The California Protons Treatment Center has five treatment rooms in 100,000 square feet. Now, hospitals can opt for a single-room center that fits the area of a tennis court, and costs only about $20-25 million. This is a huge cost reduction that is allowing many more centers to be built around the country, and is making proton therapy more affordable and available.

Equipment and software advances now permit the use of "pencil-beam scanning," which is analogous to 3-D printing. The dose goes very precisely into the target structure, as the scanning beam is directed by magnets, giving a dose layer by layer (each layer only 1 mm thick!) as the protons stop at a pre-determined depth, in a

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beam that is only 3-5 mm in diameter. The depth and dose are computer-controlled, and daily adjustments can be made as desired and appropriate.

There are now 37 operational proton treatment centers in the USA, with more than 18 of various sizes under construction or in planning. Most either have or are retrofitting pencil-beam scanning delivery systems. Construction can be done within 24 months from groundbreaking to first patient treatment.

For imaging/targeting, CT and MRI are complementary. CT is good at showing bone anatomy and for calculating proton stopping power. MRI shows internal anatomy in the prostate, and delineates gross areas of disease, as well as delineating structures to avoid: the neurovascular bundles, and the penile bulb. Now PSMA scans are starting to be available to further help identify tumor locations.

See the video and slides for impressive pictures of how well the dose with proton treatment spares the surrounding tissues, compared to X-ray treatments.

Recent publications: A University of Florida study showed that patients with low or intermediate risk prostate cancer treated with protons had lower biochemical recurrence rates than others treated with IMRT, despite the fact that ADT was used more frequently and for longer duration in the IMRT patients. Also, toxicity (to the rectum or bladder) was significantly lower in the proton therapy patients, despite their being given a higher median dose. A study at Northwestern University showed that 5-year overall survival of intermediate-risk patients was 93.6% for proton treatment, and 87.9% for IMRT patients. The difference was explained by an increase in "secondary malignancies" beginning to appear after three years, with the 5-year rate being 6% vs. 10.6%, respectively, especially in pelvic malignancies and leukemias. This is likely due to the protons stopping at target, vs. X-rays passing clear through the body.

A Proton Collaborative Group trial compared Protons vs. IMRT in locally-advanced prostate cancer. Patients who received pelvic radiation therapy using PBT (proton beam therapy) experienced significantly less acute GI toxicity. The risk of a second cancer type occurring in a patient after radiation treatment(s) was only one-fifth as high for PBT vs. IMRT or 3-dimensional conformal radiation therapy for non-metastatic prostate cancer, according to a report in *Cancer* in 2020, based on records of patients from 2004 to 2019. However, the overall rate of a second malignancy is very low.

Conclusions:

Particle Therapy is no longer "boutique", equipment is available from numerous manufacturers and becoming less expensive.

This will, in fashion analogous to the introduction of Cobalt 60 and Linac (linear particle accelerator), lead to increased utilization and optimization.

Published data demonstrates less toxicity with protons as compared to IMRT:
- Lower incidence of GI toxicity.
- Less bone marrow suppression.
- Less testosterone suppression.
- Lower incidence of radiation-induced second cancers

We ultimately need to get to the point that the cost to the payor of delivering particle therapy is similar to cost of x-ray treatment.

Questions:

Is the endorectal coil or rectal rod better? The endorectal coil is no longer used by most MRI scan practitioners, because it's not needed with a 3T magnet.

Can radiation cause some pain? About 25-30% of patients may have a short pain flare, but mainly radiation is used to reduce/eliminate bone pain.

Is it too soon to test PSA two weeks after HDR brachytherapy? Such an early test is likely to be "unreliable." Dr. Seibert tests after 3 months, but the PSA is likely to continue to decline over years, so there's no urgency to test. After surgery, meaningful PSA results may be obtained after a few weeks or a month. After radiation, it takes several tests over an interval of time to develop a good picture of PSA behavior.

Before a first biopsy, would you recommend an mpMRI or PSMA test, for a patient with a rising PSA? There is solid evidence for doing the MRI first. It's "standard of care" in Europe, and is becoming such in the US, but insurance doesn't yet widely cover it. It's excellent for indicating where to target the biopsy needles, and in some cases may suggest a biopsy is not needed. PSMA is FDA approved, but not for pre-biopsy scans, and is anyway not yet covered by insurance. You would need to find a research group willing to do such a scan on an experimental basis. It's not likely to be any more helpful than the MRI.

What dose of daily radiation is used in the ETHOS technique? Could be 2 grey per day for 7-8 weeks, or could be used for faster treatments, all the way to the SBRT approach, where 7-8 grey daily is given for five

days.

How high does the PSA need to be, to use the MSI MRI technique, particularly after prostatectomy? Below 0.5 would be hit or miss, but above that, there would be reasonable hope. Comparisons are being made vs. PSMA, but that also doesn't give good diagnostics below 0.5.

What about Foundation One liquid biopsy? Such tests can identify genetic alterations, and help to provide targets for new therapies. UCSD has a large database in cooperation with Foundation One. Dr. Rana McKay and Dr. Sandeep Patel are experts in this and immunotherapies at UCSD. Trials involve Cabazanthamid, PSMA bispecific antibody and a CAR-Tcell therapy targeting PSMA.

Is there additional radiation associated with the ETHOS approach? Daily pre-scans use only a tiny bit of radiation, much less than a normal CT scan or the daily dose.

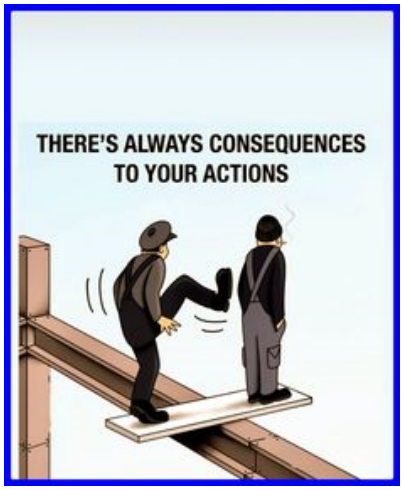
RSI-MRI studies are currently available for localized, not-yet treated disease, and for metastatic disease, or suspected metastatic disease (high PSA) after prostatectomy (with scans before & after treatment). Contact Dr. Seibert at UCSD (tseibert@healh.ucsd.edu) for further information and enrollment.

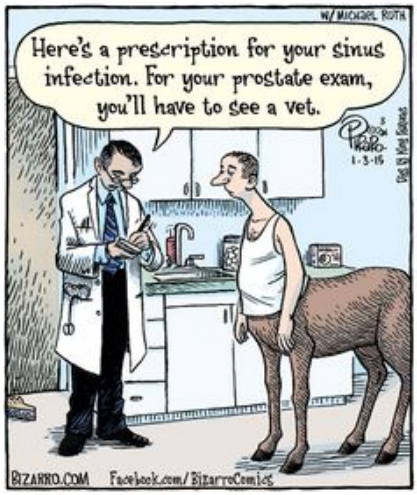
Do the scan techniques discussed apply well to other types of cancer? Yes, almost any solid tumor. And note that RSI-MRI would be able to "see" very advanced prostate cancer that has become de-differentiated, and is not producing PSMA.

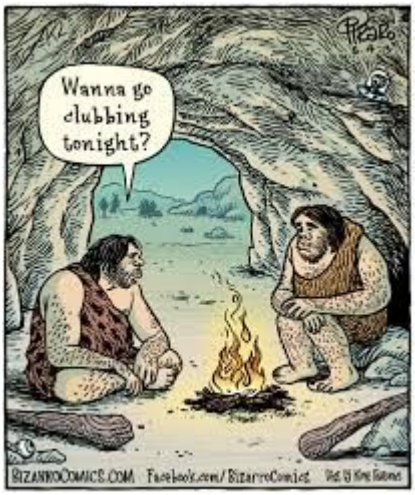
We recommend that you watch the video online for more definitive information about the talks and slides: https://www.youtube.com/watch?v=EPG2OoU0WqQ&feature=youtu.be

A dvd of the talks and Dr. Rossi's slides will be available for purchase from the IPCSG next month.

On The Lighter Side







"The guy on YouTube makes this look so danged easy."

Articles of Interest

Oncologic outcome of radical prostatectomy versus radiotherapy as primary treatment for high and very high risk localized prostate cancer - Emam - 2021 - The Prostate - Wiley Online Library

onlinelibrary.wiley.com

Ahmed Emam MD, PhD
James L. Mohler MD

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First published: 20 January 2021

Abstract

Objective

To compare the oncologic outcomes of radical prostatectomy (RP) versus external beam radiotherapy (EBRT) ± androgen deprivation therapy for primary treatment of high risk localized prostate cancer (CaP).

Methods

We retrospectively reviewed a prospectively-populated database for cases who underwent primary treatment for high risk localized CaP, had more than 2 years follow-up, and were treated since 2006. A total of 335 cases were studied of whom 291 underwent RP and 44 underwent EBRT. Clinical characteristics, biochemical progression-free survival (BPFS), metastasis-free survival (MFS), cancer-specific survival (CSS) and overall survival (OS) were compared.

Results

EBRT cases were older ($p < .01$; mean 71 years vs. 61 years) and had longer PSA doubling time (PSADT) ($p = .03$; median 4.8 years vs. 3.5 years) than RP. Race, pretreatment PSA and biopsy Gleason score were similar. Median follow-up was 5.1 (range: 2.3–12.8) years for RP versus 3.3 (range: 2–12.4) years for EBRT. Three- and 5-year BPFS were 42% and 36% after RP versus 86% and 75% after EBRT ($p < .01$). The rate of adjuvant/salvage therapy was 58% after RP versus 20% after EBRT ($p < .01$). Three- and 5-year MFS were 80% and 77% after RP versus 91% and 91% after EBRT ($p = .11$). Three-year CSS was 98% in both groups and OS was 97% after RP versus 94% after EBRT ($p = .73$).

Conclusions

RP had higher rates of biochemical failure and adjuvant or salvage treatment versus EBRT in high risk localized CaP. MFS trended toward benefit after EBRT, but CSS and OS remained high in both groups.

CCR Score Can Guide Treatment After Radiation in Prostate Cancer

medscape.com

M. Alexander Otto, PA, MMS

The combined clinical cell-cycle risk (CCR) score — derived from both clinical and genetic factors — can identify patients with intermediate- and high-risk localized prostate cancer who could potentially forgo androgen deprivation therapy (ADT), a retrospective study suggests.

The score can identify patients in whom the risk of metastasis after dose-escalated radiation is so small that adding ADT no longer makes clinical sense, according to investigator Jonathan Tward, MD, PhD, of the Genitourinary Cancer Center at the University of Utah, Salt Lake City.

His group's study, which included 741 patients, showed that, below a CCR score of 2.112, the 10-year risk of metastasis was 4.2% with radiation therapy (RT) alone and 3.9% with the addition of ADT.

"Whether you have RT alone, RT plus any duration of ADT, insufficient duration ADT, or sufficient ADT duration by guideline standard, the risk of metastasis never exceeds 5% at 10 years" even in high- and very-high-risk men, Tward said.

He and his team found that half the men in their study with unfavorable intermediate-risk disease, 20% with high-risk disease, and 5% with very-high-risk disease scored below the CCR threshold.

This implies that, for many men, ADT after radiation "adds unnecessary morbidity for an extremely small ab-

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solute risk reduction in metastasis-free survival," Tward said at the 2021 Genitourinary Cancers Symposium, where he presented the findings (Abstract 195).

Value of CCR

The CCR score tells you if the relative metastasis risk reduction with ADT after radiation — about 50% based on clinical trials — translates to an absolute risk reduction that would matter, Tward said in an interview.

"Each patient has in their own mind what that risk reduction is that works for them," he added.

For some patients, a 1%-2% drop in absolute risk is worth it, he said, but most patients wouldn't be willing to endure the side effects of hormone therapy if the absolute benefit is less than 5%.

The CCR score is a validated prognosticator of metastasis and death in localized prostate cancer. It's an amalgam of traditional clinical risk factors from the Cancer of the Prostate Risk Assessment (CAPRA) score and the cell-cycle progression (CCP) score, which measures expression of cell-cycle proliferation genes for a sense of how quickly tumor cells are dividing.

The CCP test is available commercially as Prolaris. It is used mostly to make the call between active surveillance and treatment, Tward explained, "but I had a hunch this off-the-shelf test would be very good at" helping with ADT decisions after radiation.

"Uncomfortable" Findings, Barriers to Acceptance

"People are going to be very uncomfortable with these findings because it's been ingrained in our heads for the past 20-30 years that you must use hormone therapy with high-risk prostate cancer, and you should use hormone therapy with intermediate risk," Tward said.

"It took me a while to believe my own data, but we have used this test for several years to help men decide if they would like to have hormone therapy after radiation. Patients clearly benefit from this information," he said.

The 2.112 cut point for CCR was determined from a prior study that was presented at GUCS 2020 (Abstract 346) and recently accepted for publication.

In the validation study Tward presented at GUCS 2021, 70% of patients had intermediate-risk disease, and 30% had high- or very-high-risk disease according to National Comprehensive Cancer Network criteria.

All 741 patients received RT equivalent to at least 75.6 Gy at 1.8 Gy per fraction, with 84% getting or exceeding 79.2 Gy. About half the men (53%) had ADT after RT.

Genetic testing was done on stored biopsy samples years after the men were treated. Half of them were below the CCR threshold of 2.112. For those above it, the 10-year risk of metastasis was 25.3%.

CCR outperformed CCP alone, CAPRA alone, and NCCN risk groupings for predicting metastasis risk after RT.

Though this validation study was "successful," additional research is needed, according to study discussant Richard Valicenti, MD, of the University of California, Davis.

"Widespread acceptance for routine use faces challenges since no biomarker has been prospectively tested or shown to improve long-term outcome," Valicenti said. "Clearly, the CCR score may provide highly precise, personalized estimates and justifies testing in tiered and appropriately powered noninferiority studies according to NCCN risk groups. We eagerly await the completion and reporting of such trials so that we have a more personalized approach to treating men with prostate cancer."

The current study was funded by Myriad Genetics, the company that developed the Prolaris test. Tward disclosed relationships with Myriad Genetics, Bayer, Blue Earth Diagnostics, Janssen Scientific Affairs, and Merck. Valicenti has no disclosures.

This article originally appeared on MDedge.com, part of the Medscape Professional Network.

Another new urine test for risk of prostate cancer | THE "NEW" PROSTATE CANCER INFOLINK

prostatecancerinfolink.net

As we have mentioned previously, data on the use of a variety of methods of urine testing in assessment of risk for clinically significant prostate cancer (and therefore the need for a follow-up biopsy) continues to evolve.

A very recent paper by Tosoian et al. in the Journal of Urology, reports data from a prospective study of a urine-based test known as the MyProstateScore test from a company called LynxDX. This test was developed in association with the University of Michigan. Dr. Tosoi-

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an and two of his coauthors are shareholders in LynxDX. Additional; information is available in a media release from Michigan Medicine – The University of Michigan.

According to the data from the paper by Tosoian et al. and the associated media release, the MyProstateScore test

measures levels of cancer-specific genes in a patient's urine. It is based on … research that discovered that half of all prostate tumors harbor a certain genetic anomaly in which the genes TMPRSS2 and ERG relocate on a chromosome and fuse together — creating an on-switch for prostate cancer development.

This test was used in a validation study including biopsies and post-digital rectal exam urine samples (prior to biopsy) and transrectal ultrasound (TRUS)-guided biopsies from 1,525 previously biopsy-naive men suspected of having prostate cancer on the basis of a PSA tests and other clinical findings and who were seen at either academic or community medical centers.

Among these 1,525 men

977 were enrolled at academic medical centers (and had a median PSA level of 4.5 ng/ml).

548 were enrolled at community medical centers (and had a median PSA level of 4.9 ng/ml).

338 men (22.2 percent) were found to have a Grade Group of ≥ 2 on biopsy (equating to potentially clinically significant prostate cancer)

Using a MyProstateScore test threshold of 10 as a surrogate for Grade Group ≥ 2 on biopsy, the MyProstateScore test provided

97 percent sensitivity and

A negative predictive value of 98 percent

Thus the MyProstateScore test could have been used to

Prevent 387/1,525 biopsies (33 percent)

Missed 10/338 Grade Group ≥ 2 cancers (3.0 percent)

Among 1,242 patients who met all relevant guideline-based criteria, a MyProstateScore of ≤ 10 provided

96 percent sensitivity

A negative predictive value of 97 percent

and would have

Prevented 32 percent of biopsies

Missed 3.7 percent of Grade Group ≥2 cancers

The validation study included patients seen at academic health centers and in community health settings. Among these 1,525 patients, 338 — 22% — had cancers detected on biopsy that were group grade 2 or higher, meaning they were serious enough to warrant immediate treatment.

If the MyProstateScore test had been available to patients in the study, 387 biopsies that found no cancer or slow-growing cancer could have been avoided, the study found. Meanwhile, the test would have missed only 10 clinically significant cancers that would have warranted immediate treatment.

The authors conclude that:

In a large, clinically pertinent biopsy referral population, MyProstateScore ≤10 provided exceptional sensitivity and negative predictive value for ruling out grade group ≥2 cancer. This straightforward secondary testing approach would reduce the use of more costly and invasive procedures after screening with prostate specific antigen.

Two things are particularly worthy of note from this paper:

The urine samples for this test all had to be taken after a digital rectal examination or DRE, which is something that many men refuse and which can be done with varying levels of "vigorousness".

It is not clear from the abstract of this paper or from the associated media release that all biopsy specimens were subject to central pathology review (i.e., seen by the same pathologist) — although we suspect that that was probably the case.

As we have said before, there is increasing clarity that urine tests are going to become key to the differentiation between men with

- Probably no prostate cancer
- Probably clinically insignificant prostate cancer, i.e., men with Grade Group 1 who don't need a biopsy (but who may need to be monitored annually over time for at least a while)
- Possibly clinically significant prostate cancer (i.e., Grade Group 2) who may need a biopsy but who may still be manageable on active surveillance
- Probably clinically significant prostate cancer (i.e., Grade Group 3 to 5) who will need additional; tests and potentially early treatment with curative intent

However, what is not yet clear at all is whether we are going to need all of these tests as opposed (perhaps) to only one or two of them because these one or two tests have the highest level of discriminatory value when it comes to risk assessment and may be usable not only to assess risk but also to manage men effectively on active surveillance.

NETWORKING

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

Member and Director, 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 are 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

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These tests are also going to call into question the value of MRI scans as methods for the accurate evaluation of clinical risk for prostate cancer. It is starting to seem as though the value of MRI scanning (and of other scans such as gallium-67 PSMA scans in early stage disease) may be limited to men who need a biopsy based on one of the new urine tests … but there will be a way to go before we can have any certainty about all of this, and (in the view of the sitemaster) it is going to be essential that the new urine tests will need to be validated against each other in head-to-head studies in order to be sure that only the most accurate of these tests can and should be in regular use.

There will be little value to a test with 90 percent accuracy in the identification of no prostate cancer, clinically insignificant prostate cancer, or clinically significant prostate cancer if another test can do these things with 99 percent accuracy. And then there is going to be the question of whether we need to go on doing PSA and similar blood-based tests when it is becoming clear that some of these urine tests are significantly more accurate for assessment of prostate cancer risk.

The diagnosis and work-up of prostate cancer is probably going to change significantly (again) over the next 5 to 10 years, and its management will probably also change for the same reasons.

Lu-177-PSMA-617 vs Jevtana (cabazitaxel): which should I do next? | THE "NEW" PROSTATE CANCER INFOLINK

prostatecancerinfolink.net

We saw recently (see this link) that of chemotherapeutic and hormonal medicines for treatment of metastatic castration-resistant prostate cancer (mCRPC), Jevtana (cabazitaxel) is the preferred third-line treatment after Taxotere (docetaxel) and Zytiga (abiraterone acetate) or Xtandi (enzalutamide). But when should radiopharmaceuticals — either approved ones like Xofigo (radium-223), or prospective ones (like Lu-177-PSMA-617) — be used in the optimal sequencing?
Hofman et al. have now reported the results of the Phase II TheraP randomized clinical trial (RCT). They randomized some well-selected patients to receive either Lu-177-PSMA-617 or Jevtana. Patients were selected according to the following criteria:

Must have mCRPC (PSA≥20 ng/ml and rising)
Must have had docetaxel
Must have had either Zytiga or Xtandi or both
Must have been otherwise healthy, with good liver, kidney, and blood function

In addition, all patients received both an FDG PET scan and a PSMA PET scan. They were excluded from the trial if either:

Their metastases were insufficiently PSMA-avid (10 percent excluded)

There were many metastases that showed up on FDG but not on PSMA PET scans (as described here) (18 percent excluded)

Of the 200 patients actually eligible for study treatment,

85/101 patients were treated with Jevtana
98/99 patients were treated with Lu-177-PSMA-617

The endpoint used was the percentage of patients whose PSA declined by at least 50 percent (PSA50) from baseline after the treatment.

After a median follow-up of 13 months:

Lu-177-PSMA-617 had a PSA50 of 66 pecent vs 37 percent for Jevtana.

PSA progression occurred in 31 percent fewer patients among those treated with Lu-177-PSMA-617 relative to those treated with Jevtana.

At 12 months of follow-up,

Progression-free survival was 19 percent for Lu-177-PSMA-617 vs 3 percent for Jevtana

Pain improvement was better for Lu-177-PSMA-617 (60 percent) than Jevtana (43 percent).

It is too early for data on overall survival.

Serious/life-threatening adverse events occurred in 33 percent of those taking Lu-177-PSMA-617 vs. 53 percent of those taking Jevtana.

The most common adverse events reported by those taking Lu-177-PSMA-617 were fatigue, pain, nausea, dry mouth/eyes, low platelets, and anemia. Only one patient discontinued for toxicity.

The most common adverse events reported by those taking Jevtana were fatigue, pain, diarrhea, nausea, loss of taste, neuropathy, dry mouth, and neutropenia. Three patients discontinued for toxicity.

Given the comparatively low toxicity, it seems like Lu-177-PSMA-617 should usually be the preferred third-line treatment, over Jevtana, although longer follow-up will be needed to see if there will be a survival difference.

This study further highlights the importance of get-

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ting both an FDG and a PSMA PET scan at about the same time.

PSMA expression is highly variable. It is not expressed in low-grade cancer in the prostate. PSMA expression increases as metastases develop, reaches a peak, and then decreases. PSMA expression also increases when second-line hormonal agents are first used, but then decreases with continued use. Given this variation over time and treatment, several questions about PSMA-targeted therapy remain unanswered:

Should it be used soon after second-line hormonal agents?

Should it be used before or soon after docetaxel?

Would the problem of heterogeneity be minimized if Jevtana and Lu-177-PSMA were given simultaneously (if this is clinically possible)?

Should it be used in minimally metastatic patients?

Should it be used in newly diagnosed metastatic patients?

Should it be used with immunotherapies (e.g., Provenge, checkpoint inhibitors)?

Will PARP inhibitors enhance the cell-kill rate?

Is PSA the best biomarker of effectiveness?

What are the best radionuclides to use (e.g., Ac-225, Th-227)?

What are the best/most specific ligands to use (e.g., PSMA-617, PSMA-I&T)

Are there better surface proteins to target, perhaps simultaneously (e.g., FAPI, bombesin, uPAR)

How do they compare to PSMA BiTE therapies?

How does it compare to Xofigo for bone metastases?

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

AI tool shows promise in predicting biochemical recurrence in prostate cancer | Urology Times

Jason M. Broderick

The integrated radiomic-clinicopathologic nomogram (RadClip) was a better prognosticator of biochemical recurrence-free survival and adverse pathology than other standard tools.

An artificial intelligence (AI) tool showed early promise at predicting biochemical recurrence following radical prostatectomy (RP) in men with prostate cancer, according to a study published in *EBioMedicine*.[1,2]

The AI tool, which is an integrated radiomic-clinicopathologic nomogram (RadClip), uses AI algorithms to evaluate "subtle differences in heterogeneity and texture patterns inside and outside the tumor region on pre-operative MRI to predict patient outcome following surgery."

The study demonstrated that RadClip was a better prognosticator of biochemical recurrence-free survival (bRFS) and adverse pathology (AP) than other standard prognostic tools, including CAPRA and the Decipher genomic test.

"This tool can help urologists, oncologists, and surgeons create better treatment plans so that their patients can have the most precise treatment," Lin Li, a doctoral student in Case Western Reserve's Biomedical Engineering Department and a member of the team that developed the tool, stated in a press release. "RadClip allows physicians to evaluate the aggressiveness of the cancer and the response to treatment so they don't overtreat or undertreat the patient."

The retrospective analysis included 198 patients with prostate cancer treated across 4 institutions between 2009 and 2017. The institutions included Cleveland Clinic, The Mount Sinai Hospital, University Hospitals, and the Hospital of the University of Pennsylvania.

All patients received pre-operative 3 Tesla MRI followed by RP and had available follow-up data including post-surgery serum PSA levels. Patients were excluded if they had received neoadjuvant or adjuvant therapy, received radiotherapy as the definitive treatment, or had PSA persistence after RP.

Using statistical models, the investigators compared methods to determine which approach was the best predictor of bRFS and AP in this population. Concordance index (C-index) was the comparison measure for bRFS prediction and AUC was the comparison measure for AP prediction.

At a median follow-up of 35 months, the C-index for RadClip (0.77) was higher than the C-index for CAPRA (0.68) and Decipher (0.51). The C-index was comparable between RadClip and CAPRA-S (0.75). Further, RadClip's AUC for predicting adverse pathology (0.71) was higher than bother Decipher's (0.66) and CAPRA's (0.69).

-"We're bringing together and connecting a variety of information, from radiologic scans like MRI to digitized pathology specimen slides and genomic data, for providing a more comprehensive characterization of the disease," Anant Madabhushi, PhD, CCIPD director**,** Don-

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nell Institute Professor of Biomedical Engineering at Case Western Reserve and the study's senior author, stated in the press release.

"Genomic-based tests cost several thousand dollars and involve destructive testing of the tissue," Madabhushi added. "Prognostic predictions from an MRI scan provide a non-invasive method for making both short-term and long-term decisions on treatment."

The authors listed several limitations of their study, including that it was a retrospective analysis; the study used biochemical recurrence as a surrogate marker for metastasis because follow-up time post-prostatectomy was not long enough; and the study was "prognostic and not predictive of added benefit of neoadjuvant or adjuvant therapy."

Going forward, the investigators suggest that clinical trials are needed to show whether RadClip can be used to identify which patients undergoing prostatectomy should receive additional treatment.

References

1. Artificial intelligence tool for reading MRI scans could transform prostate cancer surgery and treatment. Posted online January 14, 2021. https://bit.ly/2KfmbU9. Accessed January 14, 2021.

2. Li L, Shiradkar R, Leo P, et al. A novel imaging based Nomogram for predicting post-surgical biochemical recurrence and adverse pathology of prostate cancer from pre-operative bi-parametric MRI. *EBioMedicine*. 2020;63:103163. doi: 10.1016/j.ebiom.2020.103163.

Improving PET scans are good news for doctors and patients alike - Harvard Health Blog - Harvard Health Publishing

health.harvard.edu

Charlie Schmidt

A recent blog post discussed a newly approved imaging agent with an unwieldy name: gallium-68 PMA-11. Delivered in small amounts by injection, this minimally radioactive tracer sticks to prostate cancer cells, which subsequently glow and reveal themselves on a positron emission tomography (PET) scan. Offered to men with rising PSA levels after initial prostate cancer treatment (a condition called biochemical recurrence), this sort of imaging can allow doctors to find and treat new tumors that they might otherwise miss. With currently available imaging technology, such tumors could potentially escape detection until they were larger and more dangerous.

But while gallium-68 PMA-11 is the latest PET tracer to win FDA approval, not everyone can get it. In the United States, it's currently available only to patients treated at the University of California, Los Angeles, or the University of California, San Francisco, where the tracer is manufactured. However, two other PET tracers approved for prostate cancer imaging in the US are becoming more accessible.

In January 2021, a team at Stanford University published findings showing that one those tracers, called fluciclovine F18 (trade name Axumin), identified significantly more metastatic cancers than other conventional types of imaging. Axumin was approved in 2016, and these are among the first data to show how well the tracer performs in real-world settings.

The Stanford researchers reviewed medical records from 165 men who had been given Axumin PET scans between September 2017 and December 2019. All the men had biochemical recurrence, and 70 of them were also imaged with other technologies, including CT scans, bone scans, or MRIs.

Axumin PET scans outperformed all the other tests with respect to tumor detection. In all, 110 men had PET-detected metastases, and no one with a negative PET scan was positive for cancer on other imaging tests. PET imaging found cancer in nine of 31 men who had negative results on CT scans. Similarly, six of 31 men with negative results on an MRI had PET-detected tumors. The technology also detected skeletal tumors in one man with a negative bone scan.

Importantly, tumor detection rates were greatest for men with high and rapidly rising PSA levels. That's to be expected, since prostate cancer cells release PSA; as tumors grow and proliferate, PSA levels will rise in tandem. In fact, prior research shows that Axumin PET scans are unlikely to detect cancer if PSA is less than 1 nanogram per deciliter (ng/mL) in blood.

Positive PET scans also led to treatments that doctors might not have started if only negative findings with other imaging tests were available. Most of the 102 men who were subsequently treated got radiation delivered specifically to the tumor sites, in some instances combined with drugs that block testosterone, a hormone that speeds prostate cancer growth.

The study had some limitations, including that it was conducted at only one facility. Furthermore, in only seven cases were PET findings confirmed by a pathologist's review of removed tissue samples. That's because in most cases, the detected lesions were too small — less than a centimeter in size — to biopsy. PET-detected cancers were confirmed instead by declines in PSA after

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treatment.

"Axumin scanning, along with newly developed gallium scanning, is changing the way in which prostate cancer is staged and ultimately treated," says Dr. Marc Garnick, the Gorman Brothers Professor of Medicine at Harvard Medical School and Beth Israel Deaconess Medical Center, editor of the Harvard Health Publishing *Annual Report on Prostate Diseases*, and editor in chief of HarvardProstateKnowledge.org. "The increased sensitivity of these new scanning technologies is both identifying patients with metastatic disease who otherwise would have been considered to be free of metastases, as well as helping to confirm the absence of metastatic deposits. Both situations will alter that way in which treatment decisions are made, and this will provide more precision in terms of what we can offer our patients. These new technologies are good news for doctors and patients alike."

On The Lighter Side