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

Thursday, February 17,

FEBRUARY 2022 NEWSLETTER

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STREAMING ONLINE LIVE

Volume 15 Issue 02

- **Next Meeting Saturday, FEB 19, 2022 IPCSG - Live-Stream Event, 10:00am PT**.
- Speaker Dr. Charles Metzger - Management of Rising PSA After Primary Treatment
- Dr. Metzger will be discussing rising PSA after single or multiple treatments and what additional options are available. He practiced Urology for 41 years in Glendora, California.
- March Meeting—members will share their experiences
- 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
- **If you would like some copies of our new brochure by mail for distribution to your friends or physicians, please send email to Newsletter@ipcsg.org or call Gene at 619-890-8447**

January 2022 Informed Prostate Cancer Support Group Meeting
Summary by Bill Lewis
Updates on Radiation Oncology

Speakers:

1. Arno J Mundt MD FASTRO FACRO, Professor and Chair, UCSD Dept. of Radiation Medicine & Applied Sciences.
2. John Einck MD FACRO, Professor, UCSD Dept. of Radiation Medicine & Applied Sciences; California Proton Therapy Center.
3. Carl Rossi MD, Professor, UCSD Dept. of Radiation Medicine & Applied Sciences; California Proton Therapy Center.
4. Brent Rose MD, Assistant Professor, UCSD Dept. of Radiation Medicine & Applied Sciences; UCSD Department of Urology.

UCSD has a group of 32 Radiation Oncologists, ten of whom specialize in prostate cancer and other genitourinary cancers. The "pillars" of PCa treatment are surgery (especially prostatectomy, often with robotics), medical therapy (hormone treatment and "chemo") and radiation therapy (external beam radiation therapy with photons or protons, and brachytherapy).

External beam radiation therapy (EBRT) can be given in different numbers of doses, ranging from

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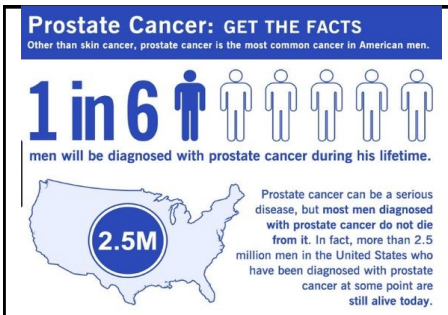

Organization

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

IPCSG

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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:

Bill Lewis produced a short summary of the last stream video, a very informative talk on the state of the art in radiation therapy by Dr. Mundt and his team from UCSD.

Articles of Interest:

Sens. Moran, Tester Introduce Bill to Expand Treatment & Research for Prostate Cancer in Veterans | United States Senate Committee on Veterans' Affairs *maybe the VA will get its act together on PCa*

An AI-assisted Tool For Efficient Prostate Cancer Diagnosis *Could computers beat pathologists in diagnosis?*

Diving into our role in 50 top cancer drugs The long winding road for the NHS to develop a PCa drug. *Ours is different, but is it better?*

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"conventional fractionation" (about 8 weeks of small daily doses) to "hypofractionation" (moderate daily doses over 5-6 weeks) and to "stereotactic body radiotherapy" (SBRT; large daily doses over one week or less). Brachytherapy is internal radiation therapy, in which radioactive pellets are implanted permanently ("low dose rate"), or for brief exposure through tubes ("high dose rate"). For PCa, EBRT may be combined with or followed by brachytherapy or hormone therapy, for better long-term suppression or cure of the cancer.

Sometimes, EBRT is given after prostatectomy, either because of "positive margins" (i.e., cancer is found in the tissue at the edges of the removed prostate gland, suggesting some cancerous cells were left behind), or a rising PSA (sometimes years later). Due to the stress to the body from the surgery, the radiation is given using "conventional fractionation," not using higher dose rates. Since the prostate has been removed, there is no gland remaining in which to give brachytherapy. Sometimes, hormone therapy is also given.

UCSD has a high-risk prostate cancer multi-disciplinary clinic, combining the skills of a medical oncologist, a urologist, and a radiation oncologist.

Brent Rose spoke to the group about "Prostate Cancer 101 – What you need to know to make the best decisions for your cancer." He discussed prostate anatomy, and questions such as "Is my cancer causing my trouble urinating? Is my cancer causing difficulties with my erections? What does the prostate actually do?"

PSA (prostate specific antigen) is a protein that is made both by the normal prostate, and [to a much greater extent] by cancerous prostate cells, and is measured by a blood test. The results are used for screening, for risk stratification (how aggressive is the cancer – that is, how fast does the PSA rise), for monitoring during "active surveillance," and to detect cancer recurrence after treatment. PSA is not a great screening test for prostate cancer, but is the best available, inexpensive test for now. PSA above 4 is often called "high" and may prompt a biopsy [but an MRI and MRI-guided biopsy is better than a traditional "random" biopsy]. 15% of men with PSA less than 4 will have prostate cancer. Over 50% of men with PSA over 10 will be found to have cancer. There are several causes of elevated PSA besides PCa, namely benign enlargement of the prostate, infection (prostatitis), recent ejaculation, a digital rectal exam, or even bicycle riding. After prostate cancer has been diagnosed, the PSA is used to rank the aggressiveness of the cancer, from low risk (PSA <10), or intermediate risk (PSA 10-20), to high risk (PSA >20).

Typically, biopsies are done with 12 needles inserted through the rectum [but see Dr. Richard J. Szabo's talk on Transperineal vs. Transrectal Biopsies -- https://youtu.be/4GLr_E6Bvec -- or see the summary in the IPCSG October 2021 newsletter]. The traditional approach can undersample the disease in about 30% of cases, particularly missing lesions in the front of the prostate or near the urethra. The cores removed from the needles are microscopically examined, and given "Gleason" grades based on how abnormal the cells appear, one number for the most common pattern of abnormality, and a second number for the second-most common pattern. The sum becomes the Gleason Score, which can range from 6 to 10. For scores of 7 to 9, there are different ways to reach the particular sum, and a Gleason 4+3 is found with experience to represent a more aggressive disease than 3+4. A new system lumps the various Gleason scores into Grading Groups, which correspond to Risk Groups, as shown in the table below.

MRI of the prostate can be helpful to make sure the disease is adequately sampled, particularly when the biopsy is "normal" or Grading Group = 1, but the PSA continues rising. It can also help to stage the primary tumor – see the meeting summaries in the May and June 2021 IPCSG newsletters. And it can best localize lesions for targeting "focal therapy." However, Dr. Rose favors giving radiation to the whole prostate, with a higher dose at the primary lesion, because PCa is usually multifocal, with bits of disease all over the prostate.

Determining whether the cancer has spread is traditionally assessed with a bone scan or CT or MRI scan, but a newly available test is the PSMA-PET scan [see also Axumin scan info in prior newsletters].

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GLEASON GRADING SYSTEM

How do prostate cancer cells look and the likelihood of the cancer advancing or spreading

Grading group	Gleason score	Definition	Risk group
1	3+3 = 6	Only individual, discrete well-formed glands	Low
2	3+4 = 7	Predominantly well-formed glands with lesser component of poorly formed, fused and/or cribriform glands	Intermediate favourable
3	4+3 = 7	Predominantly poorly formed, fused and/or cribriform glands with lesser component of well-formed glands	Intermediate unfavourable
4	4+4 3+5 = 8 5+3	Only poorly formed, fused and/or cribriform glands Predominantly well-formed glands with lesser component lacking glands Predominantly lacking glands with lesser component of well-formed glands	High
5	4+5 5+4 = 9 5+5 = 10	Lack gland formation (or with necrosis), with or without poorly formed, fused and/or cribriform glands	Very high

Prostate MRI can be helpful to make sure the disease is adequately sampled, particularly when the biopsy is "normal" or a low Gleason grade group, but the PSA continues rising. It is helpful for staging the primary tumor, and for targeting focal treatments. Radiation oncologists prefer to treat the whole prostate, rather than just the tumor areas visible by MRI, because there are likely other tumors present that are too small to be seen in the MRI scan, so they will give a greater dose to those identified tumor areas.

The most likely areas of spread of PCa beyond the prostate gland and associated seminal vesicles are the lymph nodes of the pelvis or abdomen, or the bones. Standard imaging would be done with a CT scan, MRI or bone scan. Newly available tests are PET-CT scans, either Axumin or PSMA-PET, which are very helpful to find small metastases that are not so easily visible with standard imaging.

Localized PCa may be low risk (Gleason grade group 1), favorable or unfavorable intermediate risk (groups 2 and 3, or high risk (grade groups 4 and 5) as determined by the pathology report from prostate gland biopsy tissue samples. Metastases can occur anywhere, but are considered regional if only found in nearby lymph nodes or bones.

There are two main types of genetic tests. Germline tests look for an inherited predisposition to prostate or other cancers. These are most important to see if you might pass on the gene to your children, and are recommended for men with high risk or metastatic disease. Somatic tests look at the genes in samples from your tumors, to see how aggressive the cancer is, and whether there are specific mutations that can be targeted.

Common questions: "My doctor says I need surgery or radiation now, but I'm not sure. How urgent is this?" Don't worry too much. PCa is slow growing. Consult other doctors, and learn from groups like this one, the IP-CSG.

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"What kinds of other doctors beside my urologist (who is a surgeon) should I see?" Radiation oncologists and medical oncologists (who may recommend hormone therapy, focal therapy, or chemotherapy).

"How will treatment affect my urination, sexual function, bowel movements and sense of personal identity?" These are important discussions to have with the doctors you meet with. Also talk to patients who have had the treatment(s) you are considering.

"Who can I discuss emotional challenges of this diagnosis with?" Depression is a very common with any cancer diagnosis, and you should find people, other patients and doctors you are comfortable discussing emotional challenges with.

Dr. John Einck discussed "Individualizing Radiation Therapy for Prostate Cancer." He concluded 1) The availability of a wide variety of radiation therapy options allows us to individualize treatment to both the stage of the PCa, and the patient's personal goals. 2) Proton therapy is advantageous when treating lymph nodes, as well for post-prostatectomy salvage, and for younger men. 3) Brachytherapy improves cure rates for those with "unfavorable" PCa, but not everyone is a good candidate.

See the video for details.

Dr. Carl Rossi gave a 2022 update to "Introduction to Intensity-Modulated Proton Therapy." Proton therapy is no longer "boutique." – equipment is available from numerous manufacturers and is becoming less expensive. This will lead to increased utilization and optimization. Commonly available tools in modern radiation therapy are actively being adapted for particle therapy. Ultimately, it is hoped that the cost to the payor of delivering particle therapy will become similar to the cost of x-ray treatment. Published data demonstrates that proton treatment gives less toxicity and lower incidence of radiation-induced second cancers. Dose escalation with either protons or x-rays appears to be important for reducing the risk of PCa recurrence. See the video for details.

Questions:

Is modified hypofractionation appropriate after TURP? Yes.

What should the PSA be for best PSMA-PET scan results? Should be above 0.4.

How do focal therapies compare with radiation? They lead to high rates of recurrence, and Dr Einck does not favor their use except for salvage. He sometimes does a focal brachytherapy treatment for such patients. Dr. Rossi suggests that focal therapy always be done as part of a clinical trial, so that the results will be published for the benefit of others. Also, be aware that treating only one side of the prostate may allow tumors to grow in and metastasize from the other side.

What about radiation after prior radiation? It depends on where it has come back. He would do both an MRI and PSMA-PET scan, and if possible, follow up with a fresh biopsy. Each case must be considered individually, along with all treatment modalities. Often the recurrence is very localized, so brachytherapy, SBRT, HIFU or especially cryotherapy, may be able to eliminate it. And often the recurrence grows only slowly, so might be monitored rather than treating immediately.

With an artificial sphincter, what additional procedures or precautions are needed to undertake adjunct radiation treatment? In general, the artificial sphincter has no effect on the radiation treatment plan and the radiation has no effect on the artificial sphincter. It is generally well below the area being radiated.

We recommend that you watch the video online for more definitive information about the talk and slides: https://www.youtube.com/watch?v=Ss0KXOUz3Ng

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

Sens. Moran, Tester Introduce Bill to Expand Treatment & Research for Prostate Cancer in Veterans | United States Senate Committee on Veterans' Affairs

veterans.senate.gov

Wednesday, September 15, 2021

WASHINGTON – U.S. Senators Jerry Moran (R-Kan.) and Jon Tester (D-Mont.) – ranking member and chairman of the Senate Veterans' Affairs Committee – this week introduced legislation to expand treatment and research of prostate cancer to help diagnose and treat veterans through the Department of Veterans Affairs (VA).

"Prostate cancer is currently the number one cancer diagnosed by the Veterans Health Administration," **said Sen. Moran.** "Early detection of prostate cancer should be a priority of the VA, and this legislation will help support critical research and expedite prostate cancer diagnosis and treatment among veterans."

"With hundreds of thousands of veterans suffering from prostate cancer a year, VA needs a standardized pathway to increase detection and treatment of this disease as early as possible," **said Sen. Tester**. "Our bipartisan bill will help support critical, science-driven research that'll lead to earlier detections and save veterans' lives."

The *Veterans' Prostate Cancer Treatment and Research Act* would:

Expand upon the current VA and Prostate Cancer Foundation partnership.

Require the VA to establish and publish an interdisciplinary clinical diagnosis and treatment pathway in the VA National Surgery Office, in collaboration with the VA National Program Office of Oncology, the VA Office of Research and Development and VA Primary Care for all stages of prostate cancer, from early detection to end of life care.

Give the VA the authority to collaborate with other research entities on creation of clinical pathway including the National Institutes of Health, National Cancer Institute, Centers for Disease Control and Prevention, Centers for Medicare and Medicaid Services, U.S. Food and Drug Administration, Patient-Centered Outcomes Research Institute (PCORI) and the Department of Defense.

Require the VA to establish a prostate cancer program utilizing the clinical pathway mandated in this legislation, which will receive direct oversight from the VA Undersecretary of Health, include yearly program implementation evaluation, be metric and data driven, and include an education plan for patients and providers.

Direct the VA to produce a plan to Congress detailing funding through the VA Office of Research and Development for supporting prostate cancer research to make certain no funding included is duplicative.

Direct the VA to submit a report to Congress on the barriers and challenges associated with creating a national prostate cancer registry to include recommendations for centralizing data about veterans with prostate cancer in an effort to improve outcomes and research.

Urge Your Senator: Support a Clinical Pathway at the VA | ZERO - The End of Prostate Cancer # # #

An AI-assisted Tool For Efficient Prostate Cancer Diagnosis

biorxiv.org

View ORCID Profile Mustafa Umit Oner

Abstract

Pathologists diagnose prostate cancer by core needle biopsy. For low-grade and low-volume cases, the pathologists look for the few malignant glands out of hundreds within a core. They may miss the few malignant glands, resulting in repeat biopsies or missed therapeutic opportunities. This study developed a multi-resolution deep learning pipeline detecting malignant glands in core needle biopsies to help pathologists effectively and accurately diagnose prostate cancer in low-grade and low-volume cases. The pipeline consisted of two stages: the gland segmentation model detected the glands within the sections and the multi-resolution model classified each detected gland into benign vs. malignant. Analyzing a gland at multiple resolutions provided the classification model to exploit

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both morphology information (of nuclei and glands) and neighborhood information (for architectural patterns), important in prostate gland classification. We developed and tested our pipeline on the slides of a local cohort of 99 patients in Singapore. The images were made publicly available, becoming the first digital histopathology dataset of prostatic carcinoma patients of Asian ancestry.

Our pipeline successfully classified the core needle biopsy parts (81 parts: 50 benign and 31 malignant) into benign vs. malignant. It achieved an AUROC value of 0.997 (95% CI: 0.987 - 1.000). Moreover, it produced heatmaps highlighting the malignancy of each gland in core needle biopsies. Hence, our pipeline can effectively assist pathologists in core needle biopsy analysis.

news.cancerresearchuk.org

Diving into our role in 50 top cancer drugs

"Abiraterone gave me a lifeline. In my case, it's been hugely successful at treating my cancer." Alfred Samuels is one of the thousands of people with cancer around the UK every year who receive drugs as part of their cancer treatment.

Drugs can be given for different reasons, not just with the aim of eliminating the tumour. Sometimes they're used to keep advanced disease like Alfred's at bay. In other cases, it's to prevent cancer coming back after surgery, to shrink tumours prior to surgery or radiotherapy, or make radiotherapy more effective.

To add to the complexity, there are different types of drug which work in different ways.

Some – generally called chemotherapies – target fast-dividing cells like cancer cells. Others, called immunotherapies, can be used to galvanise the body's own immune system to treat the disease.

Yet more – so-called targeted therapies – are designed to target specific molecules on or inside cancer cells. And hormone therapies – like the abiraterone used to treat Alfred's prostate cancer – work by disrupting a tumour's reliance on certain hormones.

In all, there are hundreds of drugs available to treat the disease. And they all have one thing in common: they're all the product of a painstaking global research effort.

To mark 20 years since Cancer Research UK was formed, from a merger between the Cancer Research Campaign (CRC) and the Imperial Cancer Research Fund (ICRF), we've delved into the research that led to many of the drugs in use today, and mapped these charities' contributing role.

We've focused on 3 main steps in a drug's journey to the clinic: discovery research, drug development and clinical testing. And we've identified more than 50 drugs where the hard work of scientists and doctors we've funded has helped hasten these drugs' journey to patients.

It all starts with 'why?'

Whether it's understanding how 'mustard gas' chemicals used in World Wars kill cells, or working out how growth signals are transmitted to a cell's nucleus, the first step in a drug's journey usually starts with the question 'why'? Why does a particular gene or molecule encourage cells to grow? Or, conversely, why does a chemical affect growing cells in a particular way?

In the case of early chemotherapy, it was pioneering work in the 40s and 50s that helped opened the door to the chemotherapy drugs in use today. CRC-funded chemists and biologists at the Chester Beatty Laboratories in London (now known as the Institute of Cancer Research) discovered exactly how the nitrogen mustard chemotherapy molecules damaged a cell's DNA. And in doing so, they developed 3 new drugs – melphalan, busulfan and chlorambucil.

Scientists around the world have since built on their insights, developing drugs such as carmustine and lomustine. All of these drugs are still in use today and play a key role in the treatment of a range of cancers, including leukaemias, lymphomas and brain tumours.

Thirty years later, a humble PhD student at ICRF's London Research Institute (now part of the Francis Crick Institute) uncovered something fascinating about a relatively unknown protein made by our cells, known as epidermal growth factor receptor, or EGFR for short.

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"I'd had to wait for the evening for the one of the few computers in the lab to be free before I could begin to look at the data from my experiments. That night the computer came up with a match – EGFR was almost identical to a protein produced by a virus that causes cancer in chickens. It really was a 'Eureka!' moment – our own cells contained molecules that accelerated cancer growth."

Professor Julian Downward's observation overturned widely held ideas on the causes of cancer, which many had thought was caused by infection. It triggered a wave of research around the world that ultimately led to the development of drugs that target the EGFR protein – drugs that US data suggests are playing a role in reducing deaths from lung cancer

"It may have taken years for our findings to be translated into drugs to treat people with cancer, but even then we knew it was significant – my supervisor even came back into the office late that night to see what I was seeing."

There are many more drugs built from the fundamental insights of laboratory research funded by Cancer Research UK and its predecessors.

For example, we supported work on yeast and sea urchins that's led to new drugs for breast cancer, careful genetic studies that have opened the door to effective melanoma drugs, and painstaking unravelling of cells' DNA repair mechanisms that's led to drugs for ovarian, prostate, breast and pancreatic cancers.

Turning ideas into drugs

The next stage in getting drugs from the lab to the clinic is harnessing scientific insights to develop molecules that can be given to people as drugs – a process collectively called drug discovery. And we've played an important role here too.

Take abiraterone, for example – the hormone-disrupting drug currently holding Alfred's cancer at bay. Abiraterone emerged from a quest to shut down a key step in testosterone production, and so slow or even halt cancer growth in prostate cancer.

In the early 1990s, researchers at our Centre for Cancer Therapeutics at the Institute of Cancer Research in Surrey were studying existing anti-fungal drug that could do this. But there was a problem: the body broke it down too quickly to be effective. Some clever chemistry led to a molecule they simply called '3', which was able completely shut off testosterone production in mice. Taken to our Strathclyde formulation unit in Scotland, the prototype was developed into a tablet, opening the door to clinical trials. The rest is history.

There are many more drugs whose existence has been underpinned by researchers we've supported. In the 1930s, our researchers created a synthetic form of oestrogen called stilboestrol, which became a mainstay of prostate cancer therapy for decades, and opened the door to modern hormone-blocking drugs.

Carboplatin – a widely used chemotherapy drug – arose from our researchers' work to improve platinum-based chemotherapy in the 1970s. More recently, our researchers in Newcastle and Cambridge have helped develop targeted drugs called PARP inhibitors.

Into the clinic

Once a drug has been discovered it needs to be tested in clinical trials, which are critical to ensure that the drugs are safe, effective and better than what's currently available.

It's a difficult path for a drug to walk, and it's estimated that just 1 in 10 drugs entering first-in-human clinical trials end up making it all the way to approval.

Over 120 years Cancer Research UK and its predecessors have run thousands of clinical trials, from early, first-in-human studies that look at a drug's safety and toxicity through to larger 'phase 3' studies that compare them to other treatments.

At the beginning of the clinical trial pathway sits our Centre for Drug Development, the world's only charity-funded drug development facility. A similar size to a medium sized pharmaceutical company, it's responsible for running the first-in-human clinical trials, including for 6 drugs widely available today – with 21 more in the pipeline.

One of these drugs, temozolomide, is now used worldwide as the frontline drug for people with glioblastoma, a type of brain tumour.

And beyond the vital work in bringing new treatments to patients for the first time, our research has led to the refinement of their use in later phase clinical trials.

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Our Glasgow clinical trials unit, working as part of an international consortium, led the way in showing docetaxel could benefit women with ovarian cancer. Other trials we've funded have shown the best way to use drugs like fluorouracil for liver cancer, mitoxantrone for acute leukaemia and capecitabine in stomach cancer.

Alfred received abiraterone thanks to a clinical trial called STAMPEDE, which has been testing new combinations of drugs to see which may improve prostate cancer survival.

In the last 17 or so years since the study began, STAMPEDE has already changed clinical practice 29 times. In 2015 it showed giving men docetaxel in addition to standard treatment was beneficial – this led to change in NHS guidelines and transformed clinical guidelines across the world.

A few years later it showed that adding abiraterone and the steroid prednisolone to standard hormone therapy extended survival by a similar amount.

Around 10 years after his initial diagnosis, Alfred says STAMPEDE was an opportunity for him to not let statistics rule his life. "So far, the treatment has been working and my cancer is being managed well. While I'll be on the treatment for the foreseeable future, it's given me the chance to live life. I see the world differently now and I take stock of what I'm seeing."

The (even) bigger picture

This long and winding road a new drug travels to reach people with cancer spans so many research areas, making it unsurprising that there's rarely a single research group or organisation responsible for an individual drug. Drugs come about through collaboration, competition and a collective effort.

Through careful work – combing historic research papers, searching our archives and interviewing researchers – we've built a picture of how funding from Cancer Research UK and our predecessors has contributed to more than 50 cancer drugs in use today.

These drugs have had an extraordinary impact, offering options to millions. Thanks to data collected by the National Cancer Registration and Analysis Service, we've been able to calculate that the drugs that CRUK research has contributed towards, are used to treat 3 in 4 people with cancer who receive cancer drugs in England every year.

These drugs' impact extends well beyond the UK. More than 20 appear on the World Health Organisation's drugs list of 'Essential Medicines', meeting the most pressing needs of a country's health system.

It's a legacy we're extremely proud of. But it means even more to people like Alfred. "I don't think I'd be here today if it wasn't for the trial, abiraterone and Cancer Research UK scientists who helped develop the drug," says Alfred.

"I like Cancer Research UK's approach and I see the value of what they're doing. It's real. It's keeping people affected with cancer at the heart of what they do, and making a real difference for people like me."

Catherine Pickworth is a research information manager at Cancer Research UK

On the Lighter Side

"How much do I owe you so far?"

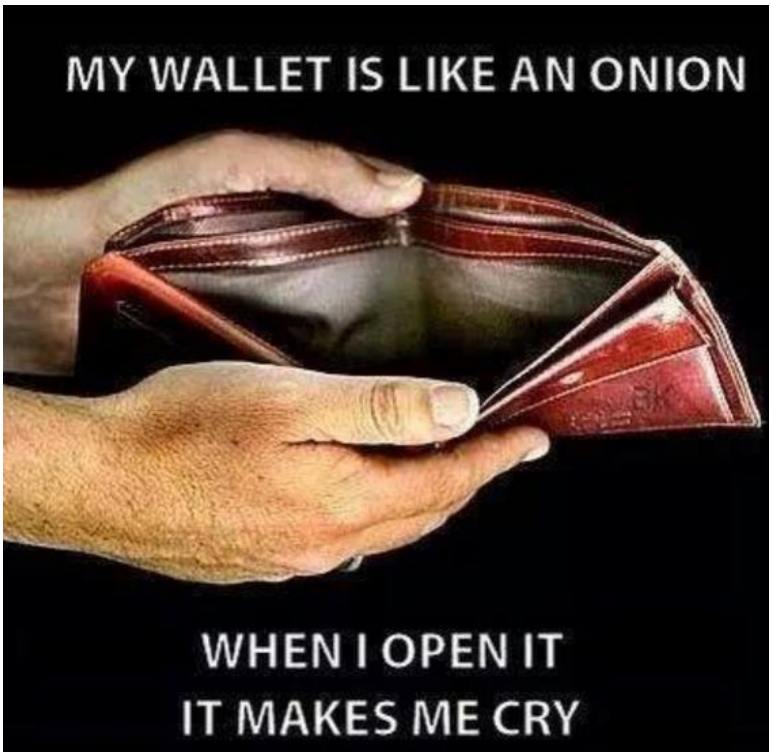
NETWORKING

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.

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

Editors Notes, Continued from Page 2

Local versus systemic treatment intensification: what is the optimal strategy for localized prostate cancer? Going after the prostate works if cancer is localized, but how to tell.

Widely-used hormone drug associated with increased risk of benign brain tumor at high doses Messing with testosterone could effect other systems.

Awaiting the perfect diagnostic test: optimal prostate cancer care begins without a diagnosis. PSA is not optimum.

Military Pilots' DNA May Hold Key to What's Causing Their Prostate Cancers Pilots have more PCa than expected.

Development of a nomogram combining multiparametric magnetic resonance imaging and PSA-related parameters to enhance the detection of clinically significant cancer across different region using two factors to reduce excess diagnosis or biopsies without missing cancer

Radiotherapy treatment modification for prostate cancer patients based on PSMA-PET/CT better images can improve treatment

Personalization of Treatment Intensity for Intermediate-Risk Prostate Cancer intermediate level is hardest to plan.

NEAR trial: A single-arm phase II trial of neoadjuvant apalutamide monotherapy and radical prostatectomy in intermediate- and high-risk prostate cancer apalutamide alone or with other treatments.

New blood test combined with image-based prostate cancer screening reduces harms and costs now combined modes help diagnosis.

Prostate Cancer: a comparison of focal therapy and radical prostatectomy can you keep your prostate, or do you need to cut it out.

Breast cancer risk genes linked to prostate, pancreatic and stomach cancer breast cancer in the female side of your family can increase your PCa risk.

Robot performs first laparoscopic surgery without human help how much can the robot take over from the surgeon, and will it reduce dependence on experience?

AI Holds Its Own vs Pathologists for Prostate Cancer Diagnosis AI was as good as expert pathology.

Newer Hormone Treatments for Prostate Cancer May Raise Risk of Depression ADT could be depressing.

We've Never Really Understood the Prostate— Wolinsky reviews Ericka Johnson's new book, A Cultural Biography of the Prostate understanding some of the psychology for men and their helpers.

Articles of Interest continued from page 9

About the project: We investigated the contribution of CRUK/CRC/ICRF funding to more than 80 individual cancer drugs in 3 separate research areas (underpinning research, discovery and development and clinical trials) through a comprehensive literature review and interviews with the research community. We identified more 56 drugs where contributing research was CRC/ICRF/CRC funded. We then used NHS Digital's SACT database, which captures prescribing information of SACT drugs, to calculate the proportion of patients who are prescribed one of these 56 drugs, and therefore the proportion who have received at least one drug built on CRUK's research.

Local versus systemic treatment intensification: what is the optimal strategy for localized prostate cancer?

nature.com

Zumsteg, Zachary S.

In clinical trials spanning several decades, the two most common intensification strategies investigated for improving outcomes in patients with localized prostate cancer undergoing definitive radiotherapy (RT) have been androgen deprivation therapy (ADT) and radiation dose-escalation. Although both strategies have been adopted as standard components of modern therapeutic paradigms for prostate cancer, they have divergent impacts on clinical outcomes. Randomized trials have consistently shown improved overall survival, prostate cancer specific mortality (PCSM), and distant metastasis (DM) rates when comparing combined ADT and radiation to radiation alone in intermediate- and high-risk prostate cancer [1,2,3,4], whereas dose-escalation trials have largely shown improved PSA recurrence rates only, without survival improvements [5]. Despite this, for years there have been those who have argued that dose-escalation can abrogate the need for ADT in prostate cancer treatment.

To try to clarify the relative benefits of ADT and dose-escalation in prostate cancer, Jiang and colleagues analyzed 40 randomized trials enrolling 21,429 patients with prostate cancer undergoing definitive radiation with median follow-up of 9.2 years [6]. Five different treatment strategies were compared: (1) low-dose RT alone (≤74 Gy), (2) high-dose RT alone (>74 Gy), (3) low-dose RT with short-term ADT, (4) low-dose RT with long-term ADT, and (5) high-dose RT with short-term ADT. Given so many possible pairwise comparisons of these five treatment strategies, interpretation of the results is somewhat complex, and multiple hypothesis corrections were applied. The following are some take-aways from the reported comparisons. First, no differences in PCSM or DM were observed with dose-escalation, either in patients treated with RT alone or RT with short-term ADT. Second, in patients treated low-dose RT, ADT was associated with improved PCSM and DM. Third, there was no associated in improvement in PCSM with short-term ADT and dose-escalated RT versus dose-escalated RT alone (although there was lower PCSM associated with long-term ADT and low-dose RT versus high-dose RT alone). Last, none of the treatment arms was associated with differences in overall survival after correcting for multiple hypothesis testing.

The authors should be commended for executing a thorough analysis of the available data. It is hard to argue with the authors' conclusion that the benefit of adding ADT to low-dose RT outweighs the benefit of dose-escalation based on the totality of prior evidence to date. However, the limitations of the methodology of this particular study preclude making any strong further conclusions or trying to parse the data too finely. Although the data analyzed are derived from randomized trials, the comparisons presented are not aggregated randomized comparisons, as is common in many meta-analyses, but rather are cross-trial comparisons of grouped individual arms from various trials. This largely eliminates any balancing of measured and unmeasured confounders resulting from randomization, making the comparisons prone to bias. This is further exacerbated by the fact that these comparisons involve trials that span more than two decades during an era that has seen significant stage migration as a result of Gleason score inflation and increased imaging utilization. As an illustrative example, the low-dose RT alone group includes patients from RTOG 8531 (100% high-risk, enrollment midpoint 9/1989) [3], and whereas the high-dose RT group includes both arms of PROFIT (0% high-risk, enrollment midpoint 1/2008) [7]. Thus, although outcome differences in the treatment groups could be in part due to the treatments delivered, they are unquestionably also a result of completely different populations and eras of the trials involved. To their credit, the authors adjusted comparisons for median age, midpoint of study enrollment, and proportion of high-risk patients. However, given the lack of individual patient data, there can only be fairly rudimentary adjustments, and more refined balancing of confounding factors is not possible.

Ultimately, there is no question that the preponderance of the evidence supports ADT as having a stronger influence on metastasis and PCSM than dose-escalation in unfavorable-risk prostate cancer. Thus, dose-escalation cannot abrogate the need for ADT without prospective randomized evidence. Rather than focusing on the specific radiation dose employed, studies that aim to more accurately identify patients with high enough absolute risk of metastasis and PCSM to derive a clinically meaninful benefit from ADT, such as the forthcoming NRG GU010 GUIDANCE trial (NCT05050084), likely represent a more promising strategy to optimize the risks and benefits of ADT in prostate cancer patients undergoing definitive RT.

Widely-used hormone drug associated with increased risk of benign brain tumor at high doses

sciencedaily.com

High doses of a widely-used drug used in the hormonal treatment of conditions such as excessive hair growth, early puberty, prostate cancer, are linked to an increased risk of meningioma -- the most common type of benign brain tumour, finds a University of Bristol-led study of over 8-million patients. The study is published in *Scientific Reports* today [Friday 4 Feb 2022].

Typically slow-growing, meningiomas are benign tumours, which are often revealed incidentally by imaging but can cause significant disability due to compressing or squeezing the adjacent brain, nerves and vessels and pressure effects within a fixed cranial vault.

Recent studies have reported an association between the growth of meningiomas and hormonal treatments, particularly prolonged and high dose use of the drug cyproterone acetate (CPA).

High doses of cyproterone acetate (> 50 mg/day) is usually prescribed to male patients with inoperable prostate cancer, a condition which leads to excessive hair growth known as hirsutism, or male-to-female transsexual hormonal therapy. Lower doses (2-10 mg/day) of the drug are typically used in combination with oestradiol to treat androgen-associated alopecia or female seborrhoea.

Given the drug's widespread use, researchers at the Universities of Bristol, Cambridge and the National University of Singapore, conducted a systematic review and meta-analysis study using four studies comprising a sample of 8,132,348 patients, to assess the evidence of the association between cyproterone acetate and incidence of meningiomas.

The sample included 165,988 patients who were identified as taking cyproterone acetate at varying dose amounts. Using this data, the team analysed the occurrence of meningioma in patients using high versus low dose cyproterone acetate and found a significant association between high dose usage and increased risk of meningioma. However, this association was not found with low doses.

Keng Siang Lee, a medical student and the study's lead author from Bristol Medical School at the University of Bristol, said: "The cause of meningiomas is controversial but there is strong evidence to suggest a plausible role for sex hormones in the onset of meningioma. We know it has a predilection for females especially after puberty. Furthermore, fluctuations in meningioma growth during the menstrual cycle, pregnancy, and breastfeeding have also been well-documented. We are also aware of the well-characterised distribution of progesterone, oestrogen, and androgen receptors in certain meningiomas located at the base of the skull.

"In light of these results, prescription of high-dose cyproterone acetate, especially for off label indications, should be considered carefully. Additionally, we suggest that routine screening and meningioma surveillance by brain MRI offered to patients prescribed with cyproterone acetate is likely a reasonable clinical consideration if given at high doses for long periods of time.

"However, our study underscores the current limited evidence about the risk of intracranial meningioma associated with low dose cyproterone acetate. It is still unknown whether or not cyproterone acetate below a certain threshold may be completely safe in terms of the risk of meningioma. The results obtained herein suggest the necessity for further clinical research on intracranial meningioma associated with cyproterone acetate."

Story Source:

Materials provided by **University of Bristol**. *Note: Content may be edited for style and length.*

nature.com

Awaiting the perfect diagnostic test: optimal prostate cancer care begins without a diagnosis

Tosoian, Jeffrey J.

Given the limitations of PSA as a marker for prostate cancer, there is a critical need for diagnostic tools that can reduce the use of unnecessary biopsies while preserving early detection of potentially-lethal cancers. In patients presenting with elevated PSA, the current diagnostic approach suggests that clinicians offer multi-parametric magnetic resonance imaging (mpMRI) and consider serum- or urine-based biomarkers to better define the risk of high-grade cancer prior to biopsy [1]. Still, the optimal use and interpretation of current diagnostic tools are not clearly defined, in large part due to the limitations of available clinical data [2].

In the current report, Hendriks et al. performed both urine-based SelectMDx-testing and mpMRI prior to biopsy in 599 biopsy-naïve men with PSA ≥ 3 ng/ml [3]. All men underwent systematic biopsy, and patients with suspicious mpMRI also underwent MR-guided biopsy. The authors then assessed projected clinical outcomes under each of

four potential testing strategies: (1) SelectMDx-testing-only, with biopsy performed if the SelectMDx test was positive; (2) mpMRI-only, with biopsy performed if mpMRI was positive (PI-RADS ≥ 3); (3) SelectMDx-testing followed by mpMRI if the SelectMDx test was positive, and biopsy performed if mpMRI was positive (conditional-strategy; biopsy performed only if *both* tests were positive), and (4) SelectMDx-testing and mpMRI in all patients, with biopsy performed if either test was positive (joint-strategy). Projected outcomes included the number of biopsies avoided, detection of high-grade (Grade Group [GG] ≥ 2) cancer, and detection of low-grade (GG1) cancer. SelectMDx was considered negative for scores less than −2.8, a cutoff associated with a 13% risk of detecting GG ≥ 2 cancer on biopsy after a negative test [4].

Using each strategy, the proportion of men who would have undergone SelectMDx testing and mpMRI are listed with the subsequent clinical outcomes in the Table 1 As could be expected, the sensitivity for detecting GG ≥ 2 cancer was associated with the proportion of patients who underwent biopsy under each strategy. For example, the joint strategy – under which patients proceeded to biopsy if *either* SelectMDx or mpMRI were positive – led to the highest rate of biopsy (72%) and the highest rate of detecting GG ≥ 2 cancer (98%). The conditional strategy – under which biopsy was performed only if *both* SelectMDx and mpMRI were positive—led to the lowest rate of biopsy (40%) and the lowest rate of GG ≥ 2 cancer detection (87%), while notably also providing the greatest reduction in overdiagnosis of GG1 cancers (58% reduction). On decision curve analysis, the mpMRI-only strategy—under which 51% of men underwent biopsy and 95% of GG ≥ 2 cancers were detected—demonstrated the highest net benefit. The conditional strategy (i.e. biopsy performed only if both tests were positive) provided the second-highest net benefit across the majority of risk thresholds.

Table 1 Tests performed and projected clinical outcomes under four diagnostic testing strategies.

	Determined by testing strategy		**Clinical impact of test results**		
Testing strategy	SelectMDx performed (%)	mpMRI performed (%)	Biopsies avoided (%)	GG ≥ 2 PCa detected (i.e., sensitivity)	Reduction in overdiagnosis of GG1 PCa
(1) SelectMDx-only	100%	0%	38%	90%	35%
(2) mpMRI-only	0%	100%	49%	95%	44%
(3) Conditional (biopsy if both tests positive)	100%	62%	60%	87%	58%
(4) Joint (biopsy if either test positive)	100%	100%	28%	98%	21%

The use of mpMRI has been shown to improve diagnostic yield of prostate biopsy and has emerged as a key component of diagnostic testing [5]. Clinically, the greatest concern with population-wide adoption of mpMRI is its highly variable accuracy across institutions and among individual radiologists [6, 7]. For example, Sonn et al. found the negative predictive value (NPV) of mpMRI for GG ≥ 2 cancer ranged from 40 to 87% across radiologists at a single academic center [6]. In a recent meta-analysis, Sathianathen et al observed a pooled NPV approximating 90%, although published values ranged as low as 62% by study [7]. Moreover, these data were obtained largely from experienced academic centers, as the authors acknowledged there are insufficient published data for planned analyses of nonacademic centers. Notably, the positive predictive value (PPV) of mpMRI appears to be similarly variable. In a meta-analysis of 26 experienced imaging centers [8], PI-RADS 4 lesions had an estimated overall PPV of 39%, with an interquartile range (IQR) of PPVs extending from 25 to 55%. Similarly, the interquartile range of PPVs for PI-RADS 5 lesions extended from 61 to 82% across centers. As previous authors have emphasized [7], in light of inter - and intra-institutional variability of mpMRI reading and interpretation, determining the potential utility of mpMRI in a given practice setting requires knowledge of local mpMRI data.

Considering these data and practical limitations of mpMRI (e.g., access to high-quality imaging; adherence to technical standards; time, labor, and cost associated with testing) [9], objectively-measured biomarkers obtainable in routine practice could be more practical for initial reflex testing after PSA. In the current study, it is notable that

mpMRI provided 95% sensitivity for GG ≥ 2 disease—a value likely exceeding what would be expected from population-wide use of mpMRI [6, 7, 10]. Still, the conditional strategy of initial biomarker testing, followed by mpMRI for positive biomarker tests only, resulted in the greatest reduction in biopsy (60% of patients avoided biopsy), the greatest reduction in overdiagnosis of GG1 cancers (58%), and maintained reasonably high detection of GG ≥ 2 cancers (87%). As the authors report, this approach provided the second-highest net benefit across the majority of pertinent risk thresholds. Thus, a conditional, biomarker-first testing approach – likely to be most feasible for population-level application—may also prove most clinically-beneficial under "real-world" (i.e. de-centralized) interpretation of MRI or using an alternative biomarker (or alternative cutoff of the current biomarker) with different performance metrics [11].

Ultimately, the authors are to be commended for this well-performed, prospective assessment of two clinically-available diagnostic tools. While additional studies, including head-to-head comparisons and cost-effectiveness analyses, will continue to inform the optimal diagnostic approach, these prospective data provide benchmarks of relative risks and benefits under combined testing approaches. As clinicians, a working knowledge of such data allows us to best identify which available tools can inform decision-making with the level of certainty sought by each of our patients. As the late, great Donald S. Coffey often responded when asked how much risk of prostate cancer death (in exchange for reduced morbidity) was too much risk: "That's not a medical question, that's a personal question." Until the perfect diagnostic test emerges, guiding our patients through personalized, shared decision-making will remain a most essential component of prostate cancer care.

defenseone.com

Military Pilots' DNA May Hold Key to What's Causing Their Prostate Cancers

By Tara Copp Senior Pentagon Reporter, Defense One

While military pilots are getting the first acknowledgment that they are at higher risk of certain types of cancers, they still don't know why, whether it's something in the cockpits or on the flight decks—or something completely unrelated—that they were exposed to during their flying careers.

But one study is betting the answer may be found in their cells and DNA.

Dr. Jeffrey Jones, a career flight surgeon, retired Navy captain, and current chief of urology at Houston's VA medical center, is shaping a study to look at the one of the markers that various toxic exposures leave on the cells of military pilots who have been diagnosed with prostate cancer. This marker, called DNA methylation, often precedes a mutation that leads to cancer, Jones said.

"If we find these areas of methylation, often the cancer is very close by there," Jones said. "In other words, there's been a field change associated with some exposure that produced methylation, and then later, the cell's development of frank carcinoma. So there seems to be a progression from 'normal,' to a methylation event, that leads to a subsequent cancer."

The idea is that each different type of exposure, whether to solvents, fumes or the electromagnetic radiation emitted from radars and magnetrons, will produce a distinguishable methylation pattern, whether it's found on a DNA strand or another of the microscopic components of a cell.

"We don't think it's going to be exactly the same, but we think it's going to be a similar pattern so that hopefully we could recognize it," Jones said.

Looking at methylation patterns has also been used to show links between cigarette smoking and cancer.

Jones said his researchers would also be looking for other signatures that toxic exposure can leave on DNA or elsewhere in a cell. He said these might include specific types of chromosomal aberrations; copy number alterations, which occur when the numbers of copies of a specific gene that get replicated change; and other mutations of either the nuclear or mitochondrial DNA.

Mike Crosby, a retired Navy commander who served as an F-14 radar intercept officer and now leads the non-profit group Veterans Prostate Cancer Awareness, has also been pressing industry to study the levels and types of radiation that each piece of equipment emitted.

Pilots spent hundreds, and sometimes thousands of hours sitting just behind powerful avionics equipment that was placed in the Tomcat's nose cone. He questions whether there was adequate shielding in those older jets.

"It's long overdue that the services conduct an in-cockpit test to measure the radiation effects they are being exposed to," Crosby said.

It's hardly just a problem for military aviators. For years, service members who have suspected their cancers or other illnesses were caused by toxic exposure—for example breathing in particulate matter from massive burn pits or getting exposed to radiation or chemical weapons hazards—have struggled to get the Department of Veterans Affairs to recognize their claims.

That has begun to change. A flurry of legislation and momentum generated by private veterans organizations and within the VA has begun to take the onus off the veteran to prove a link.

"It's very hard to determine if a specific exposure causes a particular effect in retrospect," Jones said. "That's why we need to look for patterns of change that are similar in these individuals, which can define a molecular signature, and begin to make an attribution of different types of exposure."

The study will be limited to prostate cancers to further reduce variables. Prostate cancer manifests in a similar way in about 85 percent of men, Jones said.

But it's also personal for Jones; as a Navy flight surgeon assigned to the U.S. Marine Corps, he flew hundreds of hours on a variety of aircraft, including the EA-6B Prowler, the F-18 Hornet, AH-1s, C-40s, and C-130s.

In 2019, at 59, he was also diagnosed with prostate cancer.

An Air Force study released earlier this year found that pilots were 23 percent more likely to develop prostate cancer than non-flying service members and 19 percent more likely to develop prostate cancer than the U.S. general population.

Jones said about 1,000 military aviation veterans have signed up to be part of the study, which is being supported by Veterans Prostate Cancer Awareness. The study would examine the service histories of those veterans—where they served, what they flew, what ordnance and equipment was on board, and other health factors to begin to isolate causes.

The study has not yet begun, Jones and others are still working to secure funding for it and hosting a fundraiser with Veterans Prostate Cancer Awareness aboard the retired aircraft carrier USS Midway in San Diego this month.

Development of a nomogram combining multiparametric magnetic resonance imaging and PSA-related parameters to enhance the detection of clinically significant cancer across different region

onlinelibrary.wiley.com

Zhien Zhou MD

Abstract

Objective

Prostate cancer (PCa) is the most prevalent cancer among males. This study attempted to develop a clinically significant prostate cancer (csPCa) risk nomogram including Prostate Imaging-Reporting and Data System (PI-RADS) score and other clinical indexes for initial prostate biopsy in light of the different prostate regions, and internal validation was further conducted.

Patients and Methods

A retrospective study was performed including 688 patients who underwent ultrasound-guided transperineal magnetic resonance imaging fusion prostate biopsy from December 2016 to July 2019. We constructed nomograms combining PI-RADS score and clinical variables (prostate-specific antigen [PSA], prostate volume (PV), age, free/total PSA, and PSA density) through univariate and multivariate logistic regression to identify patients eligible for biopsy. The performance of the predictive model was evaluated by bootstrap resampling. The area under the curve (AUC) of the receiver-operating characteristic (ROC) analysis was appointed to quantify the accuracy of the primary nomogram model for csPCa. Calibration curves were used to assess the agreement between the biopsy specimen and the predicted probability of the new nomogram. The χ^2 test was also applied to evaluate the heterogeneity between fusion biopsy and systematic biopsy based on different PI-RADS scores and prostate regions.

Results

A total of 320 of 688 included patients were diagnosed with csPCa. csPCa was defined as Gleason score ≥7. The ROC and concordance-index both presented good performance. The nomogram reached an AUC of 0.867 for predicting csPCa at the peripheral zone; meanwhile, AUC for transitional and apex zones were 0.889 and 0.757, respectively. Statistical significance was detected between fusion biopsy and systematic biopsy for PI-RADS score >3 lesions and lesions at the peripheral and transitional zones.

Conclusion

We produced a novel nomogram predicting csPCa in patients with suspected imaging according to different locations. Our results indicated that PI-RADS score combined with other clinical parameters showed a robust predictive capacity for csPCa before prostate biopsy. The new nomogram, which incorporates prebiopsy data including PSA, PV, age, and PI-RADS score, can be helpful for clinical decision-making to avoid unnecessary biops

Radiotherapy treatment modification for prostate cancer patients based on PSMA-PET/CT

ro-journal.biomedcentral.com

Jekunen, Antti

Abstract

Background

Prostate cancer is the most common cancer among men, and its diagnosis and treatment are improving. Our study evaluated how PSMA-PET/CT prior to treatment planning might improve the optimal management of prostate cancer radiotherapy.

Methods

This retrospective pilot study included 43 prostate cancer (PCa) patients referred to our radiation oncologist department, from the urology department, for radiation therapy. 18F-PSMA-PET/CT was ordered by the radiation oncologists mainly due to the lack of resent image staging. The patients were divided into three different groups according to their initially planned treatments: radical radiation therapy (RT) (newly diagnosed PCa patients), salvage RT (patients with biochemical recurrence after radical prostatectomy), or oligometastatic RT (oligometastatic PCa patients with good response after systemic treatment).

Results

Following PSMA-PET/CT, the initially planned RT was changed for 60.5% of the patients due to new findings (metastases and/or recurrent disease). The final treatment choice was effected by PSMA-PET/CT outcome in 60.5% (26/43) of the patients, and in 50% (16/32) of patients, the radiation treatment plan changed following PSMA-PET/CT. Only 39.5% (17/43) of the patients who underwent PSMA-PET/CT were treated according to their initial treatment plans.

Conclusions

Our results indicate that PSMA-PET/CT impacts treatment decisions and the selection of RT as well as adjuvant treatment protocols in the management of prostate cancer.

Personalization of Treatment Intensity for Intermediate-Risk Prostate Cancer

Editorial| Volume 112, ISSUE 3, P744-746, March 01, 2022

Zachary S. Zumsteg, MD

Prostate cancer is a heterogeneous collection of diseases that displays a wide spectrum of clinical behavior, ranging from indolent disease that should not be treated at all to lethal phenotypes that are refractory to all known treatments. Intermediate-risk (IR) localized disease, representing a middle ground between these 2 poles, comprises 40% to 50% of new localized prostate cancer diagnoses and has long represented a challenge in treatment optimization. 1,2

The vast majority of these patients are curable with local therapies like surgery and radiation therapy, but a nontrivial minority can recur, develop distant metastases, and experience prostate cancer–related mortality. Therefore, several treatment intensification strategies have been investigated in an effort to improve outcomes for these

patients. The most successful of these to date, by far, is the addition of short-term androgen deprivation therapy (ADT) to radiation therapy, which has improved metastasis and mortality rates in several randomized trials enrolling substantial proportions of patients with IR disease. 3,4

NEAR trial: A single-arm phase II trial of neoadjuvant apalutamide monotherapy and radical prostatectomy in intermediate- and high-risk prostate cancer

nature.com

Chua, Melvin L. K.

Abstract

Objective

Treatment efficacy of androgen deprivation therapy with radical prostatectomy for intermediate- to high-risk prostate cancer is less well-studied. The NEAR trial is a single-arm, phase II investigation of neoadjuvant apalutamide monotherapy and radical prostatectomy (RP) in the treatment of D'Amico intermediate- and high-risk prostate cancer (NCT03124433).

Materials and methods

Patients with histologically-proven, D'Amico intermediate- to high-risk prostate adenocarcinoma received apalutamide 240 mg once-daily for 12 weeks followed by RP + /−lymphadenectomy. Primary outcome was pathological complete response (pCR) rate. Secondary outcomes included rate of biochemical response (defined by PSA < 0.03 ng/mL at week 24 from starting apalutamide without subsequent PSA relapse), treatment-related adverse events, and RP complication rates. Correlative biomarker analyses were performed to examine for molecular predictors of treatment responses.

Results

From 2017 to 2019, 30 patients were recruited, of which 20 and 10 were high and intermediate risk, respectively; 25 completed treatment as per-protocol. We did not observe any pCR on trial; median reduction of cancer burden was 41.7% (IQR: 33.3%–60.0%). 18 out of 25 patients were classified as having a biochemical response (4 did not achieve PSA of <0.03 ng/mL at week 24 and 3 developed PSA relapse subsequently). Dry skin (*N* = 16; 53.3%), fatigue (*N* = 10; 33.3%) and skin rash (*N* = 9; 30.0%) were the most common adverse events, and there was no major peri-operative complication. We observed an association between tumours of low androgen receptor activity and PAM50 basal status with biochemical non-responders, albeit these molecular phenotypes were not associated with pathological response.

Conclusions

A 12-week course of neoadjuvant apalutamide prior to RP did not meet the primary endpoint of pCR in this trial. Tumours with low androgen receptor activity or of the PAM50 basal subtype may have a reduced response to apalutamide.

New blood test combined with image-based prostate cancer screening reduces harms and costs

sciencedaily.com

The combination of a novel blood test and magnetic resonance imaging (MRI) can reduce overdiagnosis of low-risk cancers as well as societal costs in prostate cancer screening, according to a cost-effectiveness study from Karolinska Institutet published in the journal *European Urology*. The results provide support for organised prostate cancer testing in Sweden, researchers say.

A barrier to the introduction of nationwide prostate cancer screening has been that PSA (prostate-specific antigen) tests combined with traditional biopsies result in the detection of numerous minor low-risk tumours. MRI has been shown to reduce this overdiagnosis but presents a challenge due to limited health resources. The STHLM3MRI trial has previously shown that a blood test called Stockholm3, developed by researchers at Karolinska Institutet, can reduce the number of MRIs by a third for a single screening occasion. Now, the same research group reports that this combination is also considered cost-effective in Sweden compared with both no screening and PSA test in MRI-based screening.

Further reduction in MRI

"Our latest results show that using Stockholm3 reduces the number of MRIs over a lifetime by 60 per cent. This also avoids unnecessary biopsies by 9 per cent, which reduces the overdiagnosis of low-risk cancers," says Mark Clements, associate professor at the Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, who is responsible for the cost-effectiveness study.

The analysis predicted that MRI-based screening combined with PSA or Stockholm3 would reduce prostate cancer-related deaths by 7-9 per cent over a lifetime compared with no screening at all. The health economic evaluation showed that, compared with no screening, screening with PSA followed by Stockholm3 and MRI in high-risk individuals is classified as a moderate cost per quality-adjusted life-years (QALY) gained as defined by the Swedish National Board of Health and Welfare. Furthermore, PSA combined with MRI is classified as a very high cost per QALY gained compared with Stockholm3 combined with MRI.

"This new combination with Stockholm3 can save healthcare resources and reduce societal costs while maintaining the health benefits from early detection of prostate cancer. This presents an interesting option for prostate cancer screening in Sweden," says Shuang Hao, PhD student at the Department of Medical Epidemiology and Biostatistics, Karolinska Institutet and the first author of the study.

Support for OPT in Sweden

Several regions in Sweden have started to plan and implement pilot projects for organised prostate cancer testing (OPT) through the regional cancer centres. The National OPT Working Group has recommended that the OPT pilots investigate the use of different strategies for prostate cancer screening.

"Our evidence provides support for using Stockholm3 as an additional test in MRI-based screening, which could be evaluated through one of the OPT pilots," says Tobias Nordström, associate professor of urology at the Department of Clinical Sciences, Danderyd Hospital at Karolinska Institutet, who is the principal investigator for the STHLM3MRI trial and a co-author of the cost-effectiveness study.

Wider application to other countries

The current health economic evaluation is specific to Sweden, but the simulation model used in this study is open source and can be readily adapted to assess the use of Stockholm3 and MRI in other countries. The Stockholm3 test is available for clinical use in Sweden, Norway, Denmark, Finland, Spain and Germany, and will be made available in additional European countries in 2022.

The research was financed by the Swedish Research Council, the Swedish e-Science Research Centre (SeRC), the Swedish Prostate Cancer Federation, Karolinska Institutet and The Swedish Cancer Society. One of the co-authors, Henrik Grönberg, has five prostate cancer diagnostic-related patents pending. Another co-author, Martin Eklund, is named on four of these patent applications. Karolinska Institutet collaborates with A3P Biomedical in developing the technology for the Stockholm3 test. Henrik Grönberg, Martin Eklund and Tobias Nordström own shares in A3P Biomedical.

Story Source:

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

Prostate Cancer: a comparison of focal therapy and radical prostatectomy

nature.com

Marks, Leonard S.

Focal therapy of prostate cancer (PCa) may have been born in the U.S. [1, 2], but it has grown to late adolescence (although not full maturity) in the UK. Early observational studies from University and Imperial Colleges in London have helped make focal therapy a reasonable consideration for many men with PCa [3, 4]. Now from the UK comes the present study by Shah, Reddy and associates, who compare results of focal therapy and radical prostatectomy. The work does not provide Level 1 evidence, but for now it provides a "next best thing", since attempts to perform a randomized trial (RCT) have failed to recruit.

What the Shah-Reddy study adds is the first meaningful comparison of focal therapy (N-246) vs a standard of care, radical prostatectomy (*N* = 246), in men with mostly intermediate-risk PCa. Methods of focal therapy were high-intensity focused ultrasound (~80%) and cryoablation (~20%). Groups were propensity-matched; data were collected prospectively from centers in the UK (*N* = 16) and Europe (*N* = 3) between 2005 and 2018; and results

were compared using the primary outcome of "failure-free survival" (FFS). At eight years of follow-up, some 80% of each group were failure-free, i.e., had received no additional treatment or developed metastases or died of PCa. When judged by FFS, radical prostatectomy offered no advantage over focal therapy; thus, with this article, focal therapy has gained a measure of credibility in a rightfully skeptical world.

Propensity score matching is a method used by statisticians who, when dealing with observational data, attempt to equalize the effect of known covariates on responses to different treatments. The authors have done an admirable job of putting all the major covariates into their model, and their complicated statistical methods have withstood peer-review. The results are convincing for what they are, a comparison of the efficacy of the two treatments using a retrospective analysis. Because men have proven unwilling to accept a random assignment to surgery or focal therapy, these data may remain the best available for the indefinite future.

The achievement of the authors in developing this comparison is commendable. However, to cite two of the several limitations: more than one-third of men in each group had Gleason Score 3 + 3 = 6 lesions, which would substantially increase the FFS of each group; today they would likely enter active surveillance. And the success rate for focal therapy (FFS) would have almost certainly been lower than 80%, had success been based on biopsy. Follow-up biopsies were obtained in less than half of men (personal communication, Taimur Shah), and results are not reported in the article. The study remains in the hypothesis-generating category.

The real impetus behind focal therapy is the chance of a benefit—and an even better chance of avoiding complications—in situations where treatment is desired, but life is not in immediate danger. Such is the case for many men with intermediate-risk PCa, who are willing to trade cancer-specific survival for improved quality of llfe [5]. For men with intermediate-risk PCa, which is now the commonest cancer found on MR-guided biopsy [6], proving the exact efficacy of focal therapy may be less important than re-confirming its safety.

Breast cancer risk genes linked to prostate, pancreatic and stomach cancer

newatlas.com

By Rich Haridy

New research led by scientists from the University of Cambridge has provided strong evidence that mutations in two key genes known to heighten breast cancer risk can also be linked with increased risk of developing prostate, pancreatic and stomach cancers. The study is the first to clearly quantify increased risk from BRCA genes with more than 20 types of cancer.

The discovery of the BRCA1 and BRCA2 genes in the 1990s led to a profound shift in the way breast cancer was treated. The milestone not only helped doctors identify those women most at risk of breast cancer but the findings drove the development of new kinds of cancer treatments.

Although specific BRCA mutations could be strongly linked with certain types of breast cancers, researchers long suspected the gene variants to be associated with other cancers. Prostate cancer risk in particular has been thought to be linked with these BRCA mutations but until now precise estimates of risk have been unclear.

The study looked at health record data from around 3,000 families with the BRCA1 mutation and more than 2,000 families with the BRCA2 mutation. The research focused on calculating age-relative and absolute risks for 22 types of cancer.

"These large datasets of patients have allowed us to estimate with much greater accuracy the extent to which faulty BRCA1 and BRCA2 genes increase the risk of several cancers," said lead researcher on the project Antonis Antoniou. "We've known for some time that they're linked to breast and ovarian cancer, but there's been uncertainty about other cancers."

Looking at prostate cancer the study found men carrying the BRCA2 mutation were more than twice as likely to develop that cancer by the age of 80 than men without the gene variant. Prostate cancer risk was unaffected by the BRCA1 mutation.

The relationship between BRCA mutations and prostate cancer has been suspected for a number of years. A compelling 2020 study, for example, found a treatment specifically developed to target breast cancer was found to be significantly effective against prostate cancer.

The study also found pancreatic cancer risk was doubled by carrying either the BRCA1 or BRCA2 mutations. Stomach cancer risk was also heightened by BRCA mutations, however, the researchers noted that due to the small number of cases in the dataset, they were unable to clearly quantify that risk.

Interestingly, the study found no association between skin cancer and BRCA gene variants. Prior research has suggested associations between melanoma and BRCA but Marc Tischkowitz, a co-author on the new study, said his team's data could not validate that link.

"The link between BRCA2 and prostate cancer and pancreatic cancer is now much clearer, thanks to the data we've analyzed," said Tischkowitz. "Our data suggests that there is no strong link between BRCA2 and melanoma, which may provide greater clarity to BRCA2 gene carriers. Overall, the results will add to our knowledge on optimizing cancer screening and early detection strategies for people who are known to carry these faulty genes."

The new study was published in the *Journal of Clinical Oncology*.

Source: University of Cambridge

Robot performs first laparoscopic surgery without human help

sciencedaily.com

A robot has performed laparoscopic surgery on the soft tissue of a pig without the guiding hand of a human -- a significant step in robotics toward fully automated surgery on humans. Designed by a team of Johns Hopkins University researchers, the Smart Tissue Autonomous Robot (STAR) is described today in *Science Robotics*.

"Our findings show that we can automate one of the most intricate and delicate tasks in surgery: the reconnection of two ends of an intestine. The STAR performed the procedure in four animals and it produced significantly better results than humans performing the same procedure," said senior author Axel Krieger, an assistant professor of mechanical engineering at Johns Hopkins' Whiting School of Engineering.

The robot excelled at intestinal anastomosis, a procedure that requires a high level of repetitive motion and precision. Connecting two ends of an intestine is arguably the most challenging step in gastrointestinal surgery, requiring a surgeon to suture with high accuracy and consistency. Even the slightest hand tremor or misplaced stitch can result in a leak that could have catastrophic complications for the patient.

Working with collaborators at the Children's National Hospital in Washington, D.C. and Jin Kang, a Johns Hopkins professor of electrical and computer engineering, Krieger helped create the robot, a vision-guided system designed specifically to suture soft tissue. Their current iteration advances a 2016 model that repaired a pig's intestines accurately, but required a large incision to access the intestine and more guidance from humans.

The team equipped the STAR with new features for enhanced autonomy and improved surgical precision, including specialized suturing tools and state-of-the art imaging systems that provide more accurate visualizations of the surgical field.

Soft-tissue surgery is especially hard for robots because of its unpredictability, forcing them to be able to adapt quickly to handle unexpected obstacles, Krieger said. The STAR has a novel control system that can adjust the surgical plan in real time, just as a human surgeon would.

"What makes the STAR special is that it is the first robotic system to plan, adapt, and execute a surgical plan in soft tissue with minimal human intervention," Krieger said.

A structural-light based three-dimensional endoscope and machine learning-based tracking algorithm developed by Kang and his students guides STAR. "We believe an advanced three-dimensional machine vision system is essential in making intelligent surgical robots smarter and safer," Kang said.

As the medical field moves towards more laparoscopic approaches for surgeries, it will be important to have an automated robotic system designed for such procedures to assist, Krieger said.

"Robotic anastomosis is one way to ensure that surgical tasks that require high precision and repeatability can be performed with more accuracy and precision in every patient independent of surgeon skill," Krieger said. "We hypothesize that this will result in a democratized surgical approach to patient care with more predictable and consistent patient outcomes."

The team from Johns Hopkins also included Hamed Saeidi, Justin D. Opfermann, Michael Kam, Shuwen Wei, and Simon Leonard. Michael H. Hsieh, director of Transitional Urology at Children's National Hospital, also contributed to the research.

The work was supported by the National Institute of Biomedical Imaging and Bioengineering of the National Institutes of Health under award numbers 1R01EB020610 and R21EB024707.

Story Source:

Materials provided by **Johns Hopkins University**. Original written by Catherine Graham. *Note: Content may be edited for style and length.*

AI Holds Its Own vs Pathologists for Prostate Cancer Diagnosis

medscape.com

Artificial intelligence (AI) performs as well as expert uropathologists – and in some cases better than general pathologists – in diagnosing and grading prostate cancer, suggests a new study.

AI has shown promise in the diagnosis and grading of prostate cancer. However studies so far have been siloed, "with limited proof for generalization across diverse multinational cohorts, representing one of the central barriers to implementation of AI algorithms in clinical practice," the investigators wrote in Nature Medicine.

Wouter Bulten, from the Radboud Institute for Health Sciences, Radboud University Medical Center, Nijmegen, the Netherlands, and coauthors reported the outcomes of the international PANDA histopathology competition, in which 1,290 deep learning algorithm developers were challenged to come up with reproducible algorithms that could match the findings of human experts. Deep learning is a form of machine learning in which artificial neural networks "learn" from large datasets and apply that learning in a similar way to the human brain. At least one AI product for detecting prostate cancer – the Paige Prostate system – has already been approved for clinical use in the United States. The Food and Drug Administration authorized marketing it in September 2021, as an adjunct to – but not replacement for – pathologist review.

The developers of the new algorithms participating in the competition were given a set of 10,616 digitized prostate biopsies to learn from, then were tested against a panel of either one to six – depending on the country – experienced uropathologists on a set of 393 digitized slides. A selection of 15 teams were then invited to take part in a validation phase with an additional 1,616 slides.

Within the first 10 days of the competition, one algorithm already achieved greater than 0.90 agreement with the uropathologists; by day 33, the median performance of all the teams in the competition was greater than 0.85 agreement with the human experts.

Algorithms Correctly Detected Tumors in 99.7% of Cases

The algorithms selected for validation showed even higher levels of agreement – 0.931 on average (95% confidence interval, 0.918-0.944). These algorithms correctly detected tumors in 99.7% of cases (95% CI, 98.1%-99.7%), and correctly identified 92.9% of negative results (95% CI, 91.9%-96.7%).

When it came to classifying the prostate cancers based on Gleason grade, the algorithms showed significantly more agreement with uropathologists than did an international panel of 13 or 20 general pathologists.

"This higher sensitivity shows promise for reducing pathologist workload by automated identification and exclusion of most benign biopsies from review," the authors wrote.

The study found that the AI algorithms missed 1%-1.9% of cancers, but the general pathologists missed 1.8%-7.3%. The algorithms demonstrated a sensitivity of 96.4%-98.2% and specificity of 75%-100% for tumors, whereas the pathologists showed a sensitivity of 91.9-96.5% and specificity of 92.3%-95%.

Benign Cases Were Misclassified

The main error that the algorithms made was misclassifying benign cases as ISUP GG 1 cancer. The authors commented that this was likely caused by a shift in the distribution of cases between the training data given to the algorithms and the data set they were validated on.

They also noted that, in one validation set, the algorithms overgraded a "substantial proportion" of ISUP GG 3 cases as GG 4, whereas general pathologists tended to undergrade cases, particularly in the higher-grade cancers.

"These differences suggest that general pathologists supported by AI could reach higher agreements with uropathologists, potentially alleviating some of the rater variability associated with Gleason grading," they wrote.

The authors also pointed out that the algorithms were validated on individual biopsies from each patient, whereas in the clinical context, a pathologist would likely have multiple biopsies from a single patient.

"Future studies can focus on patient-level evaluation of tissue samples, taking multiple cores and sections into account for the final diagnosis," they wrote.

The study was supported by the Dutch Cancer Society, Netherlands Organization for Scientific Research, Google, Verily Life Sciences, Swedish Research Council, Swedish Cancer Society, Swedish eScience Research Center, EIT Health, Karolinska Institutet, Åke Wiberg Foundation, Prostatacancerförbundet, Academy of Finland, Can-

cer Foundation Finland, and ERAPerMed. The authors declared a range of grants and funding outside the study, including from Philips Digital Pathology Solutions. Several authors declared patents related to prostate cancer diagnoses, and 10 were employees of Google.

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

Meta-analysis may help guide treatment planning for patients with high-risk prostate cancer

sciencedaily.com

Results of a large study led by UCLA Jonsson Comprehensive Cancer Center researchers could help guide treatment planning for patients with high-risk prostate cancer.

An international effort consisting of a consortium of 16 research centers in collaboration with two international cooperative trial groups found that patients receiving high-dose external beam radiation therapy alone may benefit from androgen deprivation therapy (ADT) lasting longer than 18 months, while those with external beam radiation therapy and a brachytherapy boost -- the implantation of radioactive seeds to deliver a higher total dose to the prostate -- may be optimally managed with 18 months of ADT or possibly less. Results are published in the Jan. 20 issue of *JAMA Oncology*.

"Adding androgen deprivation therapy to radiation therapy has been consistently shown to improve survival when treating men with high-risk prostate cancer. However, lowering testosterone levels is associated with a number of side effects, including not only a decrement in quality of life, but possibly more serious adverse events when longer durations are used. While it has long been hypothesized that by delivering extremely high doses of radiation, one might be able to shorten the required duration of ADT, this has never been proven," said lead author Amar Kishan, MD, associate professor and vice chair of clinical and translational research in the Department of Radiation Oncology at UCLA and a researcher at the UCLA Jonsson Comprehensive Cancer Center.

The researchers analyzed individual patient data from three cohorts of patients: a retrospective cohort of patients from 16 cancer treatment referral centers between 2000 and 2014 who received either high-dose external beam radiotherapy or external beam radiotherapy with a brachytherapy boost; a cohort of patients enrolled in a randomized phase 3 trial that included patients from 23 treatment centers in Australia and New Zealand; and a cohort of patients enrolled in a randomized phase 3 trial conducted across 10 treatment centers in Spain. This is the only analysis to include both retrospective and prospective data in evaluating optimal ADT duration in high-risk prostate patients receiving these two forms of radiation therapy.

"Because of androgen deprivation therapy's unpleasant side effects, it is often underutilized, with men receiving considerably shorter durations of ADT than might be recommended. To discern the ADT duration thresholds that provide the greatest metastasis-free survival benefit for these patients, we analyzed a multi-institutional database of patients, developed hypotheses, and then evaluated our findings by analyzing individual patient data from randomized trials," said Kishan.

"The consistency of our results across multiple different patient cohorts greatly strengthens our findings," said Tahmineh Romero, senior statistician in the UCLA Department of Medicine Statistics Core and the senior author of the article.

In the retrospective cohort -- looking at ADT durations of less than six months, six to 18 months, and greater than 18 months -- a significant interaction was seen between treatment type and ADT duration. A duration of 18 months or more was associated with improved outcomes, relative to shorter durations, for patients receiving high-dose external beam radiation therapy without a brachytherapy boost. In contrast, among patients receiving radiation therapy and brachytherapy, an ADT duration of at least six months but less than 18 months was associated with improved metastasis-free survival and overall survival, compared to receipt of less than six months of ADT. But there appeared to be no improvement in metastasis-free survival for those receiving both forms of radiation therapy and more than 18 months of ADT.

With further analysis, the researchers determined that for patients receiving radiation therapy without brachytherapy, the optimal ADT duration was 26.3 months; for those treated with radiation therapy and a brachytherapy boost, the minimum threshold was 12 months. Their hypotheses drawn from the retrospective study appeared to be supported by effects observed in the randomized clinical trials.

"Contrary to findings in a previous study, our results suggest that optimal duration of ADT for patients receiving high-dose radiation therapy may be more than 18 months. This is implied by findings from all the cohorts we analyzed. A secondary conclusion, based on the retrospective dataset, is that ADT duration shorter than 18 months may be sufficient for patients undergoing both radiation therapy and brachytherapy. Although current and future studies will continue to offer clarification, individual patient meta-analyses incorporating data from various trials may provide the best current guidance for doctors and patients. We have additional studies underway to explore this concept further," said Kishan.

Newer Hormone Treatments for Prostate Cancer May Raise Risk of Depression

By Dennis Thompson HealthDay Reporter

medicinenet.com

TUESDAY, Jan. 18, 2022 (HealthDay Now)

Advanced forms of hormone therapy are very effective at keeping prostate cancer in check, but they also can double a man's risk of falling into depression, researchers have found.

Prostate cancer patients treated with the latest forms of hormone blockers were twice as likely to develop depression compared with men treated with older forms of hormone therapy or those who received no such medication at all, results from a new study show.

It's a risk that cancer doctors will need to keep in mind when prescribing these drugs to patients, said lead researcher Dr. Kevin Nead, an assistant professor of epidemiology at the University of Texas MD Anderson Cancer Center in Houston.

"Our study does not suggest that any men who are eligible for these medications should not be on them because of the risk of depression," he said. "What it does reinforce is that we have people who we know, because they have cancer, are already at increased risk for depression."

Putting them on these medications is potentially doubling their risk, and Nead said, depression in cancer patients is associated with worse survival.

"These are patients we need to pay a lot of attention to and try to have early interventions to prevent or treat their depression, because it will impact their overall outcomes," he said.

Prostate cancer feeds on male hormones like testosterone, which are also known as androgens. Doctors have long treated prostate cancer in part by blocking androgen, depriving cancer cells of their fuel.

They now have second-generation anti-androgen drugs like abiraterone and apalutamide that are even better at blocking testosterone than earlier medications, researchers said.

But a lack of testosterone increases a man's overall risk of depression, whether or not he has prostate cancer.

"Men with low testosterone are at an increased risk of depression," Nead said. "In men who have low testosterone, if you give them testosterone back, it actually improves their mood and decreases the risk of depression."

Cancer patients are at increased risk of depression anyway, given their battle with a deadly disease. Worse, depression tends to profoundly impact the outlook for cancer patients.

"We know depression in cancer patients is particularly bad in that it's associated with patients having worse cancer outcomes, including worse overall survival," Nead said.

Depression "might impact people's interest in being aggressive" with their cancer treatment, he added. "It might affect their overall health and how they can tolerate different therapies. It might affect their decisions on how they pursue their cancer care or how often they see their doctor."

To see how much additional risk of depression comes with the newer androgen blockers, Nead's team analyzed data from nearly 30,100 prostate cancer patients.

They broke the men into three groups -- those who received no hormone therapy, those who got the more established medications, and those treated with second-generation anti-androgen drugs.

"If you look across all three of these groups, the men that received second-generation anti-androgens had an increased risk of depression," Nead said.

The risk likely increases so dramatically because the second-generation drugs are so much more better at their job, said Dr. Bobby Liaw, clinical director of genitourinary oncology for the Mount Sinai Health System in New York City.

The older drugs "do very well in bringing your testosterone levels down, but they only stop testosterone production at the main factory of testosterone, which is the testes," Liaw explained.

"In reality, you do have some small amounts of androgen production from other places in the body that traditional hormone therapy would not shut down," he added. For example, the adrenal gland produces a small amount of male hormone, as do fat cells.

"You come along with a much more potent androgen receptor antagonist, it will further deprive cells already kind of starved for testosterone of even more of it," Liaw said. "It's not a big surprise it could worsen moods and depression."

Neither Nead nor Liaw felt that the depression risk from the newer drugs outweighs their benefits for prostate cancer patients, however.

"It's not to say that just because there's that risk of depression that we should entirely shy away from an otherwise very efficacious treatment, but I think it definitely warrants us being a little bit more cognizant," Liaw said. "We do need to be much more cognizant of these long-term side effects. We need to be more prepared to catch early signs of depression."

Family members and friends of prostate cancer patients can help by watching their loved ones as they undergo hormone therapy for signs of depression, the doctors said.

"Often times the patient themselves may not always be the best judge of it. From day to day, if it's a small change, they might not notice it," Liaw said.

The new study was recently published in *JAMA Network Open*.

More information

The National Institute of Mental Health has more about depression.

SOURCES: Kevin Nead, MD, MPhil, assistant professor, epidemiology, University of Texas MD Anderson Cancer Center, Houston; Bobby Liaw, MD, clinical director, genitourinary oncology, Mount Sinai Health System, New York City; *JAMA Network Open*, Dec. 23, 2021

From WebMD

We've Never Really Understood the Prostate

medpagetoday.com

Howard Wolinsky,

Special Reports > A Patient's Journey

— Wolinsky reviews Ericka Johnson's new book, *A Cultural Biography of the Prostate*

by Contributing Writer, MedPage Today January 19, 2022

The mistreatment of women on sexual health issues -- from mastectomies and hysterectomies to pregnancy and even surgery on sex organs to enhance male pleasure -- at the hands of mainly male physicians has been a major theme since the emergence of the modern feminist movement in the 1960s.

But what has been largely overlooked has been the similar sort of mistreatment and manhandling of men and their prostates at the hands of mainly male, but now also female, urologists.

It took Ericka Johnson, PhD, a professor of gender and society at Linköping University, Sweden, using feminist studies critiques, to expose this maltreatment of men in her new book, *A Cultural Biography of the Prostate* (MIT Press, 2021).

For much of history, as told by Johnson, the prostate has been unknown and unappreciated, an anonymous mass of glands, blood vessels, and muscle tissue. The great anatomic artists didn't acknowledge the existence of the prostate until the 16th century.

Once medicine got a bead on the prostate about 120 years ago, the aggression began -- a virtual war on the gland that exists to liquefy sperm, easing the way for pregnancy.

But reminiscent of the attacks on women by gynecologists and other doctors, early urologists performed orchiectomies with the ill-conceived notion that surgical removal of testicles would help men with the urinary problems from overgrown prostates. It didn't.

Surgeons at Johns Hopkins developed the destructive mastectomy and then moved on to the just as destructive prostatectomy. Breast cancer and prostate cancer are twin phenomena, though early critics focused on the breasts and ignored prostates.

In a chapter on the PSA blood test, which Johnson says is the "most feared test" for men, she describes the confusion and damage wrought by PSA screening in more contemporary times, starting in the 1990s, which resulted in a few lives saved and many men becoming the victims of impotence, incontinence, penis shrinkage, and loss of libido because they rushed into interventional treatment.

I had undergone PSA screening since my mid-50s, beginning around the year 2000. I had no warning signs of problems. But during summer 2010, my internist became alarmed as my PSA had risen from 3.2 ng/ml to nearly the threshold of trouble, 4.0 ng/ml. He sent me to a community urologic oncologist for an evaluation.

The urologist performed a transrectal biopsy in his office -- with my *lucky* wife present (talk about sharing). The first biopsy was inconclusive. So, I had a follow-up done -- no wife present -- in December 2010. A single core was found, with a one-millimeter fragment of Gleason 6. The urologists presented this as an existential threat. I know now that many urologists don't consider Gleason 6 a cancer.

The urologist tried to talk me into an immediate radical prostatectomy. He didn't support active surveillance. I got a second opinion the next day at the University of Chicago, where they offered active surveillance and I gladly accepted.

I'm not alone in this terrifying experience. Unfortunately, many men were -- and remain -- frightened by their PSA results and Gleason scores and aren't given or decline the option of active surveillance.

Since its identification, Johnson notes: "The prostate was associated with masculine physical activities, like horse-riding in the damp and cold, or long hours of office work. The historical material also contained elements of sexual morality, blaming prostate problems on sowing wild oats in one's youth, or marrying a younger wife in the autumn of one's life." Wrong again.

Johnson's views on the "absent prostate," are a tour de force. She writes: "The absent prostate, the prostate that has been surgically removed, scraped away from the inside, radiated, electrocuted, microwaved, pharmacologically shrunk, or otherwise destroyed. The missing prostate was the discursive -- and very real -- source of at least as much torment as a still-present-in-the-body prostate."

The missing prostate takes on a life of its own and may haunt its previous owners and partners for years to come -- or not.

As someone who has avoided aggressive prostate treatment, this chapter was eye-opening: the absent gland still exerts a presence on men who have had surgical or radiation treatment and experienced sexual and urinary side effects.

The missing prostate is still present in these men's lives and those of their partners. This chapter gave me a deeper understanding of the impact of treatment on friends of mine who were even driven to the brink of suicide by the consequences they and their partners or spouses experienced, including urine leakage in intercourse and retrograde ejaculation.

To most men, the prostate is an invisible organ until they experience seemingly inevitable troubles. It can be benign prostatic hyperplasia, prostate cancer, or prostatitis, which itself is a mystery within a mystery to which Johnson devotes a chapter.

She notes the need for medicine to understand the prostate issues of gay men and transgender women whose prostates are intact and can become cancerous.

In my view, Johnson should have written a chapter on active surveillance, a strategy that could help the majority of the 1.4 million men globally who annually are diagnosed with prostate cancer avoid the potentially nasty side effects of surgery and radiation therapy.

I am biased as a man who has been on AS for many years. Johnson may be biased because of what a huge success AS has been in Sweden: 55% of U.S. candidates with low-risk prostate cancer go on AS versus about 94% in Sweden.

Why the huge gap between the systems? There's more at play than the differences in the incentives for healthcare systems to provide treatments or perform surgeries.

Other topics I would have liked to have seen covered in the book include an analysis of whether Gleason 6 actually is cancer and a perspective on the ongoing debate over transrectal versus transperineal biopsies. However, Johnson's minor sins of omission are overshadowed by her insight, prose, and analytical skill.

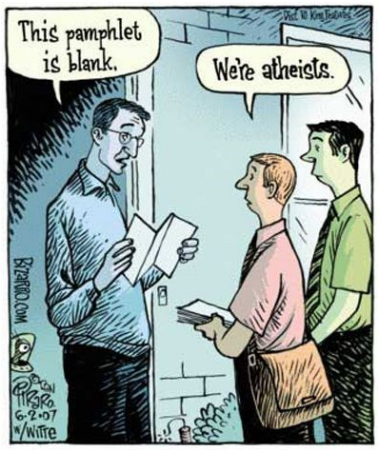
The late comedian George Burns, who played "God" in the movies, was asked what mistakes he, as God, had made. His answer? First, there was the avocado and its outsized pit. And then, there was the prostate.

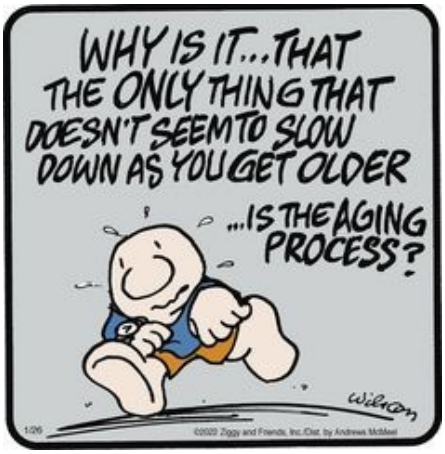
Johnson sheds light on the mistakes doctors have historically made with the prostate and the impact this has had on society, and on men with and without these underappreciated glands and their partners.

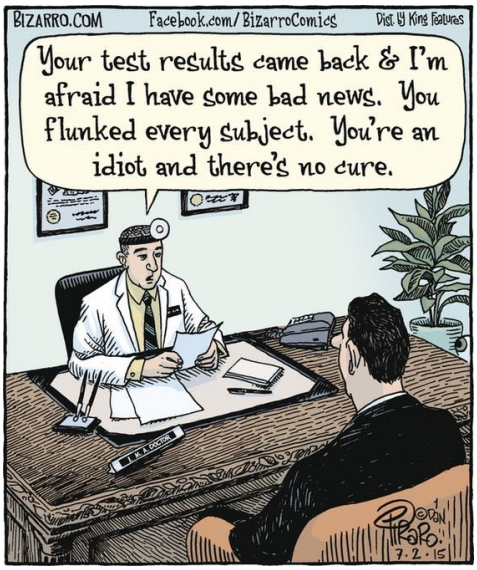
Johnson will be speaking in a webinar at 12 p.m. Eastern Time on Saturday, February 26 to Active Surveillance Patients International. You can register here.

Howard Wolinsky is a Chicago-based medical freelancer who has written this blog about his cancer journey for MedPage Today since 2016, and has been on active surveillance for very low-risk prostate cancer since 2010. He is the author of the book, Contain and Eliminate: The American Medical Association's Conspiracy to Destroy Chiropractic.

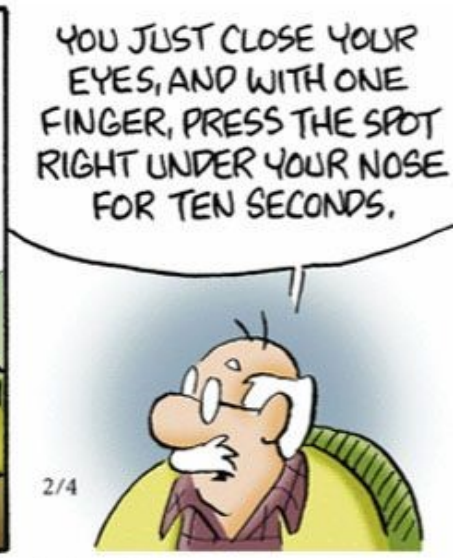
On the Lighter Side







"It's a flashlight. I couldn't find any candles."



"The doctor said you're lucky it wasn't lower."