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

December 2020 NEWSLETTER

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

Monday, January 04,

Volume 13 Issue 12

- **Saturday, January 16th, 2021 IPCSG - Live-Stream Event, 10:00am PT**
  Dr. A. J. Mundt and Dr. Tyler Seibert
  Watch your email for the meeting notice and subject of this meeting (TBD)

- 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

Role of Genetic Testing in Prostate Cancer
Richard Lam, MD, Prostate Oncology Specialists, Marina del Rey, CA

November 2020 Informed Prostate Cancer Support Group Meeting
Summary by Bill Lewis

Uses of genetic testing, overview:

- Screening to detect clinically significant prostate cancer-Is a biopsy needed?
- Decision making regarding active surveillance
- Access prognosis after treatment
- Guide treatment
- Hereditary genetics

Genetic testing involves analysis of abnormalities in the DNA of the patient. DNA segments called genes provide the molecular instructions for the creation of amino acids, which make up proteins, from which cells, tissues and organs of our bodies are made. Cancer arises from gene mutations, which can be of either of two categories. **Germline mutations** are heritable mutations that are present in the egg or sperm of the parents, and can cause hereditary cancer types. **Somatic mutations** can occur anytime in an individual's life, not by inheritance, but by some other cause, and can cause cancers, usually later-onset.

(Continued on page 3)

Organization

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

IPCSG

Officers

Lyle LaRosh President

Additional Directors

Gene Van Vleet

John Tassi

Bill Manning

Honorary Directors

Dr. Dick Gilbert

Judge Robert Coates

Aaron Lamb, ... Facilitator
Bill Manning, ...Videographer
John Tassi, ...Webmaster
Bill Bailey, ...Librarian
Jim Kilduff, ...Greeter
John Tassi .....Meeting Set-up
Stephen Pendergast ..... Editor

NEWSLETTER
Table of Contents

PROSTATE CANCER—*2 WORDS, NOT A SENTENCE*

What We Are About

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

Meeting Video DVD's

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

From the Editor

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

We will continue to post and distribute the newsletter in the interim. In order to include more articles of interest in this issue, we have included extra pages in the web distributed version of the newsletter. The mail version is limited to ten pages..

Articles of Interest

- 177Lu-EB-PSMA Radioligand Therapy with Escalating Doses in Patients with Metastatic Castration-Resistant Prostate Cancer
- Clinical Challenges: Can MRI and Biomarkers Replace Biopsy for AS in Prostate Cancer?
- Androgen receptor signaling-targeted therapy and taxane chemotherapy induce visceral metastasis in castration-resistant prostate cancer
- New high-resolution imaging scans approved for use in prostate cancer - Harvard Health Blog
- FDA approves first, oral LHRH antagonist
- Prostate cancer regulator plays role in COVID-19, providing a promising treatment lead
- Genetics, epigenetics, and the evolution of prostate cancer
- Prostate Cancer Progression and the Epigenome
- Androgen-Deprivation Therapy Linked to Worse Fitness, CV Mortality
- Early-onset prostate cancer is associated with increased risks of disease progression and cancer-specific mortality
- Whole pelvic salvage radiation may be better than precisely targeted lymph node salvage radiation

Join the IPCSG TEAM

If you consider the IPCSG to be valuable in your cancer journey, realize that we need people to step up and HELP. Call **President** Lyle LaRosh @ 619-892-3888; or **Director** Gene Van Vleet @ 619-890-8447.

(Continued from page 1)

Prostate cancer is the second most common cause of cancer in men (after skin cancer), and the second leading cause of cancer death in men (after lung cancer). It is estimated that there will be 192,000 new cases diagnosed this year, and about 31,000 deaths. A little over 3 million men are currently living with (diagnosed) prostate cancer. One in nine men will be diagnosed with it in his lifetime, and one in 41 men will die of it.

After the PSA test was introduced in 1989, the proportion of men found on initial diagnosis to have localized prostate cancer was 80%, versus 20% having advanced prostate cancer. Prior to that time, the proportions were reversed: 80% of men were found to already have advanced prostate cancer when first diagnosed, because the diagnosis followed the appearance of symptoms (itself often a sign of advanced cancer) or a lump in a routine digital rectal exam (DRE).

Despite this great benefit of PSA testing, a controversy arose in 2012 when the USPSTF (US Preventative Service Task Force) advised against PSA screening, writing that the benefits did not outweigh the risks. They asserted that it took PSA screening of 1000 men to save one additional life. Essentially the problem was that too many low-level "cancers" were found and treated, with costs and morbidity/complications (including occasional death) from biopsies and surgery. Most early cancers were slow growing and not lethal, so should not have been treated. However, the PSA test is valuable for detecting advanced disease, for which treatments to prolong life and quality of life have improved.

A goal in the "prostate cancer world" is to be able to distinguish between benign, indolent prostate cancers and "clinically significant" cancers that have the potential to spread and jeopardize survival. Genetic testing may help to detect clinically significant prostate cancer and to answer the question "Is a biopsy needed?" Apart from genetic testing, factors that may be involved in deciding the need for a biopsy are: Elevated PSA, PSA density (PSA score vs. the size of the prostate), an abnormal DRE, a lesion seen on MRI or ultrasound, the size of the lesion, and a 4K Score or Prostate Health Index score (Dr. Lam calls these "super PSA" tests – they give more information than a regular PSA test).

Genetic testing has a role in borderline cases, to avoid simply choosing to do a biopsy – which can lead to bleeding, temporary impotence and "some" pain. A commercially available genetic test called ExoDx is a urine test that predicts the presence or absence of high-grade (i.e., a Gleason score of 7 or higher) prostate cancer for men 50 years or older, with a PSA between 2 and 10, who are considering biopsy. It analyzes the levels of four "exosomal RNA" genes, and gives a score indicative of low or high risk.

A competing test, the Select-MDX, measures 3 other genes in the patient's urine sample, and has similarly high predictive value of the presence or absence of high-grade prostate cancer.

The Confirm MDX test is used when a biopsy comes back negative, but there is concern that a cancerous lesion may have been missed by the needles in the first biopsy, to indicate whether a repeat biopsy is warranted. Remember, a typical transrectal ultrasound guided prostate biopsy using 12 needles, only samples 1% of the prostate, and some areas can't be reached by the needles. Tissue from the first biopsy is tested for 3 gene variations, which are found in cells near a tumor, though the cells themselves are not cancerous. An alternative would be to test the urine, using the ExoDX or Select-MDX test.

Genetic testing in men who have been diagnosed with prostate cancer is often used to decide whether active surveillance is appropriate. Low risk prostate cancer has these characteristics: PSA<10, Digital rectal exam (DRE): T1c (no nodules) or T2a (small nodule), Gleason Score = 3+3 or "select" 3+4, <25% of cores involved, favorable genetic profile, and small or no lesions seen on MRI or ultrasound.

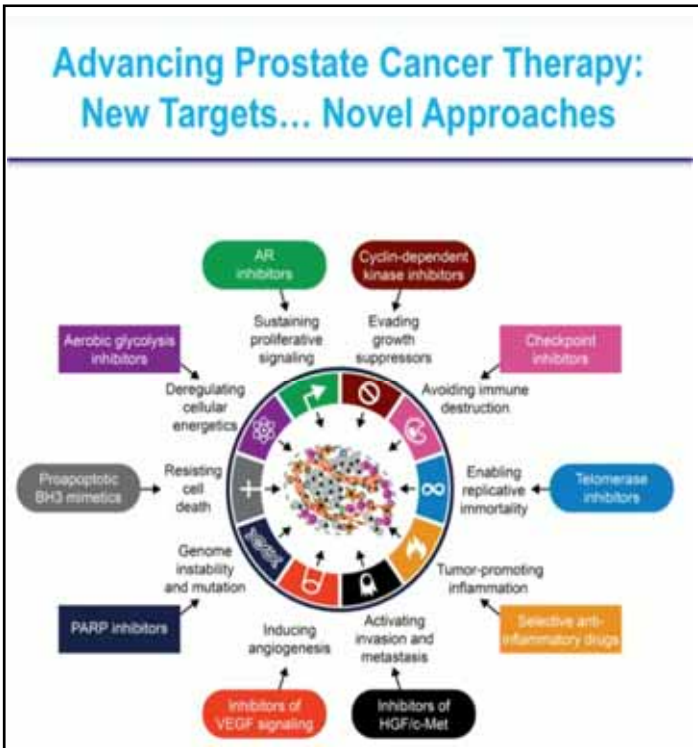
The Prolaris test (Myriad Genetics) checks for 46 genes in the biopsy sample, and compares the results with a database of men with similar biopsy results, to determine the likely aggressiveness of the cancer.

The Oncotype DX test (Genomic Health, Inc) measures the loss of the PTEN gene (and 16 others) in the DNA of tumor cells in the biopsy tissue, and its "Genomic Prostate Score" (GPS) indicates the likelihood of "favorably pathology" at the time of prostatectomy, and also the tumor aggressiveness. This helps to confirm the true risk stratification of the cancer. It is used only for low and intermediate risk prostate cancer.

The Decipher test (GenomeDx Biosciences) predicts high-grade disease (Gleason Grade 4 or 5), the likelihood of metastases within 5 years, and the 10 year prostate cancer-specific mortality. It can clarify those who may be suitable candidates for active surveillance, clarify those who may be treated with local therapy alone, and clarify those who may benefit from intense multi-modal therapy.

Dr. Lam likes the Oncotype test best, but also has been happy with the Prolaris and Decipher tests.

(Continued on page 4)



(Continued from page 3)

For assessing the prognosis after treatment, GenomeDx has a "Decipher – Post-RP" test that indicates whether adjuvant radiation after radical prostatectomy is likely to lead to lower rates of metastases. The test is done on tissue from the removed prostate, so more information is available than from other tests done on biopsy samples. They are working on tests that will help predict patient response to ADT, chemotherapy or other drugs, and Dr. Lam looks forward to data that will enable us to trust these predictions.

For patients who are metastatic and castrate-resistant, and who are progressing on standard Taxotere, Jevtana, Zytiga, Xtandi, and/or Xofigo treatments, there are genetic tests available on either cancer tissue (primary tumor or metastases) or from circulating tumor cells (CTCs) in the blood:

The Guardant 360 test is a blood test which detects cell-free DNA (much more abundant than CTCs!), and digitally sequences various genomic points to look for genetic alterations that are potentially associated with treatment options. Not surprisingly, the BRCA1 and BRCA2 genes are among the 68 genes in the panel, but 16 other genes on the list are currently being studied by various research groups as potential targets for new therapeutic treatments.

The Foundation One test is a genetic analysis using tumor tissue either from the primary tumor or a metastasis. It analyzes 315 cancer-related genes for genetic alterations, identifying genomic alterations associated with various targeted therapies (i.e., therapies that may help the patient), and quantifying clinical markers associated with immunotherapy response (i.e. indicating if an immunotherapy is likely to be of benefit). It also identifies relevant clinical trials.

The Foundation "Act" (Assay for Circulating Tumor DNA) test samples peripheral blood (like the Guardant360 test), and is used for patients who are "difficult to biopsy." It analyzes 62 of the most common cancer-causing genes that are linked to (and therefore may suggest) therapeutic options.

The first treatment that was devised based on a genetic mutation was introduced about five years ago. PARP inhibitors are medications that specifically target prostate cancer with BRCA mutations (whether germline or somatic), and/or ATM, FANCA or Chk2 genes. Olaparib was previously used for ovarian and breast cancers, but it was found that it provided a benefit to many men with metastatic prostate cancer who had such gene mutations. Olaparib and Rucaparib are both now approved for those patients. These patients also tend to respond well to platinum-based chemotherapy (e.g., carboplatinum).

Another gene abnormality that can be identified by genetic testing is "micro-satellite instability" (certain genes that are very unstable and mutate very easily). Only about 10% of patients have this condition, but for those who do, Pemrolizumab has been able to control the cancer for years.

The AR-V7 Splice Variant (AR-V7 is part of the gene that codes for the androgen receptor in prostate / prostate cancer cells) is important because it may develop in 30-40% of prostate cancer patients who are treated with either Zytiga (abiraterone) or Xtandi (enzalutamide) for a long time (until "resistance" occurs). At that point, data from this test can predict resistance to the other of these two drugs, and indicate whether it is unlikely that switching drugs would be beneficial. It can be detected in blood, in CTC's (circulating tumor cells), for example at Johns Hopkins Hospital. It is expected that new drugs will be developed to target this mutation. We're waiting for results on a new drug from a company in San Diego, called Arvinas.

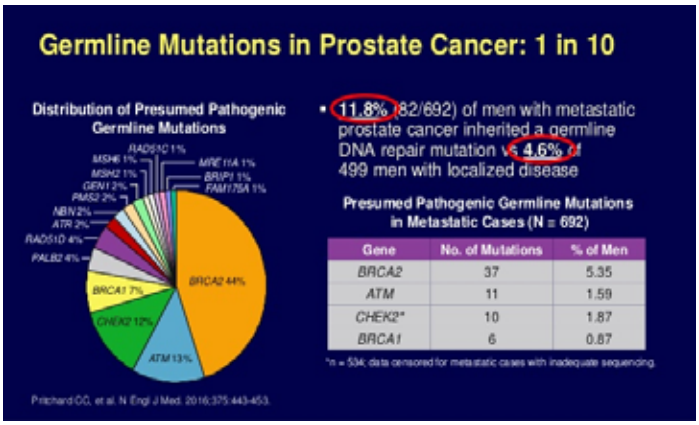
Hereditary Genetics (Germline mutations): Checked using blood of saliva. Provides info about prognosis of the patient's prostate cancer, and can guide treatments. It predicts cancer risks for the patient's offspring. When to test: Anyone with "high Gleason score" prostate can-

(Continued on page 5)

cer (whether or not they have metastases), anyone with metastases (regardless of the Gleason score) or with a family history of prostate, ovarian, or breast cancer or members with early age at diagnosis of any cancer.

BRCA1 & BRCA2: Generally means a worse prognosis (perhaps no active surveillance, even if favorable Gleason scores). There is a 50% risk of passing the defect(s) to offspring. Also associated with breast, ovarian, pancreatic, and skin cancers. Responds to PARP inhibitors.

MLHL, MSH2, MSH6, PMS2, and EPCAM: "Same" prognosis (i.e., these defects don't seem to affect the prognosis); 50% risk of passing to offspring. Also associated with colon, stomach, liver, endometrial, skin, kidney, brain cancers. Responds to anti-PD-1 drugs (e.g., Keytruda, Opdivo, Tecentriq).



Questions: After how much time should one consider a fresh genetic test, to pick up newly-identified mutations relevant to prostate cancer treatment? About 5 to 7 years. The rate of identifying new mutations is not very fast. Also note that there are "variants of unknown significance." Some gene variants are not known to be associated with a risk for a particular disease, such as the Lynch or Rad genes. But be vigilant in such cases to monitor or arrange to be notified when more information about the variants are discovered.

Do most urologists do any of these genetic tests? Dr. Lam hopes that they would use genetic testing to decide if a biopsy is needed. Urologists who are more well-read and more "cerebral" are more likely to use the ExoDx and Select-MDx urine tests and the 4K Score. That might be about a third of urologists. The urologists at UCLA that Dr. Lam has worked with do a lot of post-biopsy tests, such as Prolaris, Oncotype or Decipher before jumping in to make a treatment recommendation. He believes that urologists who manage metastatic disease do not use genetic testing. Oncologists are beginning to test, especially since they do it for other cancers as well.

Is anyone tracking genetic testing predictions vs. case outcomes – how many "low risk" patients go on to metastatic disease or fatality? Such tracking (for 5-10 years) was done before the test was introduced commercially, but he's not aware of ongoing tracking of that type.

What tests would he recommend for a man with Gleason 9 and recurrence after prostatectomy? Germline testing would be appropriate, to check for BRCA or other "bad" genes. Testing of the tumor cells would not change treatment, so he would not do it at this point.

Which imaging tests are best and not locally available? Imaging is certainly very important, and psma tests using gallium-68 (at UCSF or UCLA) and the pyl psma test (fluorine F 18 DCFPyL agent; at Stanford) give a higher chance of finding cancer at a lower PSA, whether in the lymph nodes or the bones. Formerly, using CT scans and bone scans, the cancer was not usually visible unless the PSA was 10 – 20. Now, we may even be able to see the cancer in a lymph node when the PSA is 0.5 with these experimental tests. The Axumin test is FDA approved for men who have a relapse after surgery or radiation, and has a higher likelihood of finding where the cancer is than CT or bone scans. It's a "reasonably" good test, until the psma test(s) are approved for general use.

How well do the various genetic tests correlate with each other? For pre-biopsy, about 80%, with his preference leaning toward the ExoDx test as more sensitive/accurate than the Select-MDX test, but we really need more data. If allowed, he would still do both, along with a 4K Score, before a biopsy. After the biopsy, Prolaris and Oncotype are used to help decide whether active surveillance is appropriate, or if treatment should be started. The tests don't provide information about which would be the most appropriate treatment. And all data needs to be considered, including the PSA level, PSA density, the ultrasound and MRI findings, to decide if the patient is a good candidate for surveillance instead of immediate treatment.

A patient with a 51-year-old son who has not had a PSA test yet – what concerns? If the patient has "garden variety" low or intermediate grade prostate cancer diagnosed at age 60 or above, with no family history of cancers (breast, ovarian, pancreatic, kidney, colon), then the likelihood of an inherited gene defect having led to the cancer is low, and the son is at low risk for prostate cancer. If the patient does have a causative gene defect,

(Continued from page 5)

then there is a 50% chance that the son will also have the defect. In any case, the son(s) of a cancer patient should get PSA tested beginning at age 45. But not necessarily doing germline testing.

Any information on Prostavision by Bostwick Labs? They do the PCA3 test, which is one of the components of the Select-MDX urine test. He would instead do the Select-MDX or ExoDx test.

Does a patient on active surveillance for fourteen years need to do any genetic testing? No, since the cancer is "not bad" – unless there is a significant family history of cancer.

Guardant 360 and Foundation ACT are blood-based tests – any preference? Dr. Lam is now using both, and thinks they will end up being essentially equivalent in usefulness.

What is the proper name of Genomic Health's test, and would it be helpful for Stage 4 metastatic prostate cancer? Genomic Health makes the Select-MDX urine test, which would not be helpful for such a patient.

If germline testing is negative (no inherited genes that are known to be associated with cancer), should somatic testing be done? Somatic gene defects are ones that arise "spontaneously" in the tumor(s), but Dr. Lam would not test for them unless there were some expectation of a change in treatment depending on the results. Note that germline testing is indicated for anyone with metastatic disease, but if the disease is "stable" after treatment (e.g. radiation then hormone therapy), he would not do somatic testing unless there were a relapse.

See the video online for the talk and slides: https://www.youtube.com/watch?v=K5uGWorHmo0&feature=youtu.be

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

Note: Aaron Lamb mentioned in the meeting introduction that digestive enzymes really helped him get through two months of radiation therapy for his prostate cancer. Details are available by contacting him through IPCSG.

News: On December 1st, the FDA approved the psma tests using gallium-68 (at UCSF or UCLA). They said "Ga 68 PSMA-11 is indicated for patients with suspected prostate cancer metastasis (when cancer cells spread from the place where they first formed to another part of the body) who are potentially curable by surgery or radiation therapy. Ga 68 PSMA-11 is also indicated for patients with suspected prostate cancer recurrence based on elevated serum prostate-specific antigen (PSA) levels. Ga 68 PSMA-11 is a radioactive diagnostic agent that is administered in the form of an intravenous injection." Dr. Lam has indicated by phone that it will probably take 2 to 6 months for the test to be actually available under the approval, to put billing codes into place, etc.

On the Lighter Side

Articles of Interest

177Lu-EB-PSMA Radioligand Therapy with Escalating Doses in Patients with Metastatic Castration-Resistant Prostate Cancer

jnm.snmjournals.org

Jie Zang

Research ArticleTheranostics

Journal of Nuclear Medicine December 2020, 61 (12) 1772-1778; DOI: https://doi.org/10.2967/jnumed.120.242263

Abstract

This study was designed to assess the safety and therapeutic response to ^{177}Lu-labeled Evans blue–modified prostate-specific membrane antigen (PSMA) 617 (EB-PSMA-617) treatment with escalating doses in patients with metastatic castration-resistant prostate cancer.

Methods: With institutional review board approval and informed consent, patients were randomly divided into 3 groups:

- group A (n = 10) was treated with a 1.18 ± 0.09 GBq dose of ^{177}Lu-EB-PSMA.
- Group B (n = 10) was treated with a 2.12 ± 0.19 GBq dose of ^{177}Lu-EB-PSMA.
- Group C (n = 8) was treated with a 3.52 ± 0.58 GBq dose of ^{177}Lu-EB-PSMA.

Eligible patients received up to 3 cycles of ^{177}Lu-EB-PSMA therapy, at 8-wk intervals.

Results: Because of disease progression or bone marrow suppression, 4 of 10, 5 of 10, and 5 of 8 patients completed 3 cycles of therapy as planned in groups A, B, and C, respectively. The prostate-specific antigen response was correlated with treatment dose, and the prostate-specific antigen disease control rates were higher in groups B (70%) and C (75%) than in group A (10%) (P = 0.007), but no correlation between groups B and C was found. ^{68}Ga-PSMA PET/CT showed a response in all treatment groups; however, there was no significant difference among the 3 groups. A hematologic toxicity study found that platelets decreased more in groups B and C than in group A and that grade 4 thrombocytopenia occurred in 2 (25.0%) patients in group C. No serious nephritic or hepatic side effects were observed.

Conclusion: This study demonstrated that a 2.12-GBq dose of ^{177}Lu-EB-PSMA seems to be safe and adequate in tumor treatment. Further investigations with an increased number of patients are warranted.

Clinical Challenges: Can MRI and Biomarkers Replace Biopsy for AS in Prostate Cancer?

Mike Bassett,

medpagetoday.com

by Contributing Writer, MedPage Today December 2, 2020

Can active surveillance of prostate cancer be conducted without biopsies?

While patients on active surveillance undergo periodic prostate-specific antigen (PSA) and tumor burden assessments, which typically involve periodic prostate biopsies, "these are increasingly being augmented, and, in some very careful circumstances, replaced by MRI and/or biomarker studies," said Matthew Cooperberg, MD, MPH, of the Helen Diller Family Comprehensive Cancer Center at University of California San Francisco (UCSF). "I say very carefully because there are concerns that biopsies are being replaced by MRI and biomarkers too frequently, and maybe ahead of the evidence."

"The guidelines clearly say active surveillance is based on PSA and tumor biopsy," Cooperberg told *MedPage Today*. "There are parts of the world, the U.K. for example, where they believe MRI is an adequate replacement for prostate biopsy. I and many others do not think MRI in 2020, based on the current PI-RADS system, is anywhere close to ready to replace biopsies on a routine basis. The accuracy is just not there using the PI-RADS system, and the false negative rate for high grade disease -- nearly 25% -- is too high. MRI is a great augment to biopsy, but not a replacement."

According to an article in *The Journal of Urology*, recent data from the multicenter Canary Prostate Cancer Active Surveillance (PASS) Study cohort indicate that systematic biopsy should be performed on patients with negative magnetic resonance imaging and included in the management in patients with positive magnetic resonance imaging.

This study, led by Michael Liss of the University of Texas Health Science Center in San Antonio, included 361 patients who underwent 395 prostate MRIs with median follow-up of 4.1 years (IQR 2.0–7.6). The MRIs led to reclassification in 27% of cases. Positive predictive value for detecting GG ≥2 cancer was 31% (95% CI 26%-37%), while the negative predictive value was 83% (95% CI 76% -90%), "suggesting that a negative MRI will still miss a substantial proportion of patients with GG≥2 disease."

"In addition, systematic biopsies detected a similar number of unique GG≥2 cancer as targeted MRI cores," Liss

(Continued on page 8)

(Continued from page 7)

and his colleagues wrote. "Thus, if the goal of surveillance biopsy is to identify higher-grade disease, both systematic and targeted biopsies should be obtained for men with a region of interest identified on MRI."
They also found that that while PI-RADS 5 lesions were significantly associated with upgrading or reclassification when compared to PI-RADS 1 and 2, models including PI-RADS scores were only minimally improved over models that contain clinical variables alone.
According to another recent study, published in *European Urology*, multiparametric (mp) MRI can improve the detection of clinically significant prostate cancer, but by itself it can't replace confirmatory or surveillance biopsies.
The study, led by Carissa Chu, MD, of UCSF, and co-authored by Cooperberg, included 344 men on active surveillance who had at least one mpMRI scan and biopsy after their cancer diagnosis. The men had 408 mpMRI scans during a median 71 months on active surveillance. The median time between prostate biopsies was 16.5 months.
The overall negative predictive value for mpMRI was 79.5% and ranged from 74.4% to 84.6% for all active surveillance biopsies up to the fourth surveillance biopsy. In men with PSA density ≥0.15 ng/ml/cm3, the overall negative predictive value for mpMRI was 65.5% and ranged from 57.1% to 73.3% across serial mpMRI scans.
"These findings support the hypothesis that mpMRI is helpful but insufficient to rule out pathological reclassification, especially at confirmatory biopsy or in the presence of other risk factors," wrote Chu and her colleagues.
"We are very interested in tailoring the intensity of the surveillance protocol," Cooperberg emphasized.
"Biopsies are uncomfortable, they have risks of infection, and there are costs associated with them. And patients certainly don't want to sign up for 20 biopsies over 20 years."
Cooperberg and colleagues recently identified several clinical parameters that can predict disease progression and can be used to identify patients on active surveillance who can be followed less intensively. These include maximum percent positive cores, history of any negative biopsy after diagnosis, time since diagnosis, body mass index, prostate size, prostate-specific antigen at diagnosis, and prostate-specific antigen kinetics.
The group determined that a prediction model based on these parameters, and tested on 850 men in the PASS cohort, could potentially be a less invasive way of assessing disease change, and thus avoid multiple biopsies.
As for the role biomarkers should play in active surveillance protocols, Cooperberg said tests such as Decipher, Prolaris, or Oncotype DX Prostate can provide important prognostic information.
Earlier this year the American Society of Clinical Oncology published prostate cancer biomarker guidelines in which an expert panel recommended that proprietary tests may be offered in situations in which the assay result, when considered as a whole with routine clinical factors, is likely to affect management. However, they did not recommend routine ordering of molecular biomarkers.
The panel reached a similar conclusion for use of MRI and genomics in men with newly diagnosed cancer eligible for active surveillance: "only in situations in which the result, when considered with routine clinical factors, is likely to affect management" are such assessments clearly worthwhile.
"If a biomarker test is high, that will usually drive us to do a more aggressive schedule of re-biopsy," said Cooperberg. "Can we say to a patient now, 'Your biomarker tests were low so you can now defer the interval to your next biopsy for a longer period of time'? That makes some clinical sense, but the data really do not exist to support that, yet."
As far as ultimately replacing the biopsy, Cooperberg suggested that with better studies and longer term follow-up, physicians can probably think about ways of using MRI and biomarkers to increase biopsy intervals.
"But, we're not quite there yet as far as replacing biopsy all together," said Cooperberg. "We need next generation imaging, or we need better studies about the existing biomarkers to get around concerns about tumor heterogeneity, and other factors that just decrease confidence in the current generation of markers. Eventually, the holy grail is to have a liquid test that will be less expensive, and avoid the heterogeneity concerns. But, we are still years away from that degree of evidence."

Androgen receptor signaling-targeted therapy and taxane chemotherapy induce visceral metastasis in castration-resistant prostate cancer

Hiroaki Iwamoto MD, PhD

onlinelibrary.wiley.com

Abstract

Background

Visceral metastasis (VM), an important poor prognostic factor of prostate cancer (PC), is not commonly ob-

(Continued from page 8)

served in castration sensitive status but is often observed after castration-resistant progression. However, the site, timing of emergence, and incidence of VM in castration-resistant patients have not yet been fully elucidated.

Methods

Demographic, surgical, pathological, and follow-up data of PC patients treated at Kanazawa University Hospital between January 2000 and December 2016 were retrospectively analyzed using their medical charts. From this data, risk factors of VM and survival of patients with VM were elucidated.

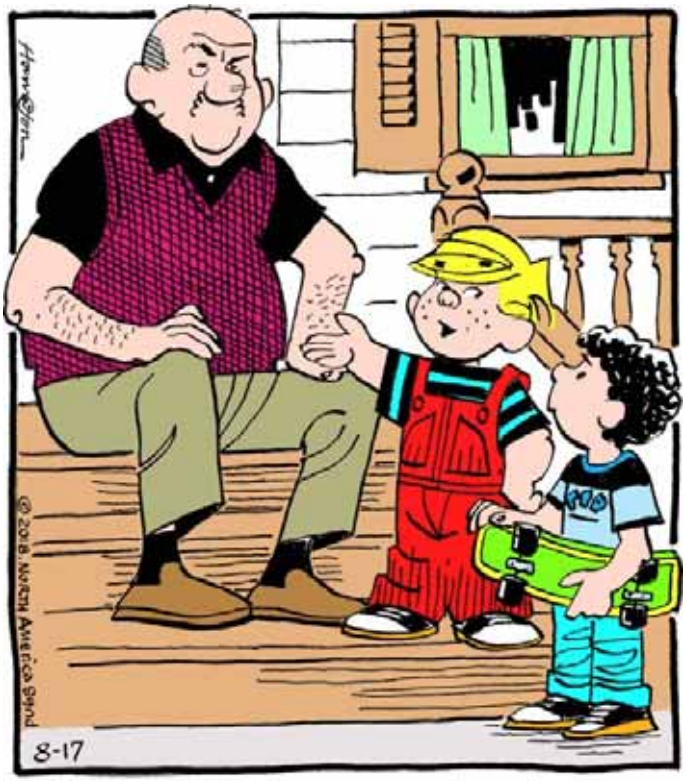
Results

Of 1364 patients, 21 (1.5%) had VM at diagnosis. Of 179 (13.1%) castration-resistant patients, 55 experienced emergence of new VM during treatment course. Incidence of new VM, especially nonlung, such as liver and adrenal metastases, increased significantly in proportion with the number of prescribed treatments. Multivariate analysis revealed that T stage, M stage, age, and treatment history with androgen receptor (AR) signaling-targeted agents and/or taxanes significantly increased the risk of VM. Compared with the group with VM at diagnosis, survival after diagnosis of VM following treatment was significantly shorter.

Conclusion

Although sequential use of new AR signaling-targeted agents and taxanes for castration-resistant PC (CRPC) is a standard treatment strategy, it often results in development of VM. Elucidating the mechanisms of VM are essential to improve survival in patients with CRPC.

On the Lighter Side



"THIS IS MY GOOD FRIEND MR. WILSON. I KNOW HE LOOKS OLD, BUT HE'S REALLY ONLY ABOUT 79."

NETWORKING

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

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

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

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

FINANCES

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

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

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

(Continued from page 9)

New high-resolution imaging scans approved for use in prostate cancer - Harvard Health Blog

health.harvard.edu

Charlie Schmidt

Imagine trying to find a single match from a book of matches in a large room. Not an easy task, right? But if the lights were dimmed and the match was lit, then its location would be immediately apparent.

This is the basic idea behind PSMA imaging, a newly approved method for detecting prostate cancer that is spreading, or metastasizing. The method relies on a minimally radioactive tracer called gallium-68 PSMA-11. Delivered in tiny amounts by injection, the tracer travels throughout the body and gloms onto a protein called PSMA that is found at high levels on prostate cancer cell surfaces. The labeled cells will then light up on whole-body imaging with a positron-emission tomography (PET) scan.

Per the FDA's new approval, doctors can give a PSMA-PET scan to hunt for metastases in men with rising PSA levels after prostate cancer treatment, or if they suspect cancer is metastasizing in a newly diagnosed patient. The scans have unparalleled resolution: able to detect tumors only a few millimeters in size anywhere in the body, they allow doctors to find and treat metastases before they become more dangerous.

The pivotal study leading to PSMA's approval was published in 2019 by collaborators at the University of California, Los Angeles and the University of California, San Francisco. The investigators enrolled 635 men with rising PSA levels after surgery or radiation for prostate cancer. All the men got a whole-body PSMA-PET scan, and suspicious findings were recorded for the prostate bed (the local anatomy in the vicinity of the prostate), lymph nodes, skeletal structures, and other organs. Teams of independent experts reviewed the PSMA-PET data, and their interpretations were in turn validated by pathologists who looked at the actual tissue samples under a microscope. When tissue samples were not available for the pathologist's review (which is called histopathology), PSMA-PET findings were confirmed or ruled out using additional imaging tools, or with PSA measures taken after cancer treatment.

Results showed that PSMA-PET scan correctly flagged metastases confirmed by histopathology 84% of the time. The accuracy was better for scans that were further confirmed with other imaging tools and PSA readings; in these cases, PSMA-PET identified metastatic tumors 92% of the time. Importantly, the higher a man's PSA, the more likely the scans were to find metastatic cancer.

The new approval applies only to gallium-68 PSMA-11 manufactured at UCLA and UCSF, and to PSMA-PET scans given at those two institutions. However, other PET imaging agents that bind to PSMA proteins are under accelerated review at the FDA, and should be approved in 2021, according to Dr. Jeremie Calais, a UCLA physician who helped lead the research.

"When this new PSMA scan becomes more widely available, it will again add to the diagnostic capabilities of physicians caring for men with prostate cancer," said Dr. Marc Garnick, the Gorman Brothers Professor of Medicine at Harvard Medical School and Beth Israel Deaconess Medical Center, editor of the Harvard Health Publishing *Annual Report on Prostate Diseases*, and editor in chief of HarvardProstateKnowledge.org. "Importantly, the scans enable a more precise evaluation of whether cancer deposits are present outside the area of the prostate gland that are not normally detected by currently available diagnostic studies. This in turn will help inform more specific treatments and enable a more accurate assessment of the effectiveness of our treatments."

FDA approves first, oral LHRH antagonist

Posted on December 18, 2020 by Sitemaster

Earlier today, the US Food and Drug Administration (FDA) approved relugolix, (Orgovyx, from Myovant Sciences), the first, oral luteinizing hormone releasing hormone (LHRH) receptor antagonist for the treatment of adult patients with advanced prostate cancer. Full information about the approval of relugolix is available in this FDA media release. LHRH receptor agonists are also referred to as gonadotropin-releasing hormone (GnRH) receptor antagonists.

The efficacy and safety of relogulix was evaluated in the HERO trial (NCT03085095). This was a randomized, open label trial in men requiring at least 1 year of androgen deprivation therapy (ADT) who had either prostate cancer recurrence following radiation or surgery or newly diagnosed castration-sensitive advanced prostate cancer. A total of 934 patients were randomized (2:1) to receive relugolix (using a 360 mg oral loading dose on the first day, followed by daily oral doses of 120 mg),or

(Continued on page 12)

(Continued from page 11)

leuprolide acetate (using a 22.5 mg injection subcutaneously every 3 months) for 48 weeks.
The main efficacy outcome measure was the achievement and maintenance of a castrate level of serum testosterone (< 50 ng/dl) by day 29 through 48 weeks of treatment. The medical castration rate was 96.7 percent in the relugolix arm of the trial.
The most common adverse reactions (occurring in > 10 percent of patients receiving relugolix) in the HERO trial were: hot flushes, musculoskeletal pain, fatigue, diarrhea, and constipation. The most common laboratory abnormalities (occurring in ≥15 percent of patients receiving relugolix) were increased glucose, triglycerides, alanine aminotransferase, and aspartate aminotransferase. Decreased hemoglobin was also observed.
The recommended relugolix dose is a loading dose of 360 mg on the first day followed by a daily oral dose of 120 mg at approximately the same time with or without food. Because it is an LHRH ***ant***agonist, relugolix does not have to be given with an initial short course of an antiandrogen like bicalutamide.
For those who are interested, the full, detailed prescribing information for physicians can be found here on the FDA web site. Myovant Sciences has yet to issue their own press release as of 1:30 p.m. Eastern today.

Prostate cancer regulator plays role in COVID-19, providing a promising treatment lead

sciencedaily.com

By taking a lesson from prostate cancer, researchers now have a promising lead on a treatment for COVID-19.
Two proteins, ACE2 and TMPRSS2, help the coronavirus gain entry and replicate within cells. TMPRSS2 is well-known to Arul Chinnaiyan, M.D., Ph.D. His lab discovered that TMPRSS2 fuses with the ETS gene to drive more than half of all prostate cancers. They also knew that TMPRSS2 was regulated by the androgen receptor. So when cancer research shut down in the spring, Chinnaiyan's lab turned its attention to the coronavirus. With a grant from the National Cancer Institute, the team used its existing knowledge and resources to determine how TMPRSS2 was regulated in the lungs.
They found that, just like in prostate cancer, TMPRSS2 is regulated by the androgen receptor in the lungs. And notably, blocking the androgen receptor led to lower expression of TMPRSS2 as well as ACE2, which led to decreased coronavirus infection in mice and cellular models. Results are published in *PNAS*.
"What's especially appealing about this is that anti-androgen treatments are already FDA-approved. This opens the door to look at these drugs, which we know work in prostate cancer, as potential COVID-19 treatments," says Chinnaiyan, director of the Michigan Center for Translational Pathology.
Using cell lines infected with SARS-CoV-2, the virus that causes COVID-19, researchers found that inhibitors of androgen receptor, including enzalutamide, apalutamide and darolutamide, inhibited the coronavirus infection. They also tested a class of drugs designed to inhibit or degrade BET proteins. BET protein activity is essential for androgen signaling and these drugs are being looked at for prostate cancer. In cell lines infected with coronavirus, the BET inhibitors decreased androgen signaling and inhibited viral infection.
The findings also provide some explanation for observations that COVID-19 affects men more than women. Researchers looked at human lung tissue and found higher androgen receptor signaling in men than women. They also found androgen signaling was highest in men over 70 and in smokers.
"This explains why elderly men who are smokers are more vulnerable to COVID-19 infection. High androgen receptor signaling allows the virus to gain entry and replicate more easily. This may explain why the disease is often particularly severe in older men," Chinnaiyan says.
Several clinical trials are underway testing androgen receptor inhibitors as a treatment for COVID-19, and additional trials are being developed to look at BET inhibitors.

Genetics, epigenetics, and the evolution of prostate cancer

Posted on December 3, 2020 by prostatecancer-infolink.net

If you are one of our readers who is really "into" the underlying causes of and development of prostate cancer, then you probably want to see if you can read a newly published article in this week's *New England Journal of Medicine.* This article by Arap et al., entitled "Prostate cancer progression and the epigenome," addresses factors that appear to be highly relevant to why some men get prostate cancer and others don't, and also to why prostate cancer progresses in some men and not in others. However, You will need some background in the biological sciences to be able to appreciate the nuances of this article.
The article does ***not*** provide simple answers to how we might be able to better manage prostate cancer

(Continued on page 13)

(Continued from page 12)

(yet).

The article ***does*** carefully note that doing research in this area is very difficult (for a multiplicity of reasons) and so it is possible that the recent "findings" discussed by Arap et al. could be fundamentally flawed because of the tools and materials currently available.

Having made these three points, what Arap et al. are telling the medical community, based largely on findings from a very large study of the genetics and epigenetics of prostate cancer by Pomerantz et al. in *Nature Genetics*, is the following:

The presence of certain specific proteins in normal prostate tissue appears to impact risk for the development and progression of prostate cancer.

There may be a strong association between factors associated with the earliest stages of prostate development (i.e., in a male fetus) and later risk for prostate cancer development.

Hereditary (germline) gene variants ***may*** impact the epigenetic activity of prostate-specific regulatory elements of gene expression, potentially leading to the development and evolution of prostate cancer.

What ***is*** very interesting about this article by Arap et al. (and the underlying research done by Pomerantz et al.) is how it points toward a spectrum of new research opportunities that ***may*** become useful in the diagnosis and management of prostate cancer in the future.

Prostate Cancer Progression and the Epigenome

Joseph F. Costello

nejm.org

Efforts to translate laboratory-based discovery into clinical applications and to transform medical-oncology problems into research questions have been made particularly challenging by the natural history of prostate cancer. To begin, widespread screening and early diagnostic programs through noninvasive testing (e.g., analysis of serum prostate-specific antigen [PSA] and urinary prostate cancer antigen 3) have restricted the amount of available tumor tissue for molecular studies. Moreover, despite the high incidence of prostate cancer in men, the disease is virtually absent in other mammals (including captive nonhuman primates), thereby eliminating natural animal models. Many prostate cancers are organ-confined when diagnosed, and long follow-up (10 to 15 years) is required to detect a survival advantage. Given these practical limitations of tumor procurement and timeline constraints, it is often difficult to obtain matched samples of normal (nonmalignant) prostate gland, organ-confined prostate cancer, and bone metastasis from prostate cancer to analyze tumor progression on a molecular level in order to advance mechanism-based treatment strategies.

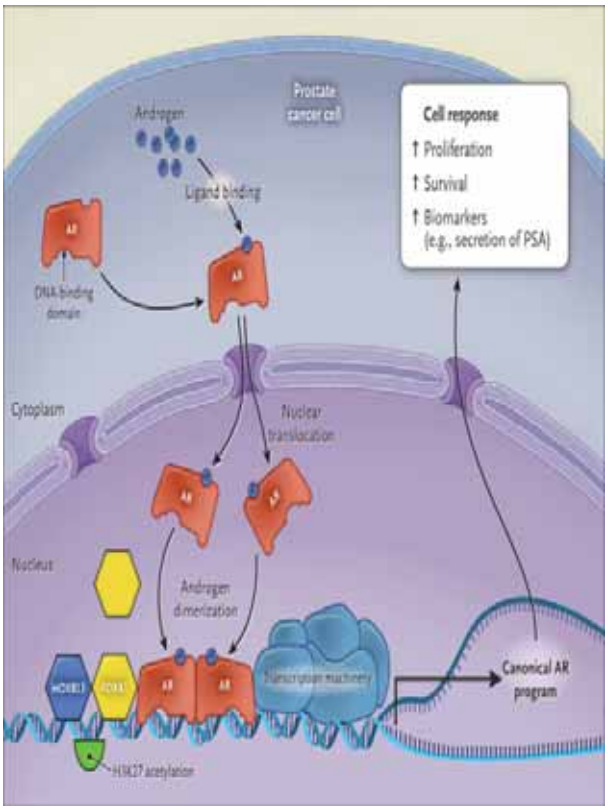


Figure 1. Androgen-Receptor Activation and Action.

The androgen receptor (AR) is activated by the binding of androgen ligands, which prompts AR dimerization, translocation to the nucleus, and activation of a canonical transcriptional program that promotes cell survival, proliferation, and the secretion of prostate-specific antigen (PSA).

Prostate cancer is driven by interrelated genetic[1,2] and epigenetic[3] alterations. Known genetic contributors to sporadic prostate cancer are the presence of germline genetic variants that increase the risk of prostate cancer and of somatic mutations, rearrangements, or irregular expression of noncoding RNAs that promote tumorigenesis and metastasis. Central to the pathophysiological mechanisms of prostate cancer is the androgen receptor, a master transcription factor (i.e., a protein that binds to DNA or chromatin and regulates the expression of a number of genes) (Figure 1).[1-3] How the epigenome contributes to tumor progression is less well understood. The epigenome includes DNA methylation and histone modifications (e.g., acetylation or methylation) that repress or activate gene expression; in some

(Continued on page 14)

(Continued from page 13)

cases, such activity perpetuates an open chromatin state, which can preserve the potential for repression or activation of gene expression. (Changes in the chromatin structure resulting from certain mutations have been linked to the development of disease.)

In a binational Dutch–American collaboration, Pomerantz and colleagues[4] integrated public epigenomic information from adult and fetal databases with a massive epigenomic data set regarding normal prostate epithelium, localized prostate cancer, and patient-derived xenograft models of metastasis. The data set regarding models of metastasis included genomewide binding patterns of the androgen receptor and two additional transcription factors — HOXB13 and FOXA1 — that are key to both prostate development and prostate cancer. It also included an epigenetic hallmark of active gene regulatory elements: acetylation of histone H3 at lysine 27 (H3K27ac).

Figure 2.

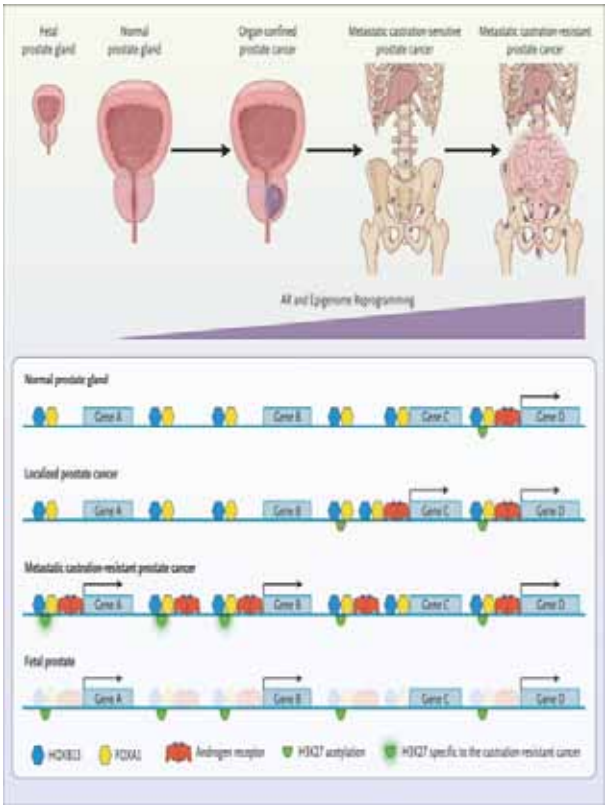


Figure 2. Epigenetic Regression with Clinical Progression of Prostate Cancer.

Pomerantz and colleagues[4] describe epigenomic patterns that occur in the transitions from the normal human prostate gland to organ-confined prostate cancer to metastatic castration-resistant prostate cancer, with their findings regarding metastasis relying largely on patient-derived tumor xenograft models. Sites of androgen-receptor binding in the genome have been associated with this transition from normal prostate gland to metastatic disease. Such binding sites are "premarked" by the transcription factors HOXB13 and FOXA1. Also, the researchers found that sites that are specific to metastatic castration-resistant prostate cancer correspond with sites in the open chromatin state in the normal prostate gland and in organ-confined prostate cancer, which indicates a lower barrier to reprogramming to a metastatic state. The epigenome (H3K27 acetylation) pattern in prostate cancer metastasis was similar to that in fetal (but not adult) prostate cells. A limitation of the study is that it does not include an analysis of circulating tumor cells or metastatic castration-sensitive prostate cancers.

During these investigations, the researchers made three discoveries. The first helps to explain how the reprogramming of the epigenome by the androgen receptor occurs during prostate cancer progression. Metastasis-specific androgen-receptor–binding sites coincide with chromatin that is already open in normal prostate epithelium and localized prostate cancer. Furthermore, these preexisting sites of open chromatin are premarked by HOXB13 and FOXA1 (i.e., the transcription factors are already present in the normal prostate gland) (Figure 2). Presumably, these proteins directly or indirectly provide access to genetic regulatory regions by the androgen receptor in metastatic tumor cells. The presence of these guideposts in normal prostate tissue presents a potential entry point for investigational intervention.

The second — and perhaps more revealing — discovery invokes the theory proposed by Conrad H. Waddington, who coined the term epigenetics to describe "the branch of biology which studies the causal interactions between genes and their products which bring the phenotype into being."[5] Pomerantz et al. asked whether prostate cancer cells require a new epigenetic program to become metastatic or whether the cells adopt an existing program from their own repertoire, such as a prior developmental stage within the prostate lineage. Multiple lines of evidence support a connection between the metastatic state and the fetal prostate. First, in their analyses of metastasis-specific sites of androgen-receptor binding, the researchers identified sets of genes that were active during prostate development, including the critical *Wnt* pathway. Second, they found that the epigenome (H3K27ac) pattern in prostate metastasis was distinct from that in adult epigenomes (including in the

(Continued on page 15)

(Continued from page 14)

prostate) and in metastases of other cancers, yet strongly resembled the epigenome of an embryo-derived cell line from the urogenital sinus, a structure with cells fated for prostate development. Finally, the genes that were tagged by H3K27ac in metastases of human prostate cancer were expressed to a higher degree in embryonic mouse prostate tissues than they were in the postnatal prostate. These data support the hypothesis that the epigenome in prostate cancer metastases resembles that of an earlier developmental period in the prostate-cell lineage, when developing prostate cells are actively proliferating and migrating. With the inclusion of the role of the androgen-receptor reprogramming in the metastatic process, this epigenomic recapitulation may plausibly promote metastasis, rather than being a reflection of it.

The third finding is that genetic regulatory sequences that were identified through the androgen receptor and H3K27ac patterns in metastatic prostate cancer overlap substantially with germline genetic variants linked to the heritability of prostate cancer. Perhaps these variants (or variants in their close vicinity) affect epigenetic activity of prostate-specific regulatory elements of gene expression.

From a clinical viewpoint, a shortcoming of the work of Pomerantz et al. — and one that may limit the accuracy of their models of prostate cancer — is their reliance on tumor xenograft models with poor "take" rates. (Xenografts that are derived from samples obtained from patients with prostate cancer are notoriously hard to establish, with success rates of approximately 10 to 15%, which potentially introduces unknown biases, including a selection bias toward proliferating cells.) Moreover, the study did not include some key phases of prostate cancer development such as nonmetastatic biochemical recurrent prostate cancer (PSA-only failure) after primary tumor treatment (which affects the second largest group of patients with prostate cancer in the United States) and metastatic castration-sensitive prostate cancer, another common phase of the natural history of the disease. Future research could include more experimentation on samples of human metastatic prostate tumors (rather than on xenografts initiated by human prostate cancer cells) and the epigenetic analysis of circulating tumor cells, once refinement of single-cell assays allows it. Currently, several epigenetic modulators are being used in prostate cancer clinical trials; unfortunately, none are specific to genomic regions or epigenomic programs. Perhaps this situation will change, since the work of Pomerantz et al. supports a continued focus on the epigenome as a target of experimental interventions.

Androgen-Deprivation Therapy Linked to Worse Fitness, CV Mortality

medscape.com

By Anne Harding

NEW YORK (Reuters Health) - Long-term androgen-deprivation therapy (ADT) is associated with worse cardiorespiratory fitness (CRF) and higher cardiovascular (CV) mortality in prostate cancer (PC) patients with high CV risk at baseline, new research shows.

"Reduced CRF may in part mediate the increased CV risk that we observed and may represent a therapeutic target. The potential merit of exercise interventions concurrent with prolonged ADT prescription in patients with PC and high CV risk warrants investigation," Dr. John D. Groarke of Brigham and Women's Hospital in Boston and colleagues conclude in their report in JACC: CardioOncology.

ADT plus radiation therapy is often used as an alternative to surgical treatment of PC, and the intensity and duration of treatment has grown in recent years as longer-term therapy is associated with better outcomes, Dr. Groarke and colleagues note. Studies of ADT and CV disease and mortality have had mixed results, they add, with some using age-matched healthy controls rather than PC patients not receiving ADT.

The researchers looked at 616 patients who underwent exercise treadmill testing a median of about five years after being diagnosed with PC. About a quarter had received ADT, including 99 who had ADT for six months or less and 51 who had longer-term therapy. Just over 80% had two or more CV risk factors.

Reduced CRF (eight metabolic equivalents, or METs, or less) was identified in 49% of ADT-exposed PC patients and 33% of non-exposed PC patients. Twenty-eight patients died due to CV causes, including 17 in the non-ADT group and 11 in the ADT-exposed group.

Long-term ADT was associated with significantly increased risks of poor CRF (odds ratio, 2.71) and CV mortality (hazard ratio, 3.87). The association between short-term ADT and reduced CRF fell just short of statistical significance (OR, 1.71, P=0.052), whereas there was no evidence for a link to CV mortality (HR, 1.60; P=0.420).

Overall, reduced CRF was associated with a nearly five-fold increase in mortality risk (HR, 4.60; P<0.001).

"This builds upon some of the existing literature

(Continued on page 16)

(Continued from page 15)

that's already out there about the association between AD exposure and adverse cardiovascular outcomes, and I think it complements that literature because we know that many of the adverse metabolic consequences and adverse cardiac consequences can be cumulative in nature," Dr. Vivek Narayan of the University of Pennsylvania in Philadelphia told Reuters Health by phone. Dr. Narayan co-authored an editorial accompanying the study.

While it makes sense that longer-duration ADT would carry greater risk, "I personally don't think that this absolves shorter durations of androgen-deprivation therapy from adverse cardiovascular consequences," he added.

Instead of cutting back on ADT, Dr. Narayan said, clinicians should actively manage patients' CV risk, while being aware of the increased risk associated with this type of treatment.

Dr. Groarke was not available for an interview by press time.

SOURCE: https://bit.ly/39ugw6l and https://bit.ly/39ugsnu JACC: CardioOncology, online November 20, 2020.

onlinelibrary.wiley.com

Early-onset prostate cancer is associated with increased risks of disease progression and cancer-specific mortality

Yu-Hsuan J. Shao MHS, PhD
jonishao@tmu.edu.tw
orcid.org/https://orcid.org/0000-0002-0757-1901
Graduate Institute of Biomedical Informatics, Taipei Medical University, Taipei, Taiwan
Clinical Big Data Research Center, Taipei Medical University Hospital, Taipei, Taiwan
Correspondence Yu-Hsuan J. Shao, MHS, PhD, Graduate Institute of Biomedical Informatics, Taipei Medical University, 172-1 Keelung Rd, Section 2, Taipei 106, Taiwan.
Email: jonishao@tmu.edu.tw
Search for more papers by this author
First published: 05 November 2020

Abstract

Objective

Prostate cancer (PCa) incidence has stabilized but not in patients at a young age. We assessed patient characteristics and disease progression in early-onset PCa.

Methods

A retrospective cohort of 28,039 newly diagnosed PCa patients aged ≥35 years was constructed using the Taiwan Cancer Registry in 2008–2016. Patients were categorized by age at diagnosis (≤54, 55–59, 60–69, 70–74, and ≥75 years). The clinical stage at diagnosis, Gleason score, prostate-specific antigen level at diagnosis, Charlson's comorbidity index, and primary and secondary treatments for PCa were included in the analysis. All-cause mortality and prostate cancer-specific mortality (PCSM) were reported. Hazard ratios (HRs) and 95% confidence intervals (CIs) estimating the risks of death and of receiving secondary cancer treatment were generated by Cox hazard models.

Results

In patients aged ≤54, 55–59, and 60–69 years, about 60% of them in each group were classified into the high-risk, very high-risk, or metastatic group. However, young patients ≤54 years had a higher risk of PCSM than patients aged 60–69 years (HR = 1.22; 95% CI = 1.10–1.49). This trend of an increased risk in PCSM remained for high-risk, very high-risk, or metastatic patients (HR = 1.24; 95% CI = 1.01–1.51), but not in low- or intermediate-risk patients. Besides, young patients diagnosed with high-risk diseases had the highest risk of receiving secondary cancer treatment within 180 days after completing primary treatment among all age groups (HR = 1.32; 95% CI = 1.07–1.63).

Conclusions

PCa arising in young patients ≤54 years of age, especially those with a high risk or metastatic form, might be more aggressive than that in other age groups.

Whole pelvic salvage radiation may be better than precisely targeted lymph node salvage radiation

prostatecancerinfolink.net

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

Last week, I looked at a retrospective study of metastasis-directed therapy (MDT) at the Mayo Clinic among oligorecurrent patients (see this link). Oligorecurrent means that they had already received primary therapy (mostly prostatectomy) and some had received salvage radiation as well, but there were only 1 to 5 metastases detected. They found there was no benefit if there were any bone metastases, but there may have been a benefit if the metastases were in the lymph nodes only. Lymph nodes were treated with either surgery (called pelvic lymph node dissection — PLND) or radiation to a small

(Continued on page 17)

(Continued from page 16)

area around the detected (by C-11 choline PET/CT) cancerous lymph nodes. I ended the analysis with this statement:

Another open question is whether whole pelvic salvage radiation might have been more effective than the limited margins they used at Mayo. With the more accurate PSMA PET scans, ROs are able to treat the entire PLN area with radiation boosts given to the detected ones. The RTOG-consensus treatment area has recently been expanded (see this link). It's important that patients understand the detection limits of even the best PSMA PET scan: metastases smaller than 4 mm, and those that put out only small amounts of PSA remain invisible.

De Bleser et al. reported the results of a retrospective study to examine precisely this question among 506 oligorecurrent patients conducted at 15 different institutions throughout Europe. Patients were selected and treated as follows:

Detection of cancerous lymph nodes (LNs) was primarily (85%) with C-11 Choline PET/CT (a few with PSMA, FDG, or conventional imaging).

309 patients were treated with SBRT (at least 5 Gy per fraction, up to 10 fractions). A margin of 2-6 mm was treated also.

197 patients were treated with "Elective Nodal Radiation Therapy" (ENRT) of at least 45 Gy in 25 fractions to the entire pelvic lymph node area. Boost doses to detected LNs were allowed. A margin of 5-7 mm was treated. 60 patients also had their prostate bed simultaneously treated.

About half had already had salvage radiation to the prostate bed.

About half had already had PLND at the time of prostatectomy. The SBRT group had an average (median) of 1 positive LN at pathology, the ENRT group had 2.

Patients with adjuvant ADT for more than a year were excluded. Seventy-seven percent of the SBRT had no ADT; 40 percent of the ENRT group had no ADT. Those who had ADT, had it for an average (median) of 6 months.

Seventy-two percent had pelvic LNs only; 28 percent had extrapelvic LNs (retroperitoneal) at imaging.

Seventy-two of the SBRT group had only one LN at imaging; 50 percent of the ENRT group had 2 to 5 LNs at imaging.

Patients with bone or visceral metastases at relapse were excluded, as were patients already using ADT, and those with detected metastases before primary therapy.

After a median follow-up of 3 years:

3-year Metastasis-free survival (MFS) was 68 percent at 3 years, but only distant metastases (M1) were counted.

>Among patients who were detected with only one positive LN at baseline, MFS was twice as long with ENRT compared to SBRT

There was no difference among patients with more than one positive node at baseline.

Fifty-seven percent of patients were detected with metastases (N1 and M1) in the SBRT group — 55 percent in pelvic LNs, 19 percent in extrapelvic LNs only, 20 percent in bone, and 6 percent in visceral organs.

Thirty-eight percent of patients were detected with metastases (N1 and M1) in the ENRT group — 11 percent in pelvic LNs, 43 percent in extrapelvic LNs only, 35 percent in bone, and 8 percent in visceral organs.

ENRT provided longer-lasting N1 control, but did not delay M1 control any more than SBRT.

Castration-free survival did not differ between the two types of treatments.

There was no acute toxicity reported for 99 percent of men receiving SBRT and 94 percent of men receiving ENRT. Grade 3 (serious) toxicity was reported for five men receiving ENRT and none receiving SBRT.

Similarly, there was no serious late-term toxicity reported for SBRT, and 2.5 percent for ENRT.

We conclude that ENRT provided better local (pelvic lymph node) control than SBRT, but neither seemed to delay distant metastases better. MFS was only improved by ENRT if there was just one LN metastasis detected at baseline. Reported toxicity (acute and late-term) was low, but was lower with SBRT.

Of course, this retrospective study leaves many questions unanswered:

Does either treatment improve MFS over ADT alone

What would have happened if long-term ADT were allowed rather than just 6 months (see this link)?

What if all patients received the same radiation dose, the same treatment margins, and a standard treatment area (up through the aortic bifurcation) were used?

What would have happened if LN metastases were detected with PSMA PET/CTs rather than C-11 choline PET/CT?

What were the patient-reported quality of life outcomes?

(Continued on page 18)

(Continued from page 17)

These questions will be addressed in two ongoing randomized clinical trials:

OLIGOPELVIS2 (in France) is randomizing oligorecurrent patients to intermittent ADT with or without whole-pelvic IG/IMRT with a boost to PSMA-identified LNs (completion expected mid-2026).

PEACE V (a.k.a STORM; in Europe and Australia) is randomizing oligorecurrent patients to MDT by either SBRT/salvage PLND or ENRT. C-11 choline, PSMA or Axumin PET scans will be used for detection (completion expected end of 2023).

On the Lighter Side