Informed Prostate Cancer Support Group Inc.
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November 2020 NEWSLETTER

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Tuesday, November 17,

Volume 13 Issue 11

- **Saturday, November 21st, 2020 IPCSG - Live-Stream Event, 10:00am PT**

Dr. Richard Lam

- *"GENETIC TESTING IN PROSTATE CANCER"*

Since 2001, Dr. Lam, a double board-certified internist and oncologist has been specializing full time in the treatment of prostate cancer. He is particularly interested in utilizing state-of-the-art therapeutics for advanced prostate cancer.

Dr. Lam will be discussing genetic testing and how it's being applied for prostate cancer research, diagnosis and treatment.

- 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

October 2020 Informed Prostate Cancer Support Group Meeting

Summary by Bill Lewis

Part 1: Introduction to Intensity-Modulated Proton Therapy - 2020 Update

Carl J. Rossi, Jr., MD Medical Director, California Protons Cancer Treatment Center, San Diego, CA

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

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

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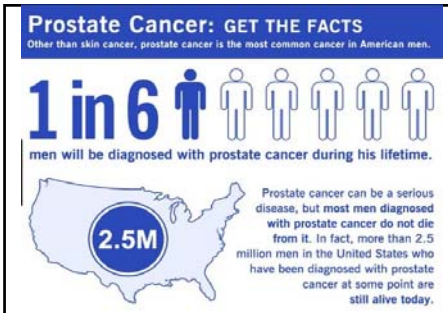

Organization

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

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NEWSLETTER
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PROSTATE CANCER—*2 WORDS, NOT A SENTENCE*

What We Are About

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

Meeting Video DVD's

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

From the Editor

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

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

- What are the Odds—The epidemiology of prostate cancer (2003-2017)
- Some things to ask the Surgeon—Improvements in surgical technique: past and more recent
- Early detection of High Risk—Gene signature predicts whether localized prostate cancer is likely to spread
- Proton Therapy for Localized Prostate Cancer: Long-term Results in 2,021 Patients
- The Swinging Pendulum of PSA Screening

Join the IPCSG TEAM

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

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cannot and does not occur, hence the "ALARA" principle (as low as reasonably achievable) when using radiation as a diagnostic and therapeutic modality.

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

- IMRT and other forms of external beam therapy with photons (X-rays or Gamma rays)
- Protons
- Brachytherapy (temporary use or permanent implants of radioactive "seeds")
- Radioimmunotherapy (a radioactive element carried by a protein or other molecule)

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

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

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

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

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

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

Equipment and software advances now permit the use of "pencil-beam scanning," which is analogous to 3-D printing. The dose goes very precisely into the target structure, as the scanning beam is directed by magnets, giving a dose layer by layer (each layer only 1 mm thick!) as the protons stop at a pre-determined depth, in a beam that is only 3-5 mm in diameter. The depth and dose are computer -controlled, and daily adjustments can be made as desired and appropriate.

There are now 37 operational proton treatment centers in the USA, with more than 18 of various sizes under construction or in planning. Most either have or are retrofitting pencil-beam scanning deliv-

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ery systems. Construction can be done within 24 months from groundbreaking to first patient treatment.

For imaging/targeting, CT and MRI are complementary. CT is good at showing bone anatomy and for calculating proton stopping power. MRI shows internal anatomy in the prostate, and delineates gross areas of disease, as well as delineating structures to avoid: the neurovascular bundles, and the penile bulb.

See the video and slides for impressive pictures of how well the dose with proton treatment spares the surrounding tissues, compared to X-ray treatments, and how effectively the SpaceOAR gel helps to separate the prostate from the rectum, thus protecting the latter from damage.

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

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

Conclusions:

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

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

Published data demonstrates less toxicity with protons as compared to IMRT:

- Lower incidence of GI toxicity.
- Less bone marrow suppression.
- Less testosterone suppression.
- Lower incidence of radiation-induced second cancers

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

Questions:

Is Proton Therapy ever appropriate for SBRT? Definitely yes. But he hasn't been happy with urinary toxicity for primary treatment. Better for salvage treatment, which can also be done with interstitial implants, or with IMRT.

Do you use the rectal balloon? He prefers the SpaceOar hydrogel, which gives a better safety margin.

Why do proton treatments sometimes give skin burns? This happens when you are trying to treat a structure close to the skin, such as ribs or breasts.

Part 2: Special Situations for the Use of Proton Therapy

Dr. John P. Einck, of UC San Diego and California Protons.

Case #1: A 56 year old man, PSA 12.3, palpable nodule on right side of prostate (entire lobe), Gleason 8 (Grade group 4), 6/7 cores on right and 0/7 cores on left, prostate volume = 25 cc. MRI showed the nodule bulging from the prostate

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"capsule," but that the lymph nodes and seminal vesicles were normal. Treatment options: Surgery would give similar long-term survival vs. radiation, but more side effects, and a significant chance of needing post-surgery treatment due to the extra-capsulary extension. Radiation after surgery would be an expected necessity. NCCN guidelines suggest three options for patients without significant comorbidities (i.e., expected to live 5 years or more): EBRT + ADT (Lupron or the like), EBRT + Brachytherapy (either low- or high-dose-rate) + ADT, or surgery + lymph node dissection. The EBRT can be done with photons or protons, but should be high dose in either case.

How to select the treatment? Depends on the goals of the patient, relating to "curing" the cancer, avoiding collateral damage, maintaining sexual function, avoiding urinary leakage, and relative convenience of the treatment(s). For this patient, Dr. Einck recommended 12 months of ADT (which improves PSA and overall survival) and 5 weeks of proton therapy to the whole pelvis using IMPT (intensity-modulated proton therapy; to provide the best treatment of lymph nodes) followed by a seed implant (brachytherapy, which gives a high dose to the prostate). The combined/extra treatment was suggested because it was found with 183 high risk patients over 18 years, that where there were two high risk factors (in this case, the Gleason score and the bulging nodule), the freedom from recurrence was significantly less over the following five years if a single treatment modality was given.

Here are situations where Dr. Einck prefers protons:

- when treating lymph nodes (to avoid irradiating adjacent organs, so less diarrhea during treatment, lower bladder dose, less risk of second malignancy),
- when doing salvage radiation (typically with irregular target areas),
- in younger patients (to reduce the small risk of a secondary cancer), and
- in patients who have received prior radiation (to precisely treat lymph nodes and other areas needing treatment, especially using the rectal balloon, with less scattered dose to the bowels/bladder/rectum). Treatment with IMPT deposits the dose more precisely, so it is easier to keep the dose out of the areas that have received prior radiation.

Another help to minimize side effects – by avoiding irradiation of the bowel – is the SpaceOar gel, which can be injected between the prostate and the rectum, providing a buffer zone so that the high dose of radiation given to the prostate does not reach the rectum. In a large randomized trial, there was no grade 3 rectal toxicity (rectal bleeding that required treatment) in the SpaceOar patients – contrasting with 5% grade 3 toxicity in patients with no SpaceOar. Somewhat surprisingly, there was improved preservation of sexual function in SpaceOar patients – 66.7% vs. 37%. And there was also improved urinary and bowel "Quality of Life."

Conclusions: The choice of treatment depends on the patient's own goals. Different forms of radiation are essentially "different shaped tools for accomplishing the same goal." There are clinical situations in some patients where protons are preferred, as discussed above. Consider SpaceOar with radiation for early stage prostate cancer.

Questions:

Please explain "Proton Beam Overshoot." Tissue density (proton stopping power) obtained from CT scans – with about 3-1/2% uncertainty – is used to prepare the plan for irradiation. Planning is done for the "worst case" and therefore leads to a little bit of overshoot beyond the target area. Varian now has an improvement based on dual-energy CT scanning, and another way to minimize the error is to do the CT scan using protons instead of photons (which also results in much less CT radiation dose to the patient).

A patient needs salvage radiation due to rising PSA and lymph node disease. Which is better, photons or protons? Dr. Einck said that both could give essentially equivalent results (in a normal course of about 35 treatments), except that bowel toxicity would be expected to be less, so if the insurance would cover it (or the patient could afford it on his own), he would recommend treatment with photons.

Is proton therapy better for "Whack-a-Mole" (treating oligometastatic disease, where there are a few tumors outside the prostate area)?

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In general, SBRT with photons or protons would be equivalent in effectiveness, if the lymph node or other remote site of disease is not too close to previously irradiated tissue. Note that such treatments only give long-term cures in about 25-30% of cases, but the value for most men is in delaying the need for other treatment, such as ADT.

In what situations do you prefer IMRT over proton therapy? Dr. Einck is not aware of any cases where proton therapy would be worse than IMRT. But he does see no advantage (except for side effects, as discussed above by Dr. Rossi) for protons in early-stage prostate cancer with the disease confined to the prostate (i.e., no lymph node involvement).

Who among you and your colleagues should I go to for my initial consultation? Drs. Einck and Rossi each have a relationship with both UCSD (as professors) and with California Protons. Any radiation oncologist in the San Diego area can get privileges at California Protons, and treat patients there, but admittedly, they are less familiar with the potential advantages and are instead likely to recommend "what they know." Getting a second opinion is very important when considering treatment options.

Why do women get skin burns with IMRT? The skin is part of what's deliberately being targeted, especially after a mastectomy. This is more naturally done with photons, rather than protons (which are more suitable for "deeper" targets).

A comment: Treating bone lesions with protons where Zytiga and ADT haven't prevented more lesions can eliminate pain and help delay the need for chemotherapy. (Agreed to by Dr. Rossi.)

What about penile bulb exposure to radiation when treating the prostate? It's one of many factors that can lead to erectile dysfunction, and is always part of treatment planning. Generally, the exposure can be less with protons, depending on patient anatomy and the specific treatment plan used.

What's the best type of imaging today, and where can it be obtained? Axumin is FDA approved. Gallium-68 and another agent have been predicted to be within a year of FDA approval … for several years now! MRI is also extremely valuable. Combining scan data gives the best information for planning treatments. There's a whole-body MRI trial ("RSI technology") going on at UCSD, that is recruiting patients with higher than Gleason 6 disease. Aaron Lamb noted that two or three of his lymph nodes were found to have disease, even when his PSA was only 0.1 or 0.2. Remarkable!

Compare brachytherapy vs. proton beam therapy? There are no direct comparisons. With either one, we can do "dose escalation," meaning to give a higher dose to a particular area within the prostate. Dr. Einck has been providing brachytherapy for 25 years, and is convinced that it is the best option for young men who want to maintain sexual function and who have low risk or favorable intermediate risk disease (i.e., Gleason 3+3 or 3+4). Cure rates approach 95%. Dr. Rossi agreed that it is a very good option, and noted that it gives the lowest radiation exposure to the body, compared to external radiation with either photons or protons. However, he also pointed out that there are fewer and fewer doctors who are expert in giving brachytherapy. Dr. Einck explained that doctors are paid much more for giving a course of external beam radiation, than for giving brachytherapy. Dr. Einck gives low-dose-rate treatments. High-dose-rate treatments are available at UCLA, Cedars or UCSF.

What about Dr. Mack Roach at UCSF switching from brachytherapy (high-dose-rate, HDR) + IMRT, to SBRT? A number of other centers have done likewise, but it doesn't seem to be about effectiveness. Some doctors, especially those with Cyberknife equipment, prefer that (SBRT) type of treatment. UCLA has both SBRT and HDR + IMRT, and freely uses both modalities. Dr. Einck believes that both work quite well.

An estimate of proton treatment cost? There are two components: the professional services, and the technical component (daily costs). The professional services costs are the same for either photon or proton treatments (mainly since the planning effort is about the same). However,

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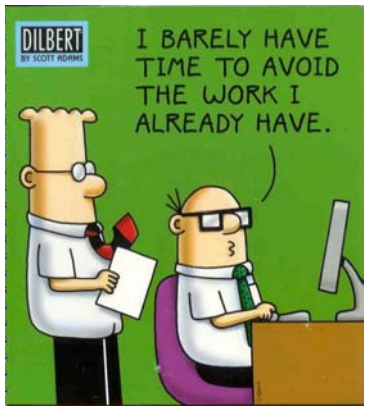
the daily costs are higher for protons. Medicare currently pays about $1100 for one fraction (1 day) of proton treatment, but about half that for photon treatment. Eventually, the proton daily cost needs to come down to closely match that for photons. California Protons currently charges the Medicare rate to patients without insurance.

Can you do SBRT with IMRT equipment? Yes.

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

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

On the Lighter Side



Articles of Interest

What are Your Odds? The epidemiology of prostate cancer (2003-2017)

prostatecancerinfolink.net

Posted on November 16, 2020

A recent report in the CDC's *Morbidity and Mortality Weekly Report* (*MMWR*) may offer one the the best analyses of an increasing risk for diagnosis with and death from advanced forms of prostate cancer over the period from 2003 to 2017 (the last year for which we have accurate data from the SEER database).

There are a number of very important points made in this analysis, which we shall quote directly, so that readers are clear that these are CDC's statements and ***not*** those of Prostate Cancer International:

- "Among 3.1 million new cases of prostate cancer recorded during 2003–2017, stage prostate cancer cases broke down in the following stages at initial diagnosis:
    - localized, 77%,
    - regional, 11%,
    - distant, 5% and
    - unknown 7%
- "Over this 15-year period, age-adjusted incidence decreased by 35% from 155 per 100,000 in 2003 to 105 in 2017."
- "During 2001–2016, 10-year relative survival for localized stage prostate cancer was 100%."
- "The percentage of distant stage prostate cancer increased from 4% in 2003 to 8% in 2017."
- "Five-year survival for distant stage prostate cancer improved from 28.7% during 2001–2005 to 32.3% during 2011–2016."
- "Overall, 5-year survival for distant stage prostate cancer improved from 28.7% during 2001–2005 to 32.3% during 2011–2016."
- "For the period 2001–2016, 5-year survival was highest among Asian/Pacific Islanders (42.0%), followed by Hispanics (37.2%), American Indian/Alaska Natives (32.2%), Black men (31.6%), and White men (29.1%)."

There are also some clarifying statements in the paper's Discussion section:

- Over the study time period "an increasing number and percentage of men have received diagnoses of distant stage prostate cancer."
- "In 2012, USPSTF concluded that the benefits of PSA-based screening do not outweigh the harms and recommended against PSA-based screening for prostate cancer for men of all ages. This recommendation likely contributed to a decrease in overall reported prostate cancer incidence and might have contributed to an increase in the percentage and incidence of distant stage prostate cancer."
- "Survival with distant stage prostate cancer has improved, but fewer than one third of men survive 5 years after diagnosis."
- Among men initially diagnosed with localized prostate cancer "≤ 6% progress to metastatic prostate cancer."
- "Survival for distant stage prostate cancer was higher for Black than White men, which is different from a past study reporting higher survival for White men than Black men during 2001–2009."

We would note that it is now nearly 4 years since the last time point encompassed by this data set. Whether anything significant has changed during that time period is something we won't know until about 2024.

The other thing that is important to understand about this study (like any other epidemiological analysis) is that there are a series of statistical and other assumptions that have to be made in carrying out such an analysis. If those assumptions are inaccurate (and we have no reason to believe that they are), it could lead to inaccurate results.

The reason that we want to bring attention to this analysis is that there is no reason to accuse the CDC of any bias in offering these data. The CDC doesn't treat patients. It doesn't pay for the treatment of patients. And it's sole interest is in providing objective information about specific disorders identified within the USA.

Has Surgery Gotten Better? Discuss with your Surgeon. Improvements in surgical technique: past and more recent

prostatecancerinfolink.net

Nearly 3 years ago now, we first mentioned a surgical technique known as "Retzius-sparing" radical prostatectomy on this web site. The degree to which this has been adopted into standard urologic surgical practice around the world is still unclear. However, what ***is*** clear is that the urologic surgical community is still seeking ways to improve patient outcomes after removal of the prostate for first-line

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treatment of localized prostate cancer, and the three things that they are most focused on are these:

- Elimination of the cancer itself
- Rapid and complete recovery of normal urinary function
- Reasonably rapid recovery of erectile function — at least the the same extent as prior to the surgeryt for each specific patient

This set of three objectives is often referred to by prostate cancer specialists as the "trifecta".

To be blunt, it remains relatively rare for all three goals to be accomplished for the majority of patients. From the surgical perspective, the primary objective is elimination of the cancer. The next is recovery of at least decent urinary function. The recovery of good erectile function still comes in as a relatively poor third.

On the other hand, we should be clear that some of the world's best prostate cancer surgeons are constantly seeking ways to improve their personal skills and techniques and then to pass these along to others. The latest such potential advance seems to be coming from the group led by Dr. Ash Tewari at the Mount Sinai Health System and the Icahn School of Medicine in New York.

In a recent article in *European Urology*, Wagaskar et al. report on what they are describing as a new "hood technique" for the conduct of robot-assisted laparoscopic prostatectomy. We aren't going to try to get into all the details of how they conduct this type of surgery, but it appears to combine aspects of the "Retzius-sparing" surgical technique with the preservation of other periurethral anatomical structures (e.g., the "pouch of Douglas"). The abstract of the actual paper is available at the prior link and there is also a summary write-up on their research on the Healio web site.

Basically, Tewari and his colleagues report data from 300 patients with localized prostate cancer, and with an average (median) age of 64 years, who were treated using this new "hood" technique between April 2018 and March 2019.

According to Tewari, as quoted by Healio:

Using the hood technique, we were able to preserve tissue which, after prostate removal, has the appearance of a hood comprising of the detrusor apron, arcus tendineus, puboprostatic ligament, anterior vessels and some fibers of the detrusor muscle. This hood surrounds and safeguards the membranous urethra, external sphincter and supportive structures.

The authors claim that among 299 of their 300 patients, 21 percent (63/299) were continent within 1 week and 95 percent (284/299) were continent within 48 weeks (nearly a year) after removal of their urinary catheters post-surgery. They further state that just 6 percent of these patients (18/299) had positive surgical margins.

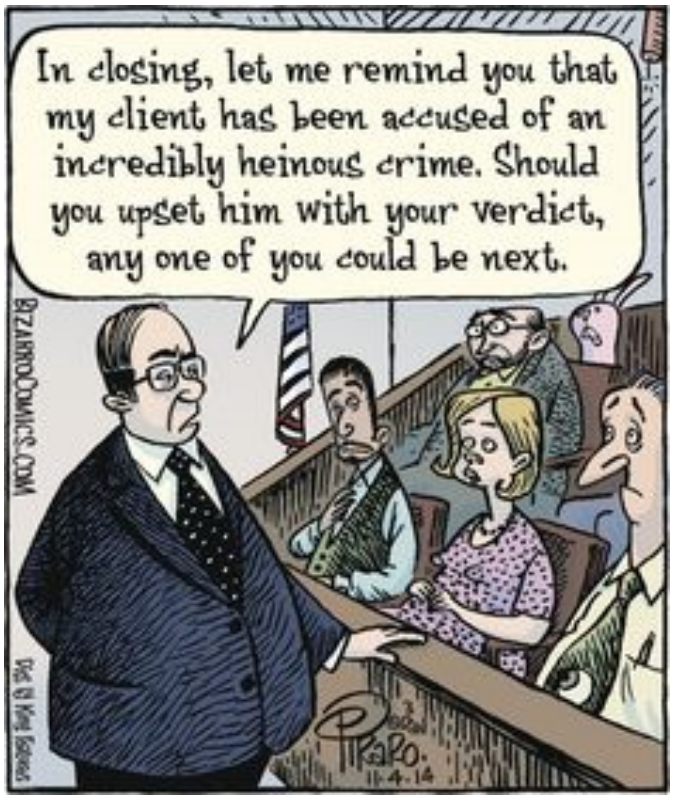
Now we do need to be clear that these are data from a single center and this was not a randomized study. We also need to be clear that (as far as we are aware) there are no reports of data on recovery of erectile function from this study (as yet).

On the other hand, we also need to be clear that, just as the radiation oncology community has slowly and surely improved their abilities to target radiation therapy and reduce the number of cycles of therapy while improving the likelihood of good long-term outcomes after radiation treatment, the urologic surgical community has also — slowly but surely — been seeking to improve outcomes post-surgery — from Dr. Walsh's introduction of nerve-sparing surgery in the early 1980s to the introduction of laparoscopic and then robot-assisted laparoscopic techniques in the last 1990s and early 2000s to the "Retzius-sparing" and "hood" techniques of the late 2010s.

It is hard to be able to say that we will ever reach a point at which any surgical technique will be able to pretty much "guarantee" a high-quality trifecta outcome for the majority of "good" patients with localized but clinically significant prostate cancer. However, progress is still being made as we gain more and more knowledge about the anatomical functionalities of the male urogenital system.

Between the recognition that large numbers of men with lower-risk forms of localized prostate cancer can be initially (at least) well-managed on active surveillance and without any immediate need for invasive therapy, and the gradual expansion of invasive treatment options and clear improvements in the use of surgery and radiation therapy, we are making strides toward the better and safer management of localized prostate cancer. The progress may be slower than we would like, but it ***is*** still progress.

On the Lighter Side



NETWORKING

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

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

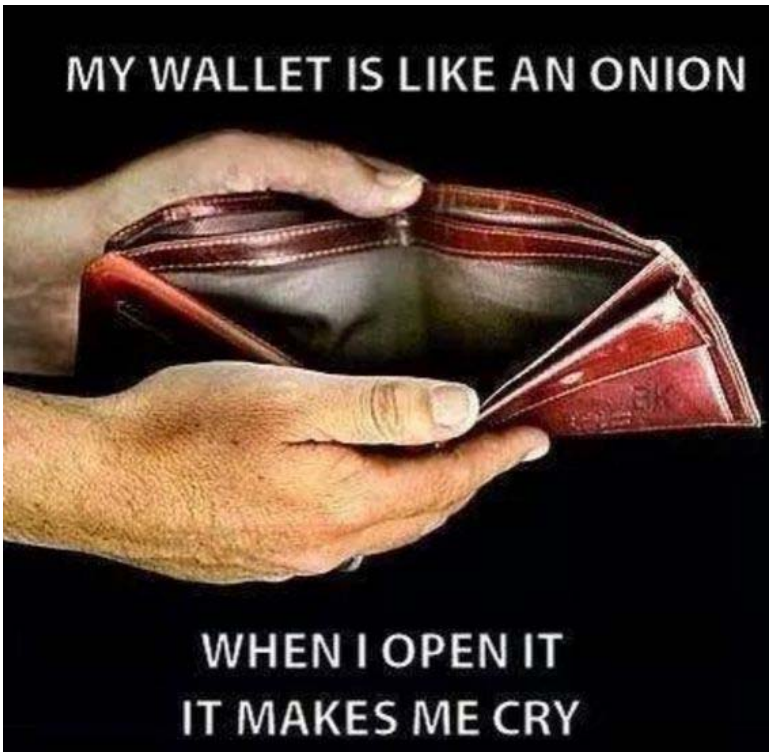
Our brochure provides the group philosophy and explains our goals. Copies may be obtained by mail or email on request. Please pass them along to friends and contacts.

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

FINANCES

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

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



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

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Gene signature predicts whether localized prostate cancer is likely to spread

sciencedaily.com

Researchers have identified a genetic signature in localized prostate cancer that can predict whether the cancer is likely to spread, or metastasize, early in the course of the disease and whether it will respond to anti-androgen therapy, a common treatment for advanced disease. The new gene signature may also be useful for evaluating responses to treatment and for developing new therapies to prevent or treat advanced prostate cancer.

"If we could know in advance which patients will develop metastases, we could start treatments earlier and treat the cancer more aggressively," says the study's senior author, Cory Abate-Shen, PhD, chair of the Department of Molecular Pharmacology and Therapeutics, the Michael and Stella Chernow Professor of Urologic Sciences (in Urology), and professor of pathology & cell biology (in the Herbert Irving Comprehensive Cancer Center) at Columbia University Vagelos College of Physicians and Surgeons.

"Conversely, patients whose disease is likely to remain confined to the prostate could be spared from getting unnecessary therapy."

The study was published online in *Nature Cancer*.

Existing Tests Can't Identify Aggressive Cancers

Prostate cancer is the second-leading cause of cancer death among men in the United States; about 33,330 men are expected to die of the disease this year.

Most prostate cancers remain confined to the prostate and can be successfully managed by active surveillance or local therapy (mainly surgery or radiotherapy), with five-year survival rates above 99%. But once prostate cancer spreads, it is considered incurable, and five-year survival rates drop to approximately 30%.

"The problem is that with existing tests, it's hard to know which cancers are which," says the study's lead author, Juan M. Arriaga, PhD, associate research scientist in molecular pharmacology and therapeutics at Columbia University Vagelos College of Physicians and Surgeons.

"We miss a lot of aggressive cancers that should have been treated earlier, and we overtreat some slow-growing cancers that probably would not have spread."

New Gene Signature First Identified in New Mouse Model

To identify a more accurate method of predicting advanced prostate cancer, the researchers first created a mouse model of prostate cancer that accurately reflects the human form of the disease, including how the cancer spreads to the bone, the tissue most often affected by prostate cancer metastases.

Using this first-of-its-kind mouse model, the researchers discovered that bone metastases have a different molecular profile than that of primary tumors. "By focusing on those differences, we were able to identify 16 genes that drive localized prostate cancer to metastasize," Abate-Shen says.

16 Genes Predict Metastasis in Patients

The genetic signature, called META-16, was then tested on biopsies from several hundred patients with localized prostate cancer. The outcomes of those patients were blinded to the researchers.

The Columbia team found that META-16 was highly effective at predicting time to metastasis and response to anti-androgen therapy (which is used to suppress androgen, the male hormone, which promotes tumor progression).

The team is currently refining the test, which they then hope to evaluate in a prospective clinical trial.

In theory, **META-16 could also be used to develop therapies against metastatic prostate cancer**.

"The genes in our signature are not only correlated with metastasis, they appear to be driving metastasis," Arriaga says. "That means that if that we can suppress the activity of those genes, we might be able prevent the cancer from spreading or at least improve outcomes."

Who needs Protons not Photons

Proton Therapy for Localized Prostate Cancer: Long-term Results in 2,021 Patients

redjournal.org

This paper is available as a PDF. To read, Please Download here.

Abstract:

Purpose

While controversial, proton therapy has been used to treat localized prostate cancer over the past two decades. The purpose of this study is to examine the long term efficacy and toxicity of proton therapy for localized prostate cancer.

Methods and Materials

This was a retrospective observational study of 2,021 patients from 2003-2014 at a single institution. Patients were classified using the risk groups defined by the National Comprehensive Cancer Network guidelines, version 4.2019. Ninety-eight percent of the patients received 74 Gy (relative biological effectiveness) in 37 fractions. Fifty-one and six percent of the patients

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received neoadjuvant and adjuvant androgen deprivation therapy, respectively. The outcomes were the time of freedom from biochemical relapse and the time to late toxicity by the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. The outcomes were estimated with the Kaplan-Meier method and were also analyzed using multivariable Cox proportional hazards models.

Results

The median follow-up period was 84 months (IQR, 60-110). The 5- and 10-year freedom from biochemical relapse rates were 100/100%, 99/88%, 93/86%, 90/79%, 88/68%, and 76/63% for the very low, low, favorable intermediate, unfavorable intermediate, high, and very high risk groups, respectively. Patients with higher risk experienced biochemical relapse after shorter periods. The 5-year rates of grade 2 or higher late genitourinary and gastrointestinal toxicity were 2.2% and 4.0%, respectively. Based on the results of multivariable analyses, **younger patients more often experienced biochemical relapse**.

Conclusions

This study demonstrates the favorable biochemical controls of proton therapy even in advanced localized prostate cancer patients with a low incidence of late toxicities, supporting the feasibility of conducting prospective clinical trials. The risk groups defined by the NCCN guidelines, version 4.2019, are useful to classify patients with localized prostate cancer. Our findings might suggest the necessity to develop a treatment strategy that takes into account the patient's age.

The Swinging Pendulum of PSA Screening

Howard Wolinsky,

medpagetoday.com

In 2012, the U.S. Preventive Services Task Force (USPSTF) -- a powerful, voluntary group that sets guidelines for primary care physicians -- came out against the mass screening of healthy men with prostate-specific antigen (PSA) blood tests for the early detection of prostate cancer.

That statement, which was somewhat reversed in 2018, has lived on and continues to fuel hot debates over the use of screening and whether the guidelines themselves caused more harm than benefit. And there likely will be more arguments in the years ahead as medical groups conduct uptakes on guidelines and new studies appear.

It all started in 2012 when the USPSTF gave PSA screening a "D" grade, meaning it caused more harm than benefit. Groups such as the American Academy of Family Physicians (AAFP) and the American College of Physicians got on board. I took it to mean they were protecting men from overdiagnosis and overtreatment of prostate cancer, especially men like me with low-risk, low-volume prostate cancer.

The American Urologic Association (AUA) took the opposite view, arguing that early detection saves the lives of men with advanced prostate cancer.

David Penson, MD, MPH, a former guideline writer for the AUA and now Chair of the AUA's Public Policy Council, said the AUA and other urologic societies attacked the USPSTF's 2012 guidelines.

"The AUA felt the recommendation was wrong and did not account for the findings from the European trials specifically; it overvalued the American trial, and it didn't consider other endpoints. And so, at that point, we as an organization voiced our displeasure," said Penson, Chair of the Department of Urology at Vanderbilt University in Nashville. "We let the USPSTF know that we disagreed with their conclusions. We did speak to elected officials, but, of course, USPSTF is an independent entity, and they're entitled to make their recommendations. We were not included in the Task Force. And so, we were not part of that discussion."

USPSTF Chair Alex Krist, MD, MPH, a family medicine researcher at Virginia Commonwealth University in Richmond, stressed the independence of the Task Force, and noted that the group bases its recommendations solely on the scientific evidence. Krist also said that although the USPSTF has no urologist members, urologists were consulted in its reviews of PSA screening.

Prostate cancer patient Rick Davis, founder of AnCan, a platform for support groups for men with prostate cancer and other diseases, said the USPSTF in 2012 failed to make the distinction that a PSA could still provide information without necessitating treatment, instead discouraging all screening based on the D-rating.

"They blamed overtreatment on the PSA test rather than on the doctors who were misusing the information gathered and initiating procedures on men where they were not warranted. This of course would have required them to be critical of their colleagues and the medical profession," he said.

In response, Krist said that the USPSTF considered all potential benefits for the PSA test as a preventive service. However, he agreed with Davis's criticism that overtreatment could have been prevented if doctors used the PSA information more judiciously.

But, he added, "Back in 2012, the data actually showed that that's not what was being done."

"In fact, 90% of men with low-grade prostate cancers were getting surgery and radiation," said Krist. "And we know today that that is overtreatment, and the treatment patterns changed between 2012 and 2018 [when USPSTF again reviewed its PSA guidelines]."

The pendulum swung based on new research in 2018 as USPSTF and AAFP gave a slightly more acceptable C-grade to PSA screening based on new evidence.

In the Oct. 16 edition of *Morbidity and Mortality Weekly Report,* David Siegel, MD, of the CDC's Division of Cancer Prevention and Control at the National Center for Chronic Disease Prevention and Health Promotion, reviewed the situation. He noted that the 2012 USPSTF recommendation "likely contributed to a decrease in overall reported prostate cancer incidence and might have contributed to an increase in the percentage and incidence of distant stage prostate cancer."

A study at Kaiser Permanente of Northern California demonstrated the problem in stark terms. While screening of the popula-

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tion of eligible men under the age of 70 grew from 404,000 to 524,000 at Kaiser, following the Task Force statement in 2012, screening rates declined 20.6%, biopsy rates declined 61.6%, and detection rates declined 48.3%, while metastatic rates increased 52%, according to Joseph C. Presti, Jr., MD, who recently presented the updated figures.

Debate over routine screening for prostate cancer using PSA testing had occurred well before the FDA approved the test for prostate cancer screening in 1994. It has been a never-ending story of balancing the potential harms of overdiagnosing and overtreating men with prostate cancer lite versus providing necessary treatment to men with advanced prostate cancer.

In his 2014 book, *The Great Prostate Hoax: How Big Medicine Hijacked the PSA Test and Caused a Public Health Disaster*, Richard Ablin, PhD, of the University of Arizona College of Medicine, who discovered PSA in 1970, stressed that PSA testing was not intended for use for mass screening but rather to follow men with advanced disease. But after the FDA approval for screening, PSA testing was marketed to combine with the digital rectal exam (DRE) to detect prostate cancer early.

Thanks to PSA screening, prostate cancers were caught so early that the DRE was virtually unnecessary. DRE is considered a "lost art" among many primary care physicians and urologists, one not missed by many men.

Early detection no doubt helped men who were looking down the barrel of aggressive advanced cancers. But it created an epidemic of overdiagnosis and overtreatment for men with low-volume Gleason 6 cancer that is not expected to ever metastasize.

For me, the cure was worse than the disease. It seems I had a bad PSA reading (only 3.9 ng/mL, up from 3.2 ng/mL) on that day in December 2010 that I got on the prostate cancer railroad. The screening test was followed with another "bad" prostate day when I was diagnosed with a Gleason 6 tumor in a 2 mm smidge of tumor.

These results have not been replicated in three other biopsies and one multi-parametric MRI (mpMRI) since 2010. I was classified as a cancer patient forever.

PSA ensnared millions of men like me who had non-aggressive cancers that would never require surgery or radiation. We were like lambs to the slaughter as we followed our doctors' advice. I refused surgery and have been on active surveillance ever since.

But had I been diagnosed with more advanced cancer I might well be thanking, rather than damning, the PSA. That's the balancing game.

I suppose the debates were inevitable because PSA testing is such a poor tool.

In 2018, the USPSTF and the AAFP set off another debate when they recommended that men ages 55 to 69 should engage in shared decision-making with their physician about PSA screening.

The new guidelines emphasized something doctors should have done and probably did all along -- discussions with patients about decisions about treating prostate cancer to make a "shared-decision."

"Shared-decision making is essential for providing patient-centered care and can aid in addressing disparities in treatment. This process is especially important for cancer screening, like PSA testing, as there are sometimes real harms associated with screening," said Ada Stewart, MD, president of the AAFP. "And it is important for physicians to initiate these conversations, because many of our patients do not know to ask these important questions."

Siegel said making the decision on whether to be screened for prostate cancer is complex for men and their doctors and ought to be based on personal risk factors. These risk factors include age, family history, and African ancestry. CDC offers new interactive decision aids to help men think about prostate cancer screening decisions.

The discussion on the USPSTF and AAFP guidelines mentioning age triggered yet another issue: Why cut off screening at 70 and above, especially if men are healthy?

Davis took issue with the USPSTF's 2018 recommendation that PSA screening not be done in men over 70. "The 2018 revision from the Task Force was impactful, although it wrote off the lives of men over 70, that I find irresponsible. In today's world, over-70s are frequently healthy contributors to society and will remain so for maybe 15 more years. Recently, we lost a 74-year-old who was diagnosed with de novo metastatic less than 12 months ago. Speak to his wife about whether men over 70 should be tested."

Krist noted that any man over 69 who has concerns or questions should talk with his doctor and decide what's right for him. "That's always important and the first step. But the studies to date have shown that screening men over the age of 69 has no net benefit. And it's not just life expectancy. It also has to do with the nature of the disease. False positives and overdiagnosis starts to go up dramatically over the age of 70, exposing men to more harms."

Krist said complications, biopsies, and treatment increase as men age. "All those things change the balance of the benefits and the harms. And the data are pretty clear that for men over 70, the net benefit is not there. But once again, individual men who think otherwise or have concerns, should talk with their doctor and think about what's right for them."

He emphasized that the guideline doesn't apply to men like me with confirmed prostate cancer.

Penson said, "The recommendation about men over age 70 is based on a clinical trial that was done 20 or 30 years ago, which compared surgery to watchful waiting in men with known prostate cancer. And they basically found that if you are over age 65 in that trial, you didn't have a benefit to surgery. So the general teaching has been that you've got to live more than 10 years to get a benefit from active therapy in terms of mortality, but that's an old trial and patients who were diagnosed in 2020 are a whole lot different than patients diagnosed in the '80s and '90s."

"And then, the other point is for a lot of guys, mortality's not the only thing they're worried about," Penson continued. "They're worried about the spread of disease. They're just worried about having cancer. So I think you really need to personalize that decision. It's important to stress in the recommendation that there are some men over age 70 that will garner a benefit. And if you look at the USPSTF recommendation, they do say that, but they bury it in the text."

Debu Tripathy, MD, editor-in-chief of *Cure Today*, observed in a recent column, "A difficult line to walk in some cancer types is that between widespread screening to detect early disease and lower the death rate versus the overtreatment and associated consequences that can arise from it. This is particularly true when it comes to prostate cancer."

He said that based on the USPSTF's recommendations, the number of men screened for prostate cancer has declined. "That surely saved some patients from overtreatment, but at the same time it seems to have driven up the rate of advanced prostate cancers. Another problem with skipping screening is that it can deny men with low-grade prostate cancers the option of undergoing active surveillance so they will know if their disease starts growing quickly and needs more aggressive therapy," he said.

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In the years ahead, these debates no doubt will continue as new research is published as these groups routinely review their guidelines.

USPSTF tends to review its guidelines every 5 years, which would mean there will be a review in 2023, or sooner if major research is published.

Penson said he doesn't think there is anything in the hopper regarding prostate cancer that will prompt AUA to immediately re-examine its guidelines on the use of PSA.

But he suspects AUA may soon begin reviewing its guidelines because of important research on mpMRI, an area where controversies are brewing over new technologies and PI-RADS, the rating system for the scans.

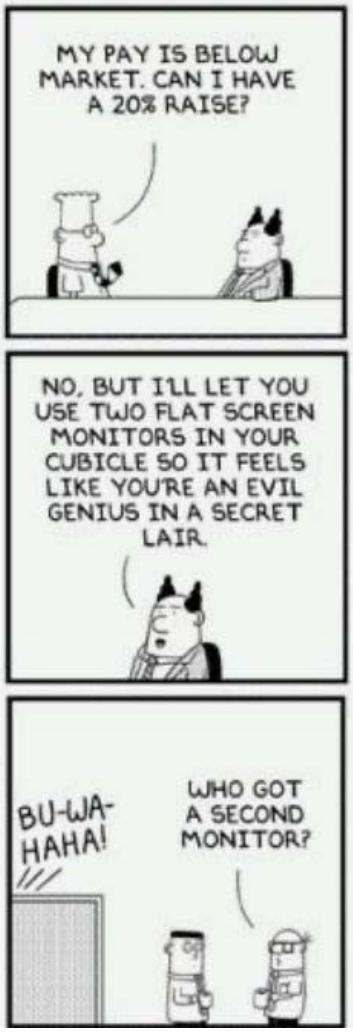
Looking ahead, Penson said of AUA's next review: "It's going to be about prostate cancer screening next time around. So, it's going to include guidance regarding the use of prostate MRI. It's going to include guidance around biomarkers such as 4K and the PHI [Prostate Health Index] test. And that is just starting now. So it's a few years away."

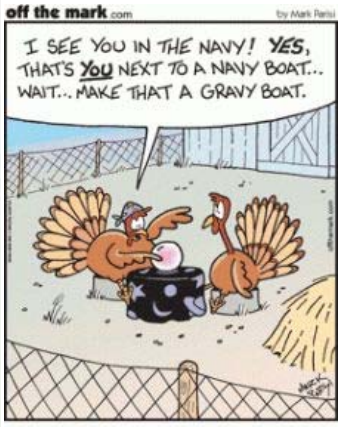
He added that he is not on the panel.

Krist said the USPSTF will review its guidelines in the next few years. An AAFP spokeswoman said her organization will follow suit when the Task Force reviews its guidelines.

Amidst the debate, it is important to remember that the PSA screening guidelines are just that: guidelines. They are not intended to dictate a standard course of screening or treatment. Rather, the guidelines are intended to serve as a guide for conversations between physicians and patients to determine what is best for each individual patient based on their health risks, family history, and screening preference.

What's needed more than new guidelines are new diagnostic approaches -- perhaps genomics combined with artificial intelligence/machine learning are most likely -- to separate those at high risk from those who aren't. If and when the science arrives, new guidelines can be written, and, potentially the debate, at last, will be over, and we can stop ducking pendulums.





On the Lighter Side