Informed Prostate Cancer Support Group Inc.
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MARCH 2021 NEWSLETTER

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Thursday, March 18,

Volume 14 Issue 03

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

.BERNADETTE GREENWOOD - IMAGING AND GENOMICS

(Replay of presentation from previous meeting)

Bernadette Greenwood – Desert Medical Imaging -- Imaging and Genomics in Prostate Cancer Management. She has a BS in radiologic sciences, earned a postgraduate Certificate in Imaging Sciences from University of Edinburgh and is working on a Ph.D. in tumor immunology imaging. Many awards and publications.The main areas Bernadette covers are: 1. The history of biopsy strategies 2. Technical aspects of MRI imaging 3. Rationale for her early work (2008-2009) on development and use of MRI-guided laser focal therapy of PCa 4. Update on NCT #02243033 (Phase II clinical trial of laser focal therapy) 5. PET (positron emission tomography) imaging with Axumin imaging agent 6. Potential role of genomic classifiers for risk stratification

- 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

February 2021 Informed Prostate Cancer Support Group Meeting
Summary by Bill Lewis

Active Surveillance 2021 – Have we come a long way baby?

Paul E Dato MD, Medical Director - Prostate Cancer Center, Genesis Healthcare Partners

Active Surveillance as a protocol for prostate cancer dates from around the year 2000. It stemmed from considerations about the treatment of "indolent disease," which is slow-growing and unlikely to cause morbidity or death. There came a recognition of overtreatment occurring in a significant number of patients. Data was accumulated, that enhanced the predictive value of baseline parameters – gathered soon after initial diagnosis – that indicated whether or not the cancer was likely to become "dangerous" to the patient. The development of mpMRI was of significant help in assessing the state of the disease. Longer follow-up (more active-surveillance experience) gave more knowledge about typical disease progression, which could assist in decisions for a particular patient.

At Genesis Healthcare, adoption of active-surveillance has now exceeded 93% for very-low risk patients, and 78% for low risk patients.

The molecular genetics of Gleason pattern 3 cells (for which active-surveillance is usually appropriate) show that they mostly resemble normal cells. They typically lack "markers" that tend toward cancer, such as increased cellular proliferation, reduced "programmed cell death," and increased activity for angiogenesis. PTEN loss (failure of the "brakes" on cancer development) may be up to 10%, in contrast to 90% in higher grade cancer – but in the absence of other markers / cofactors, such loss is not really a problem. Numerous studies have shown that "pure" Gleason 3 cells have essentially zero metastatic potential, and that only about 1-2% per year of biological grade progression to a higher grade was found even in "large volume" (many positive biopsy cores) Gleason 3 disease.

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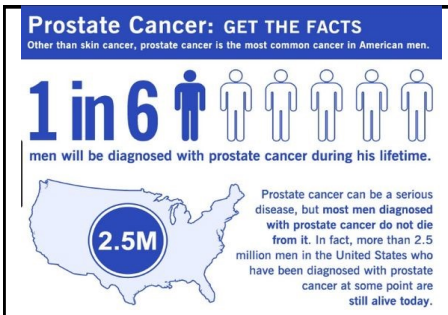

Organization

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

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

What We Are About

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

Meeting Video DVD's

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

From the Editor

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

We will continue to post and distribute the newsletter in the interim.

Notice: **Prostate Cancer Research Institute are providing a Moyad+Scholz Mid Year Update**

Articles of Interest

- **No More Surprises — New Legislation on Out-of-Network Billing**
- **How does your doctor do prostate biopsies?**
- **Novel Radiopharmaceutical Beats Cabazitaxel in mCRPC:**
- PSMA PET-CT with high risk prostate cancer before surgery or Radiation
- Androgen Cycling show promise in CRPC

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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A weak link in active-surveillance is the possibility of not detecting the co-presence of higher-grade cells, which is estimated to occur in 25-30% of patients. Thus it is very important to consider this in designing protocols and follow-up.

mpMRI scans and testing for molecular biomarkers give complementary information to help assess the true stage of the disease. The recent availability (and insurance coverage for) germline testing provides information about DNA repair weaknesses (BRCA-1 and BRCA-2, etc.) that can lead to cancer proliferation, that would mandate closer surveillance for such patients if they choose active-surveillance.

The long-term value of active-surveillance has been shown in several large trials. The ProtecT trial studied men randomized to active-surveillance vs. radical prostatectomy or radiation therapy, and found after 10 years median follow up, that there was no difference in either cancer-related or all-cause mortality rates. The active-surveillance group did have a higher risk of disease progression – but those men did not have the side effects of either form of active treatment until and unless they had progression and needed treatment. Two other studies with similar results are discussed in the video.

For Very-low Risk / Low Risk patients, active-surveillance is increasingly recognized as "standard of care." Most men in the US with prostate cancer have relatively low-risk characteristics. Active-surveillance requires careful monitoring via repeated assessments, including laboratory results (PSA and perhaps biomarkers such as Prolaris or Genome DX), imaging and biopsies. The goal is to delay or avoid the side effects (morbidity) associated with treatments (surgery, radiation, etc.). Note: tests for exosomes in urine and in blood were recently studied at Genesis Heathcare, but have not yet been published.

The risk of developing metastases is affected long-term by three factors: The Gleason Grade Group, the PSA velocity (rate of rise) and the PI-RADS score from mpMRI scans. UCSF data published last year showed that whereas 99% of 3+3 Gleason patients had no metastases after 7 years, "only" 96% of 3+4 patients did not develop any metastases in that time.

Other factors: If an initial biopsy shows cancer, but subsequent biopsies do not pick it up again, the likelihood of 10 years of survival without the need for treatments is higher – up to 84%, versus 66% for those men whose subsequent biopsies always show some cancerous cells. Ten-year cumulative data for African-American men vs. non-Hispanic white men shows a higher incidence of disease progression, and a greater need for "definitive" treatment. But surprisingly, there was no statistically significant difference in the risk of metastases, in prostate cancer-specific mortality, or in all-cause mortality.

Predictors for biopsy reclassification: High genomic score (e.g., Prolaris or Genome DX), PSA kinetics (rate of rise), PSAD ≥ 0.15 (PSA density, a surrogate for volume of disease; PSA divided by the volume of the prostate in cc's). All three factors affect the likelihood of reclassification to a higher-grade cancer within 3 years of start of active-surveillance, but only the latter two have been found to be associated with reclassification 5 years after diagnosis.

Surveillance limitations: Missing tumors of higher-grade disease, whether by "template" (random) biopsy or targeted biopsy, even with repeated biopsies. The need for frequent blood tests (to check PSA, etc.). Risks from repeated biopsies (pain; risks of bleeding or infection; expense). The lack of consensus regarding the optimal frequency of, and tests used in surveillance. Variable biology of individuals. Alterations in surveillance not based upon tumor biology but due to patient related concerns (e.g., anxiety, personal schedules, co-morbidities, COVID concerns).

Current controversies:

1. Intermediate Risk Disease / Gleason group 2 (i.e., 3+4). It's unclear if all such men should undergo definitive treatment. Cancer progression risk is best assessed with multi-variate analysis, not a single variable. Disease volume (vs. grade alone) has been shown to be a better predictor of disease progression. The Gleason pattern 4 subtype (expansile/cribriform, poorly formed, fused) is not always provided by the pathologist who examines the biopsy slides.

2. Choosing to use active-surveillance. Variable influencing factors include patient education level, his insurance type, proximity to health care facilities, and the availability of academic vs. community practices.

3. Follow up protocols: Although NCCN (National Comprehensive Cancer Network) guidelines endorse active-surveillance, little data-supported information is supplied by them regarding follow up. So protocols vary considerably between centers. Efforts are underway to address variation, but are so far mainly directed to defining classification and re-classification risk. The "Canary Institute" multicenter prospective active-surveillance cohort study involving nine North American centers developed and validated a multivariable model to identify

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who can safely "de-intensify" the regular surveillance regimen. It is used as guide for shared decision making between patient and physician. See canarypass.org/pass-risk-calculator/

Conclusions: "We have come a long way, baby." Active-surveillance is now the preferred form of treatment for Very-Low and Low Risk disease, and should be considered for carefully selected Favorable Intermediate Risk (Gleason 3+4) disease. New technologies (mpMRI, genomics, etc.) and taking into account multiple variables, appear to make it safer. Protocols for surveillance remain variable as does adoption of active surveillance. Further refinement is needed with respect to uniformity in risk assessment and follow up. Allowance is being developed for less burdensome frequency and type evaluations in the Very-Low and Low Risk groups. Possibly eligibility can be expanded to more men in the Intermediate Favorable Risk group. Nevertheless, caution remains the guideword for Gleason group 2 (Gleason 3+4) disease.

Questions:

- A personal question about having been on AS for four years, and a recent PSA rise – but after a kidney stone manipulation. Need to repeat the PSA test, after giving more time. Consider what imaging has been done, and might be appropriate now.

- What can give an increase in PSA (other than tumor growth): Sexual activity, infection, inflammation, surgical procedures, catheterization, heavy-duty cycling.

- In a targeted biopsy, the cores are only taken from the identified suspicious area, which means that about 20% of the time, other lesions are missed. Dr. Dato prefers having an MRI scan even before a first biopsy, especially if the prostate is large. If MRI shows an abnormality, he likes to have targeted cores as well as a set of 12 "template" cores. This helps to assess the volume of the disease. He also likes getting genomic data, especially in the case of 3+4 disease.

- How much tumor in a core is needed to run a genomic test? Prolaris requires 10%, but Genome DX can use as little as 3-5%.

- Is there significant variability in biopsy interpretations, from different pathologists? There can be, for higher-grade lesions, but his office has good concordance with second opinions given by Johns Hopkins.

- What's the practical value of micro-ultrasound? His office, and UCSD, have the equipment. He feels it is complementary with MRI. It is especially useful to detect malignancies in the peripheral area, although those missed by the MRI would be low-grade lesions. Still, it helps to define the volume of disease in the prostate. Very helpful for patients who cannot have an MRI for various reasons. His office uses the micro-ultrasound for all their work – they don't even have the lower-power equipment any more. Colleagues occasionally send patients to him for micro-ultrasound even before any MRI. Sometimes he is able to identify lesions in them, and often those patients come back to him for the biopsy.

- He is available for second opinions. It's great for reassurance. He does speak Spanish.

- Germline testing? Mostly uses Myriad. Also uses Invitae. Myriad has the largest library, and follows up when new information is available to indicate that a genetic variation has been found to be of significance.

- In ProtecT or the Swedish study discussed in the video, did some men decide to get a radical prostatectomy later on? Possibly, but then they would not be included in the final data.

- If a person has "symptoms" of some type while on active-surveillance, does that need to be addressed promptly? Certainly.

- What kind of doctor should be monitoring a patient who is on active-surveillance? Could it be a primary-care physician? Dr. Dato would not leave patients with a primary-care physician. They typically don't test PSA often enough, for example. The monitoring should be done by a urologist.

- Does PSA velocity have different significance in patients with small prostates vs. those with large prostates? Some, but not a great deal.

- Can MRI substitute for a biopsy, if no lesions are seen? Dr. Dato is not comfortable with that. There's even more variability in MRI interpretations than in biopsies.

- Are cyclists at higher risk than others, because of that activity? He would always look at them individually.

- Genesis healthcare organization? It has many specialists, in offices in La Mesa, on 4th Avenue, on Kearney Villa Rd., and in La Jolla, Encinitas and Rancho Bernardo. A new office is opening in South Bay. They do referrals internally, and second opinions for outside referrals. Call the main number for initial appointments.

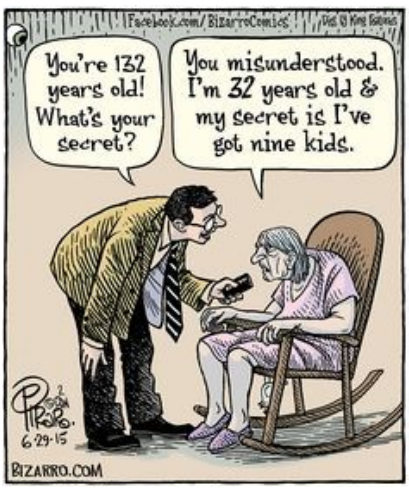
We recommend that you watch the video online for more definitive information about the talks and slides: https://www.youtube.com/watch?v=aMUkniBhCU8

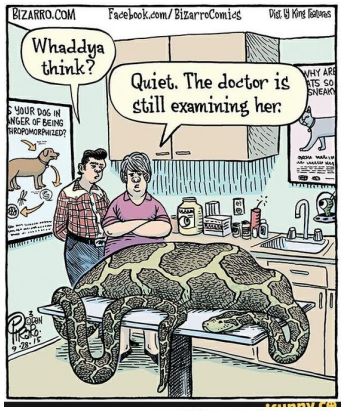
A dvd of the talk and Dr. Dato's slides will be available for purchase from the IPCSG next month.

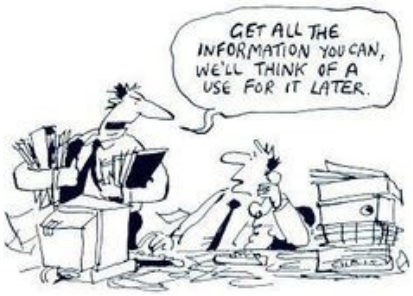
Prostate Cancer Research Institute are providing a Moyad+Scholz Mid Year Update Saturday March 27, 2021. https://pcri.org/2021-mid-year-update?utm_source=Insights+Newsletter&utm_campaign=c76c7ff828-EMAIL_CAMPAIGN_2019_10_29_06_43_COPY_01&utm_medium=email&utm_term=0_2db66599a5-c76c7ff828-127960608#an-invitation

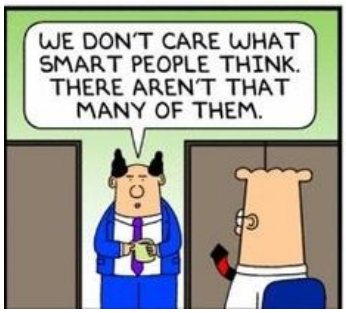
This is a FREE virtual educational event for prostate cancer patients and caregivers. For this Livestream, Thomas Hope, MD, of the University of California San Francisco will present on PSMA and Prostate Imaging, and Celestia "Tia" Higano, MD, from the University of Washington will present on Hormone Therapy and the Side Effects. This event will also feature a two-hour Q+A session with Mark Moyad, MD, MPH and Mark Scholz, MD, answering questions from the live online audience.

On The Lighter Side









Articles of Interest

nejm.org

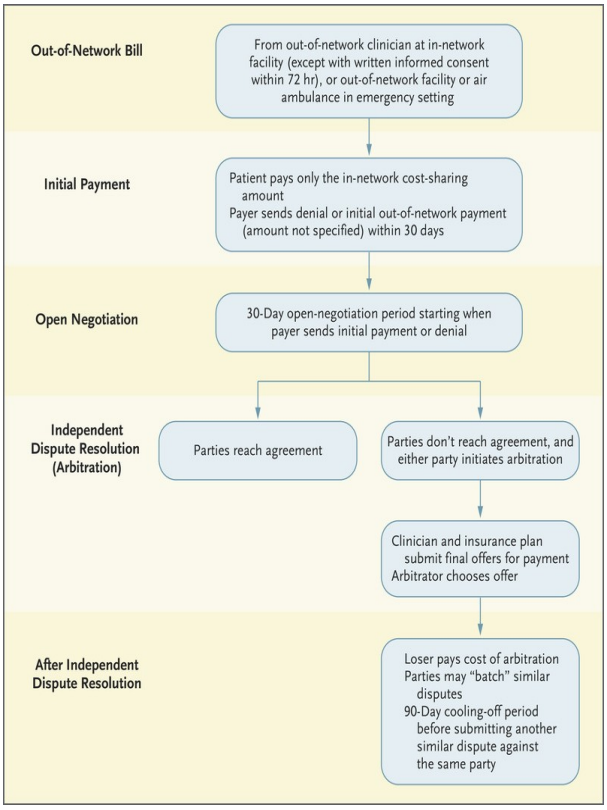
Big Surprise—No More Surprises — New Legislation on Out-of-Network Billing

Andrew M. Ryan

Article

The passage of the No Surprises Act — which banned "surprise billing" in many scenarios — on December 27, 2020, was an unexpected step forward during an otherwise dysfunctional year of U.S. policymaking. As many as one in five patients visiting an emergency department or undergoing elective surgery receives an out-of-network bill from a clinician whom they had no ability to choose, and more than 70% of ambulance rides are out of network.[1] Since insurance plans aren't required to pay out-of-network providers their full charges, clinicians may bill the patient for the difference between the insurance payment and their charges. These surprise bills can lead to thousands of dollars in unanticipated costs and have been nearly impossible for patients to avoid. Folded into the 2020 year-end spending and Covid-19 relief package, the new legislation will benefit patients and is likely to have little effect on most physicians who don't engage in surprise billing. Its effects on health insurance premiums, networks, and overall health care costs remain unclear, but they could be favorable.

Surveys show that unexpected medical bills are Americans' top financial fear. Nearly a dozen surprise-billing proposals were introduced in the 116th Congress. Despite bipartisan support, these proposals sparked intense disagreement within the health care industry about how out-of-network clinicians should be reimbursed. Insurers, employers, and consumer groups favored setting a benchmark price for services based on in-network rates, whereas hospitals and clinicians favored an arbitration process that would determine reimbursement on a case-by-case basis. In 2019, a year-end compromise was thwarted by a campaign funded by private-equity firms that control large physician-staffing companies notorious for using surprise billing as a business tactic (e.g., Envision and TeamHealth). A year later, Congress acquiesced to many of the demands of physician groups and passed the No Surprises Act.



Arbitration Process under the No Surprises Act.

Effective January 1, 2022, patients receiving out-of-network emergency services, air-ambulance transportation, or out-of-network nonemergency services at in-network facilities may be billed only the amount they would owe for an in-network provider. The law applies to all health plans, including employer-based, small-group, and individual-coverage plans. Out-of-network providers and insurers will have 30 days to agree on payment and then may invoke a binding arbitration process, in which each party submits a final offer and an arbitrator chooses between the two (see diagram). The arbitrator is instructed to consider the median in-network rate for the service, previous contracted rates between the parties, and specific information about the patient's disease and the clinician's experience but not provider charges or Medicare rates.

The law also advances billing and payment transparency. Three days before scheduled procedures, clinicians and insurers must inform patients of their expected out-of-pocket costs and clinicians' network status. Only after receiving this information and information on in-network alternatives and consenting to out-of-network bills can patients be balance-billed. This notice-and-consent exception doesn't apply to emergency services, urgent or unanticipated care, situations in which there are no in-

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network alternatives, or "ancillary" services, such as anesthesiology, radiology, pathology, or neonatology. In other words, patients cannot be balance billed in these cases or for these services, even if they provide consent.

Recent evidence may help predict the new law's effects. A similar arbitration process has been in place for several years in New York and New Jersey. One key difference is that arbitrators in these states are instructed to consider the 80th percentile of provider charges for a given service, which is typically many times higher than the median in-network rate. For example, the median in-network rate for a comprehensive emergency department evaluation in New York is $320, whereas the 80th percentile of charges is $1,211.[2] Clinicians won the majority of decisions in 2018 in both New York and New Jersey, with awards gravitating toward the 80th percentile of charges.[2,3] Because providers can receive generous arbitration awards by staying out of network, they have the upper hand in negotiating in-network rates with payers, who may prefer to pay high in-network rates over going to arbitration. This dynamic may inflate prices in the long run.

California's surprise-billing ban, by contrast, established a benchmark for out-of-network reimbursements, set at the higher of the payer's local average in-network rate or 125% of the Medicare rate, coupled with an optional arbitration process that has been used infrequently. After this law was enacted in 2017, the share of out-of-network claims in affected specialties decreased from 21.5% to 17.8%.[4] Benchmarking reduces the incentive for physicians to be out of network, since reimbursement for out-of-network services is pegged to average in-network rates. It may also reduce long-term spending, because it doesn't allow physicians to seek higher reimbursements using an arbitration approach anchored at a higher rate. This approach may reduce the negotiating leverage of physicians in hospital-based specialties linked to surprise billing. The decrease in out-of-network services suggests that the policy hasn't substantially disrupted California's provider networks, though questions remain about its effect on physician reimbursement.[4]

The No Surprises Act blends these approaches and may prevent unfair practices on both sides. Unlike in New York and New Jersey, arbitrators will be prohibited from considering charges and will instead refer to median in-network rates for services. This approach may help avoid the inflationary effects seen in these states. On the other hand, unlike California's policy, the legislation doesn't set a benchmark price and requires arbitrators to consider case-specific nuances, such as the clinician's expertise and both parties' history of good-faith negotiation — which may prevent insurers from unfairly dropping clinicians from their networks. The law will probably reduce reimbursements for providers who use surprise billing as a business tactic, such as large physician-staffing firms in emergency medicine and anesthesia. The Congressional Budget Office estimates that the law will reduce payments for some clinicians, reduce insurance premiums by up to 1%, and save the federal government nearly $17 billion over 10 years.

The law's transparency provisions — particularly the requirements to provide advance price and network-participation information — may have a larger effect on day-to-day practice than its balance-billing provisions. Providing an advance explanation of benefits for scheduled procedures requires providers to anticipate all clinicians involved in the procedure and submit their identifiers and billing codes to insurance plans, and requires insurers to cross-reference this information against provider directories and records of patients' deductibles and out-of-pocket maximums. Although standard in fields such as dentistry (and certainly worth pursuing), this process would represent a seismic change for clinicians and insurers — particularly for underresourced practices and hospitals.

Before passage of the No Surprises Act, most states had laws protecting patients from surprise bills, although they have historically applied to only fully insured health plans, which cover a minority of commercially insured people.[5] The new law defers to states' various approaches for determining out-of-network rates, including binding arbitration, nonbinding arbitration, benchmarks, or other methods. The benefits of state deference are that states can test approaches and can pass more protective standards if federal ones prove inadequate. The downsides are that state deference permits state laws that may err too far in favor of clinicians or insurers, could allow states to undermine federal protections, and leaves providers, arbitrators, regulators, and patients with a confusing patchwork of standards.

Although the new legislation is fairly comprehensive, more work on surprise billing remains. The law's omission of ground-ambulance surprise bills is an important weakness, and the ground-ambulance advisory committee it created may not be up to the delicate task of designing a policy that could upset local governments — some of which rely on balance billing to sustain their ambulance corps. Researchers and policymakers will need to evaluate the law's effects on network participation (since

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it may induce low-paid providers to go out of network or insurers to drop high-priced providers), in-network prices, physician supply, and overall health care spending.

Despite some flaws, the No Surprises Act is a major victory for the public. Like any compromise, it is imperfect and will require close scrutiny as it unfolds. Yet in a time of tremendous economic uncertainty, it represents an important step toward reducing financial harm to patients and restoring trust in the health care system.

How does your doctor do prostate biopsies? | THE "NEW" PROSTATE CANCER INFOLINK prostatecancerinfolink.net

So (in our opinion) the time has come — for a whole bunch of reasons — for actual and potential prostate cancer patients to start asking their urologists about whether they are able to carry out transperineal as opposed to transrectal biopsies.

Once upon a time — back in the 1970s — before we had PSA tests to "screen" for risk of prostate cancer, and transrectal ultrasound equipment to help guide transrectal biopsies, and a relatively low risk for biopsy-related infections with antibiotic-resistant bacteria, older forms of transperineal biopsy were a very normal way to carry out prostate biopsies. But they weren't very good and they weren't easy to do.

So, to be clear, a trans***perineal*** prostate biopsy is carried out through the skin between the rectum and the testes (sometimes referred to as the "taint"). By comparison, trans***rectal*** biopsy is carried out through the skin inside the rectum and comes with a relatively high risk for prostatic infections, including serious infections like septicemia that can lead to hospitalization and even death.

This link to information on the Mayo Clinic web site provides a pretty straightforward introduction (with pictures) to the relative merits of transperineal as opposed to transrectal biopsies. It is worth noting, in particular, the following:

•The vast majority of prostate biopsies here in the US are carried out transrectally, but in countiries like The Netherlands and the United Kingdom, nearly 50 percent of all such biopsies are now carried out transperineally

•The rate of severe biopsy-induced infection (sepsis) when biopsies are carried out transrectally in about 1 or 2 in 100. By comparison, the rate of sepsis when biopsies are carried out transperineally is just 1 in 500 (five to ten time lower).

•Most men who are given transperineal biopsies do ***not*** need to be given prophylactic antibiotics to lower risk for infection.

•Transperineal biopsies are generally much better at being able to biopsy areas like the apex of the prostate, which can be difficult to biopsy using the transrectal method.

Transperineal biopsies — like transrectal biopsies — can by guided by transrectal ultrasound and by MRI scans or both.

The reasons that most urologists here in the USA don't use the transperineal method for carrying out prostate biopsies are:

•They have never learned to do this and/or they think it is too difficult to do.

•They think it has to be done under full anesthesia — which is not true. It can be done very successfully under local anesthesia.

•They think it can't be done in an "office" setting and has to be done in a hospital — again, this is not true.

•They already own all the equipment to carry out prostate biopsies transrectally, and they would need to buy some new equipment to do these biopsies transperineally.

Like many doctors they are simply "resistant to change".

The bottom line here is that there is an increasingly credible amount of data suggesting that:

•Transperineal biopsies are more accurate than transrectal biopsies, with a low rate for false negative findings.

The risk for since effects and complications of transperineal biosies seem to be lowere than the risk when transrectal biopsies are used.

Discussion of this issue has already started to take place within the urology community (see, for example, here, here, here, and here), but the average patient simply won't have become aware that this is an important issue that potentially may impact his health and the quality of his care. This is particularly the case for those patients who may require multiple biopsies over time (e.g., those who may be on active surveillance for 5, 10, or 15 years).

Now we do need to be clear that transperineal biopsies do come with risk for some side effects. They include the following:

•Infection, and serious infections, such as sepsis (see above)

•Blood in the urine (most men, mild)

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•Blood in the semen (most men, lasting up to 3 months)

•Temporary erectile dysfunction (less than 5 percent of men)

•Bruising of the skin (most men, mild)

Urinary retention requiring catheter placement (1 percent of men)

These side effects are also common and mostly mild when a transrectal biopsy is being carried out. The other thing that is very different, however (apart from the level of risk for infection) is that there is no risk for rectal bleeding, for the very simple reason that the biopsy needles are not going through the rectal wall.

Prostate Cancer International and The "New" Prostate Cancer InfoLink believe that now is the time for serious discussion about the potential for modern forms of TRUS-guided and TRUS/MRI fusion-guided ***transperineal*** biopsies to replace transrectal biopsies, and a concentrated focus by the American Urological Association (AUA) to be specific about the preferred use of this type of biopsy in diagnostic and management guidelines for prostate cancer.

Greater awareness on the part of patients to ask their doctors about availability of this type of biopsy will be just one tool to accelerate change in this area, along with training of all new urologists to ensure that they are guided toward the use of this type of biopsy as opposed to transrectal biopsies.

Such a change in clinical practice will take time, but, in our humble opinion, this change, along with other changes in the diagnosis and management of prostate cancer over the next few years, will be highly beneficial to the quality of care of men at risk for prostate cancer.

Novel Radiopharmaceutical Beats Cabazitaxel in mCRPC: The first comparator study shows that the novel radiopharmaceutical Lu-PSMA-6170 bettered chemotherapy for metastatic castration-resistant prostate cancer (mCRPC).

medscape.com

M. Alexander Otto, PA, MMS

A novel radiopharmaceutical was more active than cabazitaxel against metastatic castration-resistant prostate cancer (mCRPC) and caused fewer grade 3/4 adverse events, according to results from the first and so for only comparator trial, known as THeraP.

Results of the phase 2 trial, which was conducted in 200 Australian men, were published online on February 11 in *The Lancet.*

The new product, a radiolabeled small molecule, lutetium-177 [^{177}Lu] Lu-PSMA-6170, is under development by Endocyte/Novartis. It binds to prostate-specific membrane antigen (PSMA) and delivers high doses of beta radiation.

The trial was conducted at 11 centers in Australia and was not blinded. Participants were men with mCRPC (median age, 72 years) who had experienced disease progression while receiving docetaxel and androgen receptor–directed therapy. They were eligible to receive cabazitaxel, which is generally considered the standard of care for this patient population.

To be eligible for the trial, men had to have metastases that expressed PSMA (detected after screening with two PET-CT scans). About one quarter of the men screened were not eligible to take part.

Participants were randomly assigned to receive cabazitaxel 20 mg/m^2 intravenously every 3 weeks for up to ten cycles or Lu-PSMA 6.0–8.5 GBq intravenously every 6 weeks for up to six cycles. The mean path length of the beta particles with Lu-PSMA was short, at 0.7 mm, limiting damage to surrounding tissues.

The primary outcome was a reduction in prostate-specific antigen (PSA) level of at least 50% from baseline. On intention-to-treat analysis, this was achieved by 66% of the men in the Lu-PSMA group and by 37% of those who received cabazitaxel ($P < .0001$).

Median progression-free survival (PFS) was 5.1 months in both arms, but at 12 months, PFS was 19% with Lu-PSMA, vs 3% with cabazitaxel, translating to a significant delay in progression after 6 months of treatment (hazard ratio, 0.63; $P = .0028$).

There are no data on overall survival, but additional follow-up is planned. Several other trials in prostate cancer are underway.

This trial provides "strong evidence that [Lu-PSMA] is more active than cabazitaxel" and is "a potential alternative," particularly when cabazitaxel is unsuitable, owing to the patient's age or comorbidities, say the investigators, led by Michael Hofman, MBBS, professor of nuclear medicine at the Peter MacCallum Cancer Center, Melbourne, Australia.

Grade 3/4 thrombocytopenia was more common with the radiopharmaceutical than with cabazitaxel (11% vs 0%), but overall, grade 3/4 adverse events were less common (33% vs 53% with cabazitaxel). These events included neutropenia (4% vs 13%) and febrile neutropenia (0% ves 8%). Patient-reported pain, fatigue, social functioning, diarrhea, and insomnia also favored Lu-PSMA. No deaths were attributed to treatment in either arm.

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

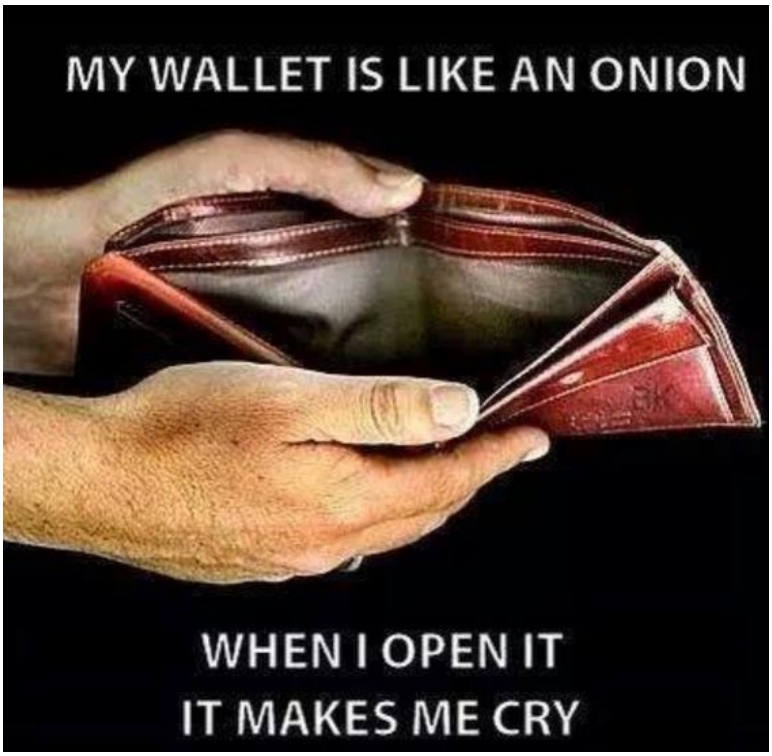
Our brochure provides the group philosophy and explains our goals. Copies may be obtained by mail or email on request. Please pass them along to friends and contacts.

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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Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective, randomised, multicentre study - The Lancet

Summary

Background

Conventional imaging using CT and bone scan has insufficient sensitivity when staging men with high-risk localised prostate cancer. We aimed to investigate whether novel imaging using prostate-specific membrane antigen (PSMA) PET-CT might improve accuracy and affect management.

Methods

In this multicentre, two-arm, randomised study, we recruited men with biopsy-proven prostate cancer and high-risk features at ten hospitals in Australia. Patients were randomly assigned to conventional imaging with CT and bone scanning or gallium-68 PSMA-11 PET-CT. First-line imaging was done within 21 days following randomisation. Patients crossed over unless three or more distant metastases were identified. The primary outcome was accuracy of first-line imaging for identifying either pelvic nodal or distant-metastatic disease defined by the receiver-operating curve using a predefined reference-standard including histopathology, imaging, and biochemistry at 6-month follow-up. This trial is registered with the Australian New Zealand Clinical Trials Registry, ANZCTR12617000005358.

Findings

From March 22, 2017 to Nov 02, 2018, 339 men were assessed for eligibility and 302 men were randomly assigned. 152 (50%) men were randomly assigned to conventional imaging and 150 (50%) to PSMA PET-CT. Of 295 (98%) men with follow-up, 87 (30%) had pelvic nodal or distant metastatic disease. PSMA PET-CT had a 27% (95% CI 23–31) greater accuracy than that of conventional imaging (92% [88–95] *vs* 65% [60–69]; p<0·0001). We found a lower sensitivity (38% [24–52] *vs* 85% [74–96]) and specificity (91% [85–97] vs 98% [95–100]) for conventional imaging compared with PSMA PET-CT. Subgroup analyses also showed the superiority of PSMA PET-CT (area under the curve of the receiver operating characteristic curve 91% vs 59% [32% absolute difference; 28–35] for patients with pelvic nodal metastases, and 95% vs 74% [22% absolute difference; 18–26] for patients with distant metastases). First-line conventional imaging conferred management change less frequently (23 [15%] men [10–22] *vs* 41 [28%] men [21–36]; p=0·008) and had more equivocal findings (23% [17–31] *vs* 7% [4–13]) than PSMA PET-CT did. Radiation exposure was 10·9 mSv (95% CI 9·8–12·0) higher for conventional imaging than for PSMA PET-CT (19·2 mSv *vs* 8·4 mSv; p<0·001). We found high reporter agreement for PSMA PET-CT (κ=0·87 for nodal and κ=0·88 for distant metastases). In patients who underwent second-line image, management change occurred in seven (5%) of 136 patients following conventional imaging, and in 39 (27%) of 146 following PSMA PET-CT.

Interpretation

PSMA PET-CT is a suitable replacement for conventional imaging, providing superior accuracy, to the combined findings of CT and bone scanning.

Androgen Cycling Shows Promise in Castration-Resistant Prostate Cancer | MedPage Today

medpagetoday.com

— Results comparable to enzalutamide in post-abiraterone setting

by Charles Bankhead, Senior Editor, MedPage Today
February 23, 2021

A treatment strategy based on manipulation of testosterone levels showed promise as a potential aid for managing castration-resistant prostate cancer (CRPC), according to a randomized proof-of-principle trial.

Following disease progression with abiraterone (Zytiga), treatment with bipolar androgen therapy (BAT) or enzalutamide (Xtandi) led to a median progression-free survival (PFS) of 5.7 months (clinical or radiographic progression). A similar proportion of patients in each treatment arm had at least a 50% reduction in baseline PSA level (PSA50 response), and overall survival (OS) did not differ significantly between the groups, reported Samuel R. Denmeade, MD, of Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins in Baltimore, and colleagues.

The median time to PSA progression (PSA-PFS) with enzalutamide increased from 3.8 months after abiraterone to 10.9 months after crossover from BAT (*P*=0.008). The results suggested BAT might have a role in altering the adaptive process that transforms hormone-sensitive prostate cancers into CRPC, they stated in the *Journal of Clinical Oncology*.

"I think the key result of this study is that sequencing testosterone and then anti-testosterone therapy, in this

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case enzalutamide, seems to be the ideal way [to modify the adaptive process]," Denmeade told *MedPage Today*. "A tumor seems to be sensitive and then adapts and becomes insensitive, so you switch treatments."

Background

As a therapeutic concept, BAT evolved from the long-recognized conversion of prostate cancer from hormone-sensitive to hormone (castration)-resistant disease during prolonged androgen deprivation therapy (ADT). Therapeutic resistance to ADT is almost universal, Denmeade and colleagues noted. Newer androgen-receptor (AR) inhibitors have become standard second-line therapy, but resistance increases with each line of AR-directed treatment.

In response to low-androgen conditions created by antiandrogen therapy, prostate cancer cells can develop resistance by means of adaptive upregulation of AR, the authors continued. Preclinical studies showed that the adaptive process can make prostate cancer cells vulnerable to supraphysiologic testosterone levels. Episodic exposure to supraphysiologic testosterone can induce downregulation of AR and potential resensitization of cancer cells to androgen-ablative treatment.

Preliminary clinical investigations demonstrated the feasibility and safety of BAT or rapid cycling between supraphysiologic and near-castrate serum levels of testosterone. The work formed the basis for the multicenter randomized phase II TRANSFORMER trial to compare BAT and enzalutamide in metastatic CRPC that had progressed on abiraterone but remained asymptomatic.

The study involved 195 men who received intramuscular testosterone once every 28 days or daily enzalutamide. Patients in both arms were concurrently managed with testosterone suppression by surgical or medical castration.

The primary endpoint was clinical or radiographic PFS. Crossover was allowed at disease progression. Secondary endpoints included OS, PSA50 and objective response rates, PFS from randomization through crossover (PFS2), safety, and quality of life (QoL). All analyses were based on the intention-to-treat principle and included all randomized patients.

Key Results, Future Directions

The primary analysis showed a median PFS of 5.6 months with BAT and 5.7 months with enzalutamide (HR 1.13, 95% CI 0.82-1.57). At data cutoff a year later, median PFS was identical in the two treatment arms (5.7 months, HR 1.4, 95% CI 0.83-1.55). A prespecified analysis showed the PFS results did not differ by duration of response to prior abiraterone (<6 months vs ≥6 months) but that a shorter response numerically favored BAT and a longer response favored enzalutamide.

Median OS did not differ significantly but favored BAT (32.9 vs 29.0 months). Consistent with the PFS data, shorter PFS with abiraterone favored BAT and longer PFS with prior abiraterone favored enzalutamide.

PSA50 response rate was similar in the two treatment arms (28.2% with BAT, 25.5% with enzalutamide). The time to first PSA progression was short in both groups but favored enzalutamide (3.8 vs 2.8 months, HR 1.51, 95% CI 1.06-2.16, *P*=0.02).

At clinical or radiographic progression, patients could cross over to the opposite therapy, following a 28-day washout period. Crossover was limited to patients who remained asymptomatic but excluded patients who had pain-related clinical progression.

The authors reported that 37 (39.3%) patients in the BAT arm crossed over to enzalutamide and 48 (47.6%) crossed over from enzalutamide to BAT. More than 90% of patients who crossed over did so because of radiographic progression. In general, patients who crossed over from enzalutamide to BAT fared better as compared with the opposite crossover:

- OS: 37.1 vs 30.2 months
- Objective response: 28.6% vs 7.3% (*P*=0.03)
- PSA50 (unverified): 77.8% vs 21.3%
- PSA-PFS: 10.9 vs 1.1 months (*P*=0.0001)
- PFS2: 28.2 vs 19.6 months (*P*=0.015)

Adverse event (AE) rates were similar in both treatment arms and were primarily grade 1/2. Rates of grade 3/4 AEs were 28.1% with BAT and 35.1% with enzalutamide. Serious AEs occurred in 19.1% of the BAT arm and 20.6% of the enzalutamide group. More patients discontinued BAT because of AEs as compared with enzalutamide (9.0% vs 5.2%).

Enrollment has already begun for a follow-up trial to evaluate multiple cycles of alternating testosterone extremes (supraphysiologic and castrate or near-castrate levels). BAT might also have a role in conjunction with immunotherapy as preliminary data have suggested a potential priming effect of BAT to make prostate cancer cells more responsive to immunotherapy.

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"We're at a point where we're trying to understand the best way to use this treatment," said Denmeade. "We're still working on how to incorporate testosterone into the treatment paradigm. We think it has the potential to augment and extend the response."

On The Lighter Side