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.
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 radiation injury -- which means they can be killed by radiation doses which will not kill their healthy, normal counterparts. 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. Millions of patients were treated with “2-D” radiation therapy, based on squares or rectangles drawn on the skin. Many were “cured,” but of necessity large amounts of normal tissue received large doses of radiation.

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 therapy) 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: The intestines receive 2500-3000 rads (equivalent to a curative dose for lymphoma; or to several thousand CAT scans!). Nevertheless, 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.

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. Whether we like it or not, protons will continue to fall under intense scrutiny and restricted applicability unless we can show 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

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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 (which cost something like $200-250 million) 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 28 operational proton treatment centers in the USA, with more than 18 of various sizes under construction or in planning. Construction can be done within 24 months from groundbreaking to first patient treatment. A small center in England was completed in a single year.

Imaging is critically important for directing the proton beam. However, until recently, for various reasons, imaging technologies readily available at X-ray (IMRT, etc.) centers were not available at proton centers. The California Protons Treatment Center has had since May 2016, FDA approval for its cone-beam CT scanner integrated into the gantries of three of their five treatment rooms – providing daily 3D images much superior to prior 2-D radiography. This is needed because cancer treatment is a dynamic process: Patient anatomy can change during treatment due to weight loss or gain, or to abdominal swelling due to peritoneal fluid accumulation, etc. Likewise, the tumor can change (especially with rapidly responding cancers such as lymphomas or head/neck cancers), shrinking or expanding during treatment. Any change in tumor size/configuration can impact the radiation dose to the tumor and to critical normal tissues nearby.

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 effective the SpaceOAR gel helps to separate the prostate from the rectum, thus protecting the latter from damage. Details on the SpaceOAR gel are in the Q&A section of the video. Also see an example of retreating the prostate after recurrence, either in the prostate or in regional lymph nodes.

The first proton treatment of prostate cancer was done in 1977. Since then, over 100,000 men with prostate cancer have been treated with protons. 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.

SBRT (Stereotactic Body Radiation Therapy) is an approach that allows fast (typically 5 or fewer fractions), high-dose treatment of some tumors. Although more well-known in X-ray treatments (e.g., Cyberknife), it was first done using Helium ions in the 1960’s, and a trial is now underway using protons in this approach for prostate cancer treatment. Side effects are no different than the standard 44-fraction proton treatments. Since SBRT is billed as a set amount irrespective of whether delivered with x-rays, gamma rays, or protons, many insurers who will not cover traditionally-fractionated protons (28-44 treatments) will reimburse for proton-beam-based SBRT. This means that proton therapy (given as SBRT) will be affordable for many more patients. The NCCN (National Comprehensive Cancer Network -- an alliance of 27 leading cancer centers) officially supports SBRT for low and favorable intermediate-risk prostate cancer patients.

At the time of this talk, Dr. Rossi’s first patient for this approach was being prepared for a set of 5 treatments. He is from Northern California, and can now be treated in a week, instead of five weeks. All such patients undergo hydrogel placement (SpaceOAR) to protect the rectum and carbon fiducial placement (implanted reference markers, to keep targeting accurate from one treatment to the next).

Questions:
What other cancers can be treated with protons? Any that can be treated with IMRT (X-rays).
What about radiation-induced cancers? All radiation can damage “normal tissue,” and can result in “secondary” cancers. But calculations and experience both indicate that proton therapy gives 40-50% less secondary cancers than X-ray therapy. Note that chemo drugs are carcinogenic, so similar effects can arise. George Johnson noted that his own father, a doctor practicing in the early years of radiation therapy, died at age 34 of leukemia, presumably due to X-ray dosages incidentally received in his work with patients.

Proton treatment after surgery and prior radiation? Dr. Rossi does this regularly. Often the SpaceOAR is a big help, to protect the rectum.
Treating several spots within the prostate? Those spots are given a higher dose, but the whole prostate is treated, to try to eliminate other (microscopic) tumors that are likely present.
Side effects after proton therapy? Similar in kind to those for X-ray therapy. More frequent urination is very common, for a time. Bowel problems are much less of a problem compared to X-ray therapy. Other issues are quite rare.
Radiation-induced fatigue? The amount of fatigue depends on the amount of normal tissue irradiated in conjunction with the cancer treatment, because that tissue has to recover. So fatigue is a lot less with proton therapy than with X-rays, because there is much less damage to normal tissue from proton therapy.

Differences in survival for treatment of metastases with surgery vs. protons? Published reports on survival are lacking. For surgery vs. radiation (either protons or X-rays), the main issue is one of ease of access. And surgery does have its own side effects to be considered. Proton therapy of “deep” mets is becoming more common, because with improved hormone therapy, often only one or two mets begin to grow again, whereas others are inactive.

What are the new algorithms that are coming out, and how do they help? “Monte Carlo” calculations help better predict the stopping power for protons in various tissues (so the dose will be more accurate), doing CT scans with two different X-ray energies gives better info, and faster software is beginning to al-

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low “real-time” adjustments of the treatments (what used to take two weeks can now be done in 15 seconds!). This all gives more accuracy and tighter “margins.”

What about using carbon ions instead of protons? It’s theoretically more effective biologically (being a larger particle), but the equipment is much larger and vastly more expensive. Whether there is a real advantage is being actively studied.

Why are very different doses mentioned for various treatment modalities? It depends on how fast the radiation is given. Five proton-SBRT treatments totaling 40 Gray are equal to about 120 Gray given in the standard five-week dose schedule, and is effectively a greater dose than 144 Gray given over many months by Brachytherapy implants. There are calculations that can be made of the “biologically equivalent dose,” that take the time factor into account.

Issues with treating a patient who has an artificial sphincter? The metal can cause artifacts in the CT scan, but these can be mostly subtracted out with software. It is best if the sphincter is some distance away from the area to be treated. It’s usually not advisable to consider removing the sphincter, due to scarring around it.

Will insurance companies pay for proton therapy as re-treatment after radiation therapy failure? If the X-ray treatment has been a maximum dose, then there is a recommendation for proton therapy from ASTRO (the American Society for Radiation Oncology), and insurance companies are somewhat more likely to pay than for initial therapy using protons.

Comparison of MRI vs C-11 acetate for finding recurrence? All of the PET-CT methods (C-11, PSMA, and NaF) are better than MRI for this, as they can find smaller tumors. Note that 3 Tesla MRI is better for diagnosis, and 1.5 Tesla is better for merging with CT images for treatment planning.

A member shared that he was able to get his Proton therapy paid for by insurance eight years ago, by suing them, with expert testimony from Dr. Rossi (who did the treatments) that convinced the judge that proton therapy would be best in his case. Dr. Rossi noted that this approach has worked for many others of his patients, where the insurance company wouldn’t pay even after multiple direct appeals/filings by his office.

Glioblastoma and pancreatic cancer survival rates haven’t improved much – why? Glioblastomas are unusually resistant to radiation, so extremely high doses are needed, which causes unacceptable toxicity to surrounding brain tissue. Pancreatic cancer is usually diagnosed only after it is quite advanced, and has therefore become difficult to treat. They are now getting 5-10% cure, mainly in cases where protons can shrink the tumor enough for subsequent surgery to be successful.

Treating bone metastases with protons? Similar results as with X-rays, but a little more maneuverability such as near the spinal cord, because of the stopping of protons vs. passing clear through of X-rays. Should it be done before, concurrently with, or after chemo? It varies, depending on which chemo drug is used. Dr. Rossi also noted that combining proton therapy with immunotherapy is being studied. Proton therapy seems to give better synergy than X-rays, presumably because it gives less damage to surrounding healthy tissue, which causes less immunosuppression. (Author’s note: see also combinations of immunotherapy with Nanoknife or Cryotherapy in prior talks to our support group.)

Microbeam radiation and splash radiation therapy? Microbeam is a super-narrow beam, and splash radiation is a high-dose modality, both to try to spare normal tissue, but both are still using X-rays.

Can protons be used for retreatment after Brachytherapy? Yes, Dr. Rossi has done that since 2014.

More details and images from various scans are shown in the video of this presentation, which, including the PowerPoint slides, will be available for purchase via the website shortly before the next meeting, or at the October meeting on the 20th.
ON THE LIGHTER SIDE

FUTURE MEETINGS

- Meeting Date SPEAKERS
  October 20 - Member Panel Personal Journeys

For further reading:

For Comments, Ideas and Questions,
email to Newsletter@ipcsg.org
Notable Articles

**Nutrition, ADT, and metastatic prostate cancer**

Posted on October 8, 2018

Most men who are taking androgen deprivation therapy (ADT) for metastatic prostate cancer feel the need to “do something” about their diet in order to (a) further help to control the risk for progression of their cancer and (b) help to cope with the side effects of ADT.

Another paper just published in Prostate Cancer and Prostatic Diseases this month is a review by Barnes et al. on whether current nutrition care guidelines for men with prostate cancer who are being treated with ADT are really based on good enough evidence.

The authors claim to have been able to find just 16 articles on this topic that met the inclusion criteria for their review, and they summarize their findings as follows:

Each of the 16 articles offered distinct sets of dietary interventions designed to manage the side effects of ADT.

12/16 articles combined nutritional guidelines with physical activity and/or medications and/or counseling.

4/16 articles dealt exclusively with the impacts of diet alone, and among these four articles

- Three articles measured changes to participants’ dietary intake and influence on ADT side effects.
- One article showed daily caffeinated beverages improved cancer-related fatigue.
- Two articles showed no impact of isoflavone supplementation on hot flashes, quality of life, body mass index, or blood lipids.

Among the 16 articles altogether

- Dietary intake and compliance was poorly reported (and thus provided limited knowledge of acceptability and feasibility for dietary interventions).
- Information on the nutrition care practices and views of clinicians treating men for prostate cancer is limited.
- No articles measured the impact of diet on long-term side effects of ADT.
- The methodological quality of the papers ranged from weak to strong.

Barnes et al. conclude that:

Current evidence for dietary interventions to mitigate ADT side effects is limited. Further investigations are warranted to explore the impact of changes in dietary intake on ADT side effects before practice guidelines can be considered.

We have considerable sympathy with the findings of Barnes et al. In general, our knowledge of what really “works” from a dietary and a nutritional perspective to optimize the quality of life of men with prostate cancer and of men with prostate cancer who are on ADT is poor.

While we know what is a really bad idea (e.g., diets high in red meat and carbohydrates and animal fats) and we know that some men believe they do really well on diets that are almost entirely vegetarian or vegan, the question of how well any of these diets actually work for large numbers of men has yet to be answered in any really well conducted studies.

Thus our advice to most men at the present time generally takes three forms:

Eat a well balanced diet that is significantly lower in red meat, carbohydrates, animal fats, and sugars than the average US diet today.

Eat more cruciferous vegetables (things like broccoli, cauliflower, cabbage, and brussels sprouts), nuts, and roughage.

(Continued on page 8)
Exercise regularly and work up a good sweat if you can when you do. We know these things are good for the heart and for other bodily functions too, and there is plenty of evidence to suggest they are also good for people with cancers of many types.

However, it would be really nice to know if specific diets and supplements had real, definable benefits for men on ADT. Many men swear by the value of soybean-based products as a way to down-grade the impact of ADT on hot flashes, but whether this is really true for most men — based on a well-controlled and randomized trial — remains utterly unknown.

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Personalized Medicine in Prostate Cancer: Now More Precise


Raoul S. Concepcion, MD, FACS

Over the past decade, we have witnessed an explosion of molecular testing in the urology world that will help us better diagnose and manage prostate cancer across the spectrum of the disease. All of us recognize that we have fallen behind our colleagues who treat other tumor types and for whom routine lab and tissue testing is the requirement or norm for optimal therapeutic choices. However, we are making progress.

We know that prostate cancer is an endocrine disease and the androgen receptor (AR) plays a major role in disease progression, even when serum testosterone is at castration levels of the hormone. Androgen deprivation therapy (ADT) continues to be the foundation of treatment on which all other onco-lytics are layered as the patient begins to progress. However, treatment pressure selection and tumor heterogeneity will result in cellular mutagenesis that makes ultimately eradicating the disease a daunting task. In patients with metastatic castration resistant prostate cancer, a number of these mutations, which will inevitably confer resistance to therapy, have been discovered. For example, prostate cancer cells that have been long exposed to ADT and are now starved of their fuel for survival can produce their own ligands to survive. This is comparable to a car that could produce its own gasoline (or electricity)—very nice if you are the automobile owner—but the reality is not so desirable for the patient with cancer. AR, the very target of ADT, can undergo genetic alterations that will result in downstream changes leading to resistance and cell survival.

Fortunately, we are in the early stages of developing biomolecular markers that will help the clinician to choose better therapies to try to stay ahead of these mutations. The ability to measure circulating tumor cells has led to the development and marketing of commercial assays to detect these aberrations—AR splice variants—that may be predictive of what agent should be used next in the treatment paradigm. In addition, patients who harbor homozygous mutations of inherited DNA repair genes, most notably BRCA2, may in fact respond to PARP inhibition therapy. Also, DNA sequencing to test for these gene mutations can now be clinically implemented in the appropriate patient.

Thus, just as it is difficult to keep track of all the FDA-approved therapies, their mechanisms of action, adverse event profiles, and current approval status, we are additionally challenged to stay up-to-date with the molecular tests that may ultimately be required to determine when and where to use these drugs in the appropriate sequence for each patient. The vernacular commonly used in the press is the “era of personalized medicine.” I will argue that the art of medicine has always been personalized. We as providers do not adhere to a single agent, from an antibiotic to an antihypertensive to an oncolytic, for all patients. All of us consider the patient’s medical history and comorbidities and a host of other factors to
best determine which agent to prescribe in hopes of achieving the best outcome. Now, given the complexity in understanding these malignancies and their ability to undergo evolutionary mutations to survive, we must clearly understand how to accurately test and target these dynamics to stay ahead of the changing tumor environment. Personalized yet ever more precise at the tumor level—precision medicine. This is how all of us will need to practice moving forward to continue making strides in advancing cancer care.

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What to Expect When Active Surveillance Leads to Prostatectomy | Medpage Today:

High-risk features in 39% of prostate specimens at surgery

Oncology/Hematology > Prostate Cancer

by Charles Bankhead, Senior Associate Editor, MedPage Today, September 21, 2018

A high proportion of men who entered active surveillance for early prostate cancer had one or more high-risk disease characteristics when they subsequently had radical prostatectomy, a Swedish study showed.

Medical records showed that 52 of 132 men had at least one adverse pathology feature at radical prostatectomy. All the men initially opted for active surveillance, and the median time from enrollment to surgery was 1.9 years.

Adverse pathology findings included Gleason score >3+4, extraprostatic extension, positive surgical margins, seminal vesicle invasion, and lymph node involvement, as reported in the Journal of Urology.

"Our findings can be used to counsel patients on AS (active surveillance) regarding what to expect in those who progression during surveillance and undergo deferred radical prostatectomy, as 85% of the cohort had objective signs of progression triggering treatment, including upgrading or increased cancer volume or PSA (prostate-specific antigen)," Rebecka Arnsrud Godtman, MD, of the University of Goteborg and Sahlgrenska University Hospital, and co-authors wrote.

"The results underscore the need to determine better methods of risk classification and identify progression during AS to select the best treatment strategy for each individual patient at each phase of the disease."

Another study in the same issue of the journal showed positive results with a minimally invasive technique that dramatically reduced the frequency of progression to radical prostatectomy among men on active surveillance. The 2-year rate of conversion was 7% among men who had tissue ablation with vascular targeted phototheraphy (VTP) prior to beginning active surveillance versus 32% for those who had no treatment prior to starting surveillance. At 4 years, the prostatectomy rates were 24% in the VTP group and 53% in the surveillance group, reported Inderbir Gill, MD, of the University of Southern California in Los Angeles, and colleagues.

"Absolutely," Gill told MedPage Today when asked whether VTP might address the progression issue observed in the Swedish study. "What we’re showing is that progression to radical prostatectomy occurs less often for [VTP] than with active surveillance -- about 30% less often at 4 years."

"Conversion to radical prostatectomy is primarily due to progression of the cancer," he added.

"[VTP] arrests progression and decreases the need for radical therapy up to 4 years now, and we already have 5-year data in the works."

The findings added to those that Gill reported earlier this year at the American Urological Association annual meeting. The findings came from a multicenter randomized trial of the TOOKAD VTP system (Steba Biotech), which employs low-level laser energy and light-activated padeliporfin di-potassium to induce vascular necrosis and tissue ablation. Not yet available in the U.S., the TOOKAD device has regulatory approval in Mexico, Israel, and most of the European Union.
NETWORKING

Please help us in our outreach efforts. Our speakers bureau consisting of Lyle LaRosh, Gene Van Vleet and George Johnson 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 at our meetings. Please pass them along to friends and contacts.

FINANCES

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

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

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 4201042, San Diego CA 92142

Directions to Sanford-Burnham-Prebys Auditorium
10905 Road to the Cure, San Diego, CA 92121

Take I-5 (north or south) to the Genesee exit (west).
Follow Genesee up the hill, staying right.
Genesee rounds right onto North Torrey Pines Road.
Do not turn into the Sanford-Burnham-Prebys Medical Discovery Institute or Fishman Auditorium
Turn right on Science Park Road.
Watch for our sign here.
Turn Left on Torreyana Road. Watch for our sign here.
Turn Right on Road to the Cure (formerly Altman Row). Watch for our sign here.