Bernadette Greenwood – Desert Medical Imaging -- Imaging and Genomics in Prostate Cancer Management

Bernadette started as a combat medic! But she is a researcher, not a physician, and does not give medical advice. 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. A few years ago, she founded the International Laser Network, a not-for-profit organization comprised of laser users with a goal of keeping patients safe and educating users.
She is a vocal activist for patient care.

1. **The history of biopsy strategies**: The first biopsies were done in the 1920’s. Gradually, ultrasound guidance and "systematic" biopsy grids were added, but they still miss significant tumors, even with "saturation" biopsies using very many needles. A major advance occurred when MRI guidance for biopsies was added (and officially recognized in about 2010), with standardization now worked out. Traditional screening for PCa (prostate cancer) is associated with over-diagnosis and over-treatment of clinically insignificant PCa. Systematic TRUS (trans-rectal ultrasound-guided) biopsy has a false negative rate of 30-35%, missing clinically significant PCa. And systematic TRUS biopsies under-estimate Gleason scores 30-40% because of missing the most-significant tumors. Thus, clinical staging based on TRUS biopsies underestimates pathological staging 15-25%. Furthermore, 26% of patients in active surveillance harbor undetected clinically significant PCa (i.e., tumors that probably should be treated without delay).

2. **Technical aspects of MRI imaging**: Three main parameters are used to determine the likelihood of a tumor being present in the imaged area: T2 (see April 2017 IPCSG newsletter), DWI (diffusion of water is restricted where cells are densely packed, which occurs commonly in tumors, inflammation and infection), and DCE (dynamic contrast enhancement, looking at the rate of MRI contrast (gadolinium-based contrast) entering and exiting the tumor rapidly -- because of its higher-than-normal blood supply). According to the medical literature, together they give better than 90% accuracy in detecting prostate tumors.

   Functionally, a 1.5 Tesla magnet and a 3.0 Tesla magnet in the MRI unit give the same results. Theoretically, the 3.0 would be better, but air and movement in the pelvis wash out the differences, so her group (and a local group, Imaging Healthcare Specialists) prefers the 1.5 magnet. Data presented at ASCO and AUA also support 1.5T for prostate cancer imaging as most scanners in the U.S. are 1.5T. The main drawback of 1.5T is that the sequences are slightly longer (seconds or minutes longer, not hours).

   Under current standardization, a multi-parametric MRI results in a PI-RADS score, which indicates how abnormal the suspicious areas in the image are. She feels the descriptors in the table could be more action oriented: The classification labels should indicate whether a biopsy should be performed, and at what level of urgency. As a member of the ACR Pi-RADS subcommittee on imaging standards, she has suggested the following language: 5= biopsy immediately! 4= needs a biopsy. 3= probably doesn’t need a biopsy, but wouldn’t hurt. 2= doesn’t need a biopsy. 1= don’t bother.

   She described the procedure for MRI-guided biopsies – see the video. The procedure is fast: 20-30 minutes, and very accurate. Some have promoted “Fusion” biopsies, combining MRI images with real-time Ultrasound imaging, but Bernadette explained that there is a plus-or-minus 3 mm inaccuracy (“skew in the X-Y plane”) in published accounts of such biopsies, which she considers unacceptable for biopsies of small tumors. However, her office does accept results of such biopsies from some experts in the technique, though her organization (Desert Medical Imaging) does not do them.

   Gleason scoring standards are changing, so it’s appropriate to know which standard is used in your bi-
opsy. Also, consider getting a second opinion to reduce inter-observer variability in the grading.

Biopsy samples should be sent for genomic testing – see discussion below.

3. **Rationale for her early work (2008-2009) on development and use of MRI-guided laser focal therapy of PCa:** Of all options, she felt back then that Cryo and Laser therapy were the only two potential methods for focal therapy, but Cryo gives much less control over the margins of the treatment – being more a regional treatment than a precise, focal treatment.

In laser focal therapy, the laser fiber is inserted through the same device as is used for biopsy, with a cooling catheter that only allows heating at the tip of the laser fiber. An interface allows creation of thermal maps from the MRI data, to precisely monitor the treatment every 4 seconds. After a low dose of heat from the laser, to confirm the tip placement, a therapeutic treatment dose is given for up to 120 seconds, heating the tissue to about 60-70°C (140-160°F) to necrotize or kill the tumor. Safety cursors are placed on the image to protect nearby structures, with the heating automatically cut off if the temperature at those points gets to an unsafe level. The transition zone between treated and unaffected areas is desirably very narrow, less than one millimeter – in contrast to 5-10 mm in Cryo, HIFU and Radiofrequency (RF) ablation.

4. **Update on NCT #02243033 (Phase II clinical trial of laser focal therapy):** Phase I safety and feasibility study results are to be published soon. Little to no “morbidity” (side effects). The rate of “positive margins” was 26%, which is either due to some tumor left behind, or to recurrence at the treatment site. Some tumor is often left behind to avoid getting too close to other structures such as the urinary sphincter, or when de-bulking a tumor that has extended into the seminal vesicles or bladder wall in “salvage” patients (i.e., after some other treatment).

On treatment naive patients (i.e., no prior therapy), PSA scores decreased by 35% at one year after laser focal therapy, with no statistically significant change in IPSS (International Prostate Symptom Score for urologic function) or SHIM (Sexual Health Inventory for Men) scores. “Salvage” patients had 47% decrease in the mean PSA, and no statistically significant change in the IPSS or SHIM scores (with 16 patients so far).

Current conclusions about laser focal therapy are that it is feasible and safe, with a recurrence rate of 25%, and about 5% going on to whole gland therapy. Patients are still viable for retreatment afterward, either for focal or whole gland therapy. There is a nice progression: Multiparametric MRI leads to MRI-guided biopsy, which leads as needed to MRI-guided laser focal therapy in patients who meet the study inclusion criteria.

The Phase II study (Phase I was converted in May 2016; also NCT #02243033) is 7 years into a 20-year follow-up and these results were presented at the American Association for Cancer Research, 2017.

5. **PET (positron emission tomography) imaging with Axumin imaging agent** (recently approved for commercial use; also known as FACBC): The agent is suitable for immediate imaging, 3-5 minutes after injection, and scanning takes 20-30 minutes. Examples of imaging to pick up lymph node and other metastases were shown. Other approved imaging agents are F 18 FDG (low uptake by prostate cancer; bladder excretion obscures nearby lymph nodes; used typically in patients with elevated PSA), F 18 NaF (used to assess for bone metastasis), C 11 Choline (used after initial therapy, to localize recurrence if rising PSA and inconclusive conventional imaging; requires on-site cyclotron). Details on studies and results are in the slides. Accuracy with Axumin was about 80% in pelvic scans of salvage patients with PSA >1.8. Adverse reactions were very low and mostly mild. Half-life is 110 minutes, allowing use at sites that do not have a cyclotron.

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6. **Potential role of genomic classifiers for risk stratification:** A biomarker is a measurement indicating normal or pathogenic biological processes, or response to a therapy. For prostate cancer, Desert Medical Imaging uses several non-invasive biomarker measurements, including PSA and mpMRI (for PSA density, tumor volume, tumor staging, and biopsy targeting) and uses MRI-guided biopsies for Gleason score and genomic testing.

She inquired as to any present who had genomics done on their MRI-guided biopsy? Only one.

There are many current and emerging genomic tests. Here are the most well-known:

- **ProstaVysion** – 2 genes: MRG (overexpression of this gene is bad) and PTEN (there are two versions of this helpful gene, but one or both may be missing. Surprisingly, she finds that if one PTEN is missing, it’s better, not worse, to have both missing according to her current small data set, in contrast to ProstaVysion’s scoring system.)
- **ConfirmMDx** – after negative biopsy, when cancer is still suspected, this test is run using 8-18 cores.
- **Prolaris** – 20-something genes are tested.
- **OncotypeDX** – ditto.
- **Decipher** – ditto. Until suggested 3 years ago by Bernadette, this test had only been done on prostatectomy samples, but they now offer it for analysis of biopsy cores. Produces a 5-10 year metastatic risk profile. She now uses this on every patient where the cores allow it, and with permission, submits their core samples for additional genetic testing, up to 1.4 million genes in several ongoing research studies. Cores can be tested up to 7 years after the biopsy.

Intratumoral and intertumoral heterogeneity of the prostate cancer genomics has been shown, emphasizing the importance of targeted biopsies and genomic testing for classification and prognostication of disease progression.

A final note: She recommends the NCCN.org patient prostate cancer treatment guidelines, starting on page 45 of their pdf about prostate cancer, which is available at https://www.nccn.org/patients/guidelines/cancers.aspx

**Questions:**

- **PSMA agents?** A member noted that they can be used at much lower PSA than Axumin. Bernadette is working to get 18F-DCFPyL as soon as possible – it is not commercially available yet, but is in a trial at Johns Hopkins. Gallium 68 is being used at UCSF -- 500 patients so far. Two group members have had good results there. Australia & Germany have been using Gallium 68 for many years. Other new agents were mentioned as being in active development.

- The immunological response (stimulation) after laser focal therapy? Not known yet, but she is studying tumor immunology imaging to work on it.

- **Bottom line on laser focal therapy?** “Oncological control without morbidity” -- but only studying its use on Gleason 7 or lower. The phase II trial will be completed 20 years after 1000 patients have entered the study.

- **Cost?** She has no grant money to help with costs. $25,000 entry fee to be treated. Desert Medical Imaging does not submit to insurance companies, but patients have sought reimbursement on their own. Men in financial hardship can apply for funding at www.thefocaltherpyfoundation.org, co-founded by Bernadette and her patient, Vinny Smith.

- **Use of IBM’s Watson computer system?** It will be a game-changer. She strongly favors the use of computers and automation in disease analysis and treatment planning, and is waiting for IBM to harvest her data.
Cyberknife? Appropriate in some cases. She is in favor of: standardizing treatments, making them widely available, and using treatments that are the least damaging, the least traumatic, and that offer the highest hope for oncologic control. Seek advice from your physician.

DVD’s of the meeting will be available by the next meeting date via the website: www.ipcsg.org/shop or from the library at the next meeting. Slides are included in a file on the DVD.

ON THE LIGHTER SIDE

“...and this is Ralph, your anesthesiologist.”

“Unfortunately, your insurance doesn’t cover your surgery. But, don’t worry, I can use paperclips and duct tape.”

“NOW I KNOW WHY THEY CALL IT ICU!”

“YOU TESTED POSITIVE FOR BEING TOO NEGATIVE.”
INTERESTING ARTICLES

Seven tips to help you find the right oncologist

After being diagnosed with cancer, the first thing to do is find a good oncologist. Cancer treatment is tough, so it's important to find an oncologist who supports and cares for their patients in a way you would want to be supported and cared for. We've put together a list of tips for finding the right oncologist with information from cancerdocs.org.

- Search for local oncologists.
  The first step in finding the right oncologist is to start with the ones closest to you. If you're ill, you don't want to have to travel too far for treatment if you can help it. Write down a list of local oncologists that you can then whittle down.
- Get recommendations.
  It's highly likely that you will know someone (maybe several people) who have recently been treated for cancer. Ask them about their oncologist: did they like their doctor? how would they rate them? would they recommend them?
- Research credentials.
  Research the credentials of the oncologists on your list to ensure they are fully qualified to deal with your type of cancer. In addition, you may want to know if they have any outstanding malpractice lawsuits against them or if they have a history of disciplinary action.
- Check their experience.
  Do they have a successful history of dealing with your type of cancer? How many patients have they worked with who have the same complications as you? Do they have experience performing specific procedures that may be relevant to your treatment?
- Check your insurance.
  Ensure your health insurance covers all of the treatment the oncologist is proposing.
  Choose an oncologist who is willing to work with insurance companies to ensure you get the best treatment.
- Review hospital quality and healthcare team.
  You may like the oncologist but hate the hospital they work in. Likewise, you want the oncologist's team to have the same level of commitment and care to your treatment. Does the hospital allow access to clinical trials? Is it a progressive hospital that embraces new technology and treatments?
- Do they make you feel at ease?
  You should be able to talk with your oncologist about any subject regarding your treatment without feeling silly or embarrassed. A good oncologist will take the time to explain anything you don't understand and will listen to all of your concerns and answer any questions and respect your decisions regarding your treatment.

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Understanding Why One Drug Has So Many Different Names

https://www.cancerabcs.org/new-advanced-metastatic-prostate-cancer-blog/2017/7/31/understanding-why-one-drug-has-so-many-different-names

Don’t be confused by the multiple different names for the same drugs that are used to treat not only your cancer but also every other illness and disease out there. One drug will have many different names, but it is still the same drug!

Drug names are confusing, the same drug, as it goes through the development and approval process will be given different names, usually three different names. These names include a chemical name, a trade name and a generic name. Despite having various names, the drugs are the same.

Why are there so many different names for the same drug? Let me explain the drug naming process, which will shed light on this issue.

A drug’s first name is its chemical name. This name derives from its molecular composition. The chemical name is often too long and too complicated to use in everyday interactions, so often it is only the researchers that use it, especially early in the development process.

The next name a drug is given is its trade name. The trade name is given to it when it receives approval for use. The trade name is the name under which it will be marketed. The trade name is a proprietary name owned exclusively by the drug company that owns the drug’s patent and can not be used by anyone else.

The pharmaceutical company arbitrarily makes up trade names. In the United States, the name has to be approved by the Food and Drug Administration (FDA).

The FDA is strict on granting approvals because it is concerned that drugs not be confused or mixed up with each other. The FDA rejects about four out of every ten proposed names.

Additionally, pharmaceutical companies do not want to name their products with a name that might have some cultural bias or create any confusion with another drug prompting the FDA to reject the name. To avoid these issues they will often make up meaningless names like Xtandi and Xofigo.

The result of this entire process means that our drugs have multiple names, all of them are meaningless and confusing, despite the efforts of the FDA to add clarity.

To help you navigate the names of the 2nd line treatments for advanced prostate cancer the following chart should help:

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Generic Name</th>
<th>Mode of ACTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xgeva</td>
<td>Denosumab</td>
<td>Bone Strengthening</td>
</tr>
<tr>
<td>Zometa</td>
<td>Zoledronic Acid</td>
<td>Bone Strengthening</td>
</tr>
<tr>
<td>Xtandi</td>
<td>Enzalutamide</td>
<td>Hormonal Blocking</td>
</tr>
<tr>
<td>Zytiga</td>
<td>Abiraterone Acetate</td>
<td>Hormonal Castrating</td>
</tr>
<tr>
<td>Taxotere</td>
<td>Docetaxel</td>
<td>Chemotherapy Agent</td>
</tr>
<tr>
<td>Jevtana</td>
<td>Cabazitaxel</td>
<td>Chemotherapy Agent</td>
</tr>
<tr>
<td>Xofigo</td>
<td>Radium-223</td>
<td>Targeted Radiotherapy</td>
</tr>
<tr>
<td>Provenge</td>
<td>Sipuleucel-T</td>
<td>Immunotherapy</td>
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</tbody>
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New approach to treating prostate cancer is a game-changer that could prolong patients' lives by a third

Daily Mirror columnist Dr Miriam Stoppard is hailing a recent breakthrough in the field of prostate cancer research

http://www.mirror.co.uk/lifestyle/health/new-approach-treating-prostate-cancer-10883884

Something’s always happening in prostate cancer research – and the news is invariably good. The most recent shows that combining two existing treatments can prolong patients’ lives by a whopping third.

The findings of this latest study are so powerful they will change how doctors treat patients from the very moment of diagnosis. The results are so good that experts are optimistic.

“These are the most powerful results I’ve seen from a prostate cancer trial,” says Nicholas James, lead author of the report presented at the American Society of Clinical Oncology.

“It’s a once-in-a-career feeling. This is one of the biggest reductions in death I’ve seen in any clinical trial for adult cancers.”

The approach is novel but simple. Researchers combined standard hormone therapy with a drug called abiraterone, which is typically used only as a last resort for cancer patients whose disease has stopped responding to standard hormone therapy. The research was conducted as part of the Stampede trial, an ongoing clinical study in the UK and Switzerland.

“Abiraterone not only prolonged life, but also lowered the chance of relapse by 70% and reduced the chance of serious bone complications by 50%,” says James. “Based on the magnitude of clinical benefit, we believe the upfront care for patients newly diagnosed with advanced prostate cancer should change.”

The study looked at a group of 2,000 men. Patients who received both abiraterone and normal hormone therapy were significantly less likely to die compared to those who received only hormone therapy.

Comparatively, 83% of men assigned abiraterone therapy survived versus 76% of those on standard hormone therapy. Researchers found that patients who received both medications had slightly worse side effects, especially cardiovascular and liver problems.

Nonetheless, this discovery is a huge step forward in treatment of prostate cancer.

More than 27,000 men in the US and 11,000 men in the UK die of prostate cancer each year, according to the US Centers for Disease Control and Prostate Cancer UK. In the US, aside from skin cancer, it is the most common cancer in men.

Dr Iain Frame, director of research at Prostate Cancer UK, says: “The potential benefits of giving some men abiraterone alongside hormone therapy are clearly impressive, and we will be working with all relevant bodies to make sure this treatment becomes an option available for these men via the NHS.”

This new approach is a game-changer, not just for prostate cancer patients but for all men.
NETWORKING

The original and most valuable activity of the INFORMED PROSTATE CANCER SUPPORT GROUP is “networking”. We share our experiences and information about prevention and treatment. We offer our support to men recently diagnosed as well as survivors at any stage. Networking with others for the good of all. Many aspects of prostate cancer are complex and confusing. But by sharing our knowledge and experiences we learn the best means of prevention as well as the latest treatments for survival of this disease. So bring your concerns and join us.

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: http://ipcsg.org

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.

Ads about our Group are in the Union Tribune 2-3 times 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 are again 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.