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WHAT THE HECK HAS BEEN GOING ON IN MY WORLD-PART 56!

BY MARK A. MOYAD, MD, MPH
UNIVERSITY OF MICHIGAN

Note: A total of 56 times in a row I have written and volunteered for this newsletter. I have yet to receive any financial compensation or personalized gifts for my efforts, for example, an autographed jersey and helmet from Tim Tebow or Tom Brady or Eli Manning that would say “Dear Dr. Moyad I would have been nothing in this world without you. Make my life more meaningful and I love you!” I do believe that the folks that run PAACT will eventually put some money together and buy me a new car or at least a tandem bicycle that would allow my wife and I to exercise and sing together while we traveled North America without having to spend a penny on fuel!

BREAKING NEWS STORY

215) MDV3100 is a pill for those with hormone refractory prostate cancer (HRPC, also known as CRPC…. ) from “Medivation” and “Astellas.” There is also an IV drug for metastatic HRPC known as Alpharadin from “Algeta” and “Bayer.” Both of these drugs will be available soon for men that are in need of more HRPC options right now!

(Reference: Moyad and Friends, 2011)

BOTTOM LINE:

MDV-3100 is an oral, daily drug that is used after someone no longer responds to taxotere chemotherapy. It should be available through an early access program (EAP) in the spring. Alpharadin is an IV radiopharmaceutical drug (given every 4 weeks) that also should be available in the spring, which helps men with bone pain from HRPC and also improves survival. Alpharadin is arguably less well known right now compared to MDV3100 so, if you want to see a really good video about how Alpharadin works go to http://www.algeta.no/dynside.asp?m=34568&ns=34659, scroll down and click on the “see video on ALSYMPCA clinical trial for bone metastases in CRPC patients.” Please keep in mind that this video was made before the results of their successful phase 3 trial (no big deal - still very informative).

WHAT ELSE?

If you have HRPC, metastatic prostate cancer and you feel you need more options, immediately talk to your doctor about getting either MDV3100 or Alpharadin. Alpharadin completed a successful phase 3 trial of men with bone metastasis being treated for bone pain that were running out of options; it also improved survival and the drug has a good safety profile. ANYHOW, BOTH DRUGS (MDV3100 and Alpharadin) SHOULD BE AVAILABLE FOR SOME HRPC PATIENTS THROUGH AN EARLY ACCESS PROGRAM IN THE NEXT FEW MONTHS!! EXCITING!!! TALK TO YOUR DOCTOR!!!

216) Whole body vibration (WBV) machines are expensive and do not appear to work any better than calcium and vitamin D supplements for bone loss! Ouch!


BOTTOM LINE:

Calcium and vitamin D work as well as some very expensive, novel alternative medicine options for bone loss. So, if you want to stop losing bone mineral density, please keep your heart disease risk low and get 1,000-1,200 mg a day of calcium (mostly from food) and about 1,000 I.U. of vitamin D, exercise daily and lift weights about 2 times a week. If after doing all of these for at least 6-12 months you don't get any benefit and you experience even more significant bone loss, you should talk to your doctor about the positives and negatives of going on a prescription osteoporosis drug.

WHAT ELSE?

You see these things in a lot of health clubs today! They are basically these large metal plates that you stand on. The plates vibrate and are supposed to stimulate the bones or legs and upper body to maintain or build bone mineral density. It kind of feels like you are being treated like a big human Martini drink when you stand on them, because you are being shaken a bit but not stirred (James Bond, Circa 1974). The idea behind it certainly makes sense, and it probably can help some folks that are not able to exercise, but it still needs to be tested for those individuals that are able to exercise, but are at an increased risk for bone loss. Whole body vibration (WBV) therapy machines are costly and have been advertised by some companies to improve bone density in all sorts of folks, but the machine has controversial data as to whether they work or not. A trial was needed where WBV could just be compared to calcium and vitamin D supplements in individuals at higher risk of bone loss. It would have been nice to test this machine in men on LHRH drugs for prostate cancer, but postmenopausal women are an adequate comparison group because they are a higher risk of immediate bone loss.

A total of 202 healthy postmenopausal women with osteopenia (bone loss not severe enough to be called “osteoporosis” - common in LHRH guys) were randomized to one of three groups for 12 months: low-magnitude 90-Hz WBV platform for 20 minutes daily, 30-Hz WBV platform for 20 minutes daily or to serve as control participants. The goal for each participant was to ingest 1,200 mg a day of calcium and 1,000 I.U. of vitamin D total (from diet and supplements). Bone density was determined at the beginning of the study and again at 12 months. The average age was 60, a BMI of 24-25,
Prostate Cancer Communication

Shake, Shake, Shake…Shake, Shake, Shake….Shake your bones….Shake your bones? I do not remember the words to that #1 hit song from KC and the Sunshine Band (circa 1976) going exactly like that (Wasn’t that song called “Shake your booty”)? Shaking and vibrating human feet by standing on a large plate actually may have some merit (or not) in those with spinal cord injuries or fairly immobile individuals. Otherwise, these WBV plates have become very popular with many folks that DO NOT seem to need them and they cost as much as a tiny cheap car.

Here’s the deal folks, when it comes to bone mineral density (BMD) if you reduce your risk of heart disease, engage in aerobic and resistance (aka “weight lifting”) exercise regularly, drink alcohol in moderation, stay away from tobacco, consume an adequate daily intake of calcium and vitamin D, and you are not over or underweight, then the chances that you will experience bone loss is minimized as much as possible. This is exactly what happened in this clinical trial, because these participants were too healthy to make the WBV look good. This is also what we are learning about androgen suppression or LHRH treatment for prostate cancer patients. When you are able to follow numerous healthy changes, bone loss is not even close to what was reported 10 years ago in the medical literature. This is what I call “placebo bias” or PB (hope to trademark this and make a ton of money one day, move to an island in the middle of Lake Michigan, get bored after 4 weeks and go back to work only to complain after a few days that I miss my little island…), and many research studies in the supplement and pharmaceutical world are guilty of this; where you do not allow a placebo group to make any practical and realistic changes in a study and when the study is over the supplement or drug looks so much better because the placebo group did nothing!

Well, in this study the opposite happened and WBV paid the price! The lesson here is that you do not always get what you pay for, because spending less money may actually get you more bone mineral density if you are willing to get off your gluteus maximus (I was going to use the word “rump” or “a**” but I thought I might get in trouble). I know it’s not easy to do all this stuff and it’s a pain in the gluteus maximus, but after you see all the money that you’ve saved (that can then be spent on the Moyad Beer fund), well I believe it will be worth it!!!

**217) Coffee and caffeine can reduce the risk of depression and may be good for you!** Wow, what’s the catch; do you own stock in Starbucks? You must be getting free things from Starbucks! How can this story be right if so many “bone headed” expert nutrition doctors tell me to stay away from caffeine and coffee?!


**BOTTOM LINE:**

First, I do not own any stock in Starbucks because I’m horrible at picking general non-medical stocks, and I’m not really the biggest fan of Starbucks. But I do believe my wife would leave me for a man that promised to take her to Starbucks every day and buy her a tall ______ (I forgot her favorite drink, because ordering at Starbucks means you have to memorize a cute drink name - otherwise the other customers get mad at you for taking time to figure out what the heck you want) for the rest of her life. Regardless, coffee and caffeine is healthy, in moderation, for many reasons and now we are learning that it may reduce the risk of depression! Now, that fact should make you happy! I seriously believe caffeine and even coffee consumption could be recommended to potentially improve quality of life. Viva Diet Mountain Dew! (Dr. Moyad’s Favorite Beverage next to Canadian Beer!)

**WHAT ELSE?**

The world’s most frequently consumed stimulant is caffeine, and the vast majority is from coffee. However, few large and well-done studies of caffeine, coffee and depression have ever been completed. A large study that included over 50,000 individuals (women, but the results also apply to men in my opinion), with an average age of 63 years, that did not have depressive symptoms at the beginning of the study, were followed. Coffee consumption was estimated from questionnaires. During 10 years of follow-up there were over 2,600 cases of depression that were diagnosed. Individuals consuming several cups of coffee compared to 1 or less per week had a significant reduction in the risk of depression, and a similar finding occurred for just caffeine consumption. No relationship was found for decaffeinated coffee and the risk of depression. OUCH! That’s not good news for the decaffeinated coffee drinker!

Please keep in mind that this epidemiologic study is arguably one of the best conducted in the world. Second, the results of this study are FABULOUS! I say this only because I am so sick and tired of the day-to-day assault on the wonderful quality of life benefits of some foods and beverages by bone-headed experts that claim they are looking out for our best interest, when their diet program involves removing any foods or beverages that are interesting! Remember the egg? Can’t eat them and now all of a sudden they provide benefits! Remember chocolate? Can’t eat it – now it provides benefits! Remember Macadamia nuts (too much fat and calories), now
you should eat some, because it has the healthy kinds of fat! Do not eat peanut butter - now it's good for you, because it's a great source of protein, healthy fats, and has fiber! The micro-dissection of our diets has become somewhat ridiculous, absurd and scary, because it causes a person to contemplate and analyze every single food or beverage without being able to consume comfort or really tasty foods (aka enjoy life)! The end result is a stressed out, anxiety prone, obsessive compulsive, irrational human being that does not have time for general lifestyle changes because they are told to become fixated on minutiae! It's time to encourage folks to consume coffee and caffeine, in moderation, if that's what they want to do.

It's also interesting that some past studies show a fairly consistent, inverse relationship between suicide and coffee consumption (yes, some studies actually show that increased caffeine and coffee intake is associated with a lower risk of suicide). Moderate coffee and caffeine consumption are simply associated with greater attention, energy, memory, mood, exercise performance and recovery from exercise, and it also helps you talk really fast if you get too much. It's time for doctors to encourage coffee and caffeine consumption for most individuals (okay I understand that some have bladder issues, etc. but this is a minority and has been over-hyped as causing problems). Please do not be intimidated by a group of non-evidence based folks (aka food and beverage police) that want you to believe that anything really pleasurable in life is a sin, and you will pay for these sins if you imbibe this outstanding elixir! I have one more thing to say and that is “VIVA Diet Mt Dew!” and “VIVA Everything in Moderation!” LONG LIVE COFFEE AND CAFFEINE!

PS. As a side note…I can’t stand coffee but who cares! This is a good study! Tea anyone?

218) Niacin (the drug, not the supplement), the cholesterol lowering pill, may improve erectile function in some men, but niacin has its own issues (just in case you were thinking of popping it for kicks).

(Reference: Ng C-F, Lee C-P, Ho AL, Lee VW. J Sex Med 2011;8:2883-2893.)

BOTTOM LINE:
Improving HDL cholesterol, and reducing LDL and triglycerides with niacin (vitamin B3), may help some men with erectile dysfunction (ED). Moderate and severe ED may improve with niacin alone, but side effects may be a concern.

WHAT ELSE?
Dyslipidemia (big medical term that just means “high cholesterol”)...so why didn’t I just say “high cholesterol”... because if you use big words it makes you appear smart when in reality you are not....kind of like me and some other folks I know) is associated with erectile dysfunction (ED) and past evidence has suggested that statins or cholesterol lowering alone may reduce the risk of ED. However, other medications that have been around for a long time and are cost effective, such as niacin, have not been tested in men with ED. A single center, prospective randomized, placebo-controlled, parallel group trial of 160 men (average age 58 years) with ED and “dyslipidemia” was conducted. Men were randomized to receive 1,500 mg of oral niacin daily or a placebo for 12 weeks.

No significant differences overall were found between the groups. However, when men were stratified and analyzed based on ED severity, men with mild ED showed no improvement, but men with moderate and severe ED (50% or more of men) on niacin showed a significant improvement in their ability to maintain their erections. Flushing (36% vs. 3%) and itchiness (33% vs. 9%) were significantly greater side effects with niacin compared to placebo. A total of 12 patients from the niacin group and six from the placebo group dropped out of the study.

Niacin is about as confusing to understand as political debate questions from some members of the media (“Speaker Gingrich, can you tell us if the accusations from your ex-wife that you refused to eat healthy cereal for breakfast is true and do you want to comment on that”). There are so many forms of niacin that can be purchased over the counter, but many of them have serious issues (just like the candidates in a democratic or republican debate). “No Flush” niacin has never been proven to work (aka waste of money), sustained release niacin - over the counter - has liver toxicity issues, and immediate release niacin has very bad flushing effects at low dosages so, large dosages cannot be used at one time. Therefore, I am not a big fan of the over the counter version of most niacin products, which is arguably why using the 500 mg extended-release prescription tablets made a lot of sense in this study and is one of the safest forms.

The researchers in this study did not allow the use of aspirin and told participants to take the niacin at bedtime. Yet, the decision to not allow aspirin to be used 30 minutes before taking niacin, or not recommending niacin with food (both practices clearly reduce the niacin flushing reaction) and the suggestion to take niacin at bedtime is really ridiculous because it arguably, profoundly hurt the potential beneficial results of this study. So, what have we learned? One important thing - keep your cholesterol low and your HDL (good cholesterol) high and say hello to potentially better erectile function. Heart healthy = Penile Healthy (please do not yell this in public in front of the policeman or police woman)!
219) Statins reduce the risk of dying from prostate cancer?! Come on Moyad, this has got to be BS (Bogus Science)! What is the catch?


**BOTTOM LINE:**
Aggressive cholesterol lowering with high-potency statins reduced the risk of fatal prostate cancer! And, there is a catch!

**WHAT ELSE?**
Several past studies suggest that statins may reduce the risk of advanced prostate cancer, yet no study has looked at prostate cancer deaths and the use of these drugs. This was a matched case - control study conducted in New Jersey (Heyyyyy yo--you from Jersey—my brother Andy lives in Jersey---gett outta here and forgetta abouutt it!). Okay, I have watched too many stereotyped television shows about New Jersey - at least I admit that.

Back to the study folks - Cases were those aged 55 to 79 years that died from prostate cancer between 1997 and 2000. Medication information was obtained from blinded medical chart review. Cooperation from spouses of these men was also utilized to provide more accurate follow-up information, which is really impressive when you think about it. A total of 387 cases were matched to 380 controls. Statin use was associated with a significant reduction in the risk of prostate cancer deaths; however, after adjustment of multiple confounders and specific statin types, high-potency statins were associated with a significant 73% reduction (p<0.0001) in prostate cancer deaths compared with a non-significant 31% reduction with low-potency statins. High-potency statins included simvastatin (use to be called “Zocor”) and atorvastatin (Lipitor*-now generic---YES!!) in this study and low-potency statins were fluvastatin, lovastatin, and pravastatin. WOW!

In case you are wondering, rosuvastatin (Crestor*) and pitavastatin (Livalo*) are the newer, high potency statins that are arguably as strong as any on the market, yet since they have only been available a short time they could not be examined in this study. Still, this statin and the prostate cancer story is becoming quite powerful, and now places this pill as high as any to be tested to prevent aggressive prostate cancer or to reduce the progression or recurrence of this disease. On the other hand, a negative story tends to be developing that suggests intensive statin therapy may increase the risk of type 2 diabetes. Ultimately, whether or not this diabetes risk is real or related to dosage and type of statin remains to be seen. Although, to be fair, this increased risk of diabetes with statins (if it exists at all) is small compared to the overall benefit. However, the message will never change which is moderate diet, exercise and weight management first and foremost. And, if a lower cholesterol level is not possible with lifestyle then there are statins, which should be started at the lowest dose. The individuals I get most nervous about are the ones on high dose statin therapy and they do not necessarily always need it because they have not been exercising or eating well on a regular basis. A lot of men and women could reduce the dosage of their statin drug by exercising more and eating a little better and now these folks have a good reason why they should (because they do not want to get type 2 diabetes). Still, the bottom line is there is now plenty of evidence to suggest that lowering cholesterol may reduce prostate cancer aggressiveness on presentation, progression and now death! Thanks to atorvastatin/Lipitor going off patent in late 2011 the cost of these drugs, for those that need them are no longer an issue.

220) Let me get this straight! A lower resting heart rate (RHR) can reduce your risk of dying from multiple causes! Moyad you have lost it! What is the catch on this one?!


**BOTTOM LINE:**
Resting heart rate (RHR) increases in individuals without cardiovascular disease may represent an increased risk of dying younger from other conditions.

**WHAT ELSE?**
Resting heart rate (RHR) is an independent cardiovascular risk factor. However, changes in RHR over a long period of time have not been well studied in a group of healthy individuals. In Norway, a prospective study of approximately 13,500 men and 15,800 women, without cardiovascular disease were followed for a mean of 10 years. RHR was measured on 2 occasions, 10 years apart. Over 3,000 individuals died during this period and 975 of these were due to cardiovascular events. Individuals that utilized blood pressure medications, because they can change the heart rate, were excluded from the analysis. So, what happened? Don’t be so pushy! What are you from Jersey! Forgettaboutittt! (Man, I talk to myself a lot…I need to see a therapist right away…wait, I have a full time therapist…her name is Mia, she’s my wife).

Compared to participants with a RHR of less than 70 beats/ min over 10 years, the heart disease mortality was 90% higher for participants with a RHR greater than 85 beats/min on the second measurement. In a separate analysis, the association of changes in RHR with total mortality (death from any cause) was similar to heart disease mortality but weaker (50% higher risk). In a subgroup of participants with a RHR between 70 and 85 beats/min at first measurement and below 70 beats/min 10 years later, heart disease mortality was 40% lower versus those whose RHR continued to be between 70 and 85 beats per minute at the second measurement. IN
I heard that Lance Armstrong had a RHR of approximately 32 beats per minute when he was in peak physical condition! Big deal, I can lift 5 pounds over my head with my eyes closed! Still, RHR is such a silly and cheap test that it has been dismissed in medicine during some physical examinations. The truth is that it is a fairly good barometer of the health of an individual. If the heart muscle remains strong over time there is little change in RHR, which is really the message of this study. The goal is to maintain a low RHR over time and reductions in RHR (especially if it is high) may also provide some small benefit, but a RHR that simply remains constant and low over time is the goal. Now, in this study, those with a lower RHR (less than 70 beats/min) were also more likely to exhibit a variety of other healthy behaviors (no tobacco, exercise a lot, moderate alcohol consumption…), but this was also adjusted for in the statistical analysis and the results remained the same, which suggests that RHR independently tells the patient and clinician a lot of things. It is also interesting to me that beta-blocker blood pressure medications (which maintain and reduce the heart rate) are now getting some attention for their other benefits, such as new research that suggests a potential lower risk of dying from certain cancers like melanoma. It is possible that large increases in RHR, increases the release of numerous compounds in the body that could increase the risk of and exacerbate a variety of urologic diseases including erectile dysfunction and prostate enlargement. Regardless, here is another cheap test that continues to suggest that heart healthy = all healthy in the world of medicine.

WHAT ELSE?

Researchers have been waiting a long time for the results of a recent randomized trial from Queensland, Australia to determine if sunscreen can prevent the deadliest form of skin cancer. It has been known for a long time that sunscreen can prevent certain types of skin cancer such as squamous cell carcinoma, but whether or not it prevented the deadliest form of skin cancer or melanoma needed to be tested in a clinical study. Perhaps the best place to test the potential benefits of skin cancer is arguably Queensland, Australia, which has the highest rate of melanoma in the world!

This study included 1,621 adults randomized to regular daily sunscreen use (812 individuals) or little to no use at all/discretionary use (809 individuals). The individuals in the regular sunscreen use group were given an unlimited supply of BROAD-SPECTRUM (broad-spectrum means it blocks UVA and UVB rays from the sun) sunscreen with an SPF of 16 and were asked to apply it to the HEAD, NECK, ARMS, and HANDS EVERY MORNING. Participants were also asked to reapply sunscreen after bathing, sweating, and long sun exposure. So, what happened? The treatment period was for 5 years. 10 years after the study was stopped there was a 50% reduction in the risk of being diagnosed with a melanoma in the sunscreen group!!! However, the reduction in the risk of INVASIVE MELANOMA (one that was already moving in the body) was even more impressive! Sunscreen users experienced a 73% REDUCTION in the risk of invasive melanoma. Keep in mind that all of the participants in this study were matched in terms of skin color, sunburn history, outdoor behavior, moles, history of skin cancer, even the use of hats and shade seeking behavior were similar.

Approximately 75% of the individuals in the regular sunscreen group applied the sunscreen every day, and 25% of this group also used sunscreen in areas such as the trunk, lower legs, or both despite not being instructed to do this. Since there was a reduction in melanoma at each and every body site, it may suggest that some of that benefit came from using the sunscreen from head to toe.

Strange isn’t it? Ultraviolet radiation (UV) from the sun is the only known cause of melanoma - whose exposure can be reduced voluntarily, and yet it still takes a lot of effort to convince some folks that they need to be careful and constantly use sunscreen. Keep in mind that those with fair skin, freckling, a tendency to sunburn and a family history of skin cancer or melanoma need to be even more careful. Remember sunscreen (1 full tablespoon each site) should be applied to each body area before going outside and this includes: head, neck, ears, front of trunk, back of trunk, each arm, top of hands, shoulders, lower and upper legs and top of feet. This takes time, effort, and money, but it’s worth it. Wearing wide-brimmed hats, long-sleeved shirts, long pants or other specially advertised sun protective clothing is also helpful.
And please do not forget the UVA and UVB protective sunglasses. Now, if this article does not motivate you to wear sunscreen then let me tell you what I tell some folks and that is - “Sun exposure of today is the deep wrinkle of tomorrow!” And, never forget that SUNSCREEN IN THE FALL, WINTER AND SPRING IS JUST AS IMPORTANT AS IN THE SUMMER because UVA rays that can penetrate the skin and cause aging and cancer are just as strong in the winter as they are in the summer. It is the UVB rays that decrease in intensity in the winter. So, the fall, winter and spring is when many folks no longer pay attention to sunscreen but it is just as critical! Hey, if you do not want to use sunscreen in the fall, winter and spring, GO OUT AND USE A TANNING BED! What?! Have you lost it Dr. Moyad? Why would I go to a tanning bed? Because tanning beds can give off UVA radiation that can increase the risk of skin cancer, so if you refuse to use sunscreen in the fall, winter, and summer then it’s similar to you agreeing to go to a tanning bed on a regular basis and allowing yourself to be exposed to UVA rays without protection! You get my point people! Man, Mark loves to use exclamation Marks after all sentences! Get it! Mark, and exclamation Mark?! I also love the game of word association!!!!!!!!!!!!!!!!!!!!!

222) Fiber can add years to your life, and you thought it was just good for the plumbing!

(References: Park Y, Subar A, Hollenbeck A, Schatzkin A. 2011;171:1061-1068.)

BOTTOM LINE:
Dietary fiber might actually reduce your risk of dying from cardiovascular, respiratory, and even infectious diseases. Fiber from beans and vegetables showed some protection but the biggest health benefit came from fiber of grains (cereals), but increasing your consumption of whole grains is probably the better recommendation here.

WHAT ELSE?
I love fiber! Let me say it again, “I love fiber” (not fiberglass but fiber). And, not just because it keeps you regular and allows you to catch up on your reading, but because I know it would win a Nobel Prize in medicine if it was a pill. Fiber reduces the risk of so many potential problems from acid reflux, hemorrhoids, constipation, high cholesterol, high blood pressure or blood sugar... Yet, whether or not it reduced some of these conditions enough to reduce your risk of dying from some common diseases has not been well known.

There is a quite famous, large study going on right now that is following a lot of folks (219,123 men and 168,999 women, average age 62 at the start of the study) over time and it is known as the NIH-AARP Diet and Health Study. Researchers have been following these individuals for an average of 9 years. Since the study started a total of 20,126 men and 11,330 women have passed away. Researchers found that greater dietary fiber intake was associated with a significant, 22% lower risk of dying in men and women. Dietary fiber also lowered the risk of dying from cardiovascular, infectious and respiratory disease by 34-59% in women and 24-56% in men. There also appeared to be a lower risk of dying from cancer in men, but this was not found in women. Interestingly, dietary fiber from grains appeared to be responsible for the benefit, not any other types of fiber.

Fiber is a carbohydrate, but unlike most things that we eat, fiber is not absorbed at all and works like a broom cleaner across your intestines. It actually can draw water into the intestines and make bowel movement faster and easier. This allows very little time for anything bad or carcinogenic to stay in your body or bowels for very long. Fiber is also partially or completely fermented in the large intestine, which allows for more friendly bacteria to stay in the gut and provide immune protection. Fiber also acts as an anti-inflammatory medicine not only in the gut but other parts of the body by keeping many harmful compounds from being absorbed.

Men and women in the higher category of fiber intake (that was providing the health benefits) were getting 25-30 grams a day, which is really what the current medical recommendations are for men and women! More specifically the recommendation is to get 14 grams of fiber for every 1,000 calories that you eat. Most individuals consume about 2,000 or more calories per day, which is why getting 25-30 grams of fiber per day is right on the mark (GET IT—RIGHT ON THE MARK! I am a poet and I did not even know it)!

However it is also interesting to me that even though the researchers found all these independent benefits of fiber you can't dismiss the fact that men and women getting more fiber also:

- Weighed less
- Consumed less calories
- Exercised more often
- Were less likely to use tobacco
- Consumed less alcohol and red meat

Still, the benefits of getting more fiber were dramatic in this study, especially in the area of respiratory and infectious disease protection! This probably adds more credibility to the finding that fiber from whole grains may reduce inflammation and keep the immune system strong. Keep in mind that whole grains are a lot of things apart from just your breakfast cereal and include: Amaranth, Barley, Brown and Wild Rice, Buckwheat, Corn, Oats/Oatmeal, Quinoa, Rye and Wheat. Whole grains or foods made from them...
usually contain all the essential parts and natural nutrients of the whole grain seed (not processed).

Finally, I apologize for getting on my soapbox for a second, but there was another interesting finding from this new study that is quite sobering. More healthy men (8,244 vs. 5,248) and women (4,927 vs. 2,417) in this study died from cancer compared to cardiovascular disease. This represents a new shift in medicine that is expected to continue unless better preventive and treatment therapies become available. Cardiovascular disease has been the number 1 cause of death in men and women for over 100 years, but cancer is catching up and is expected to be the number 1 cause of death in the future. These newer more recent studies of older men and women are beginning to reflect what is going to be observed in the future. This, in my opinion, is why we need to constantly increase cancer research funding.

THAT IS ALL FOLKS! And, yes I was there in November of 2011 when we BEAT OHIO STATE IN FOOTBALL!!!! YEAH!!!! I will not rub it in (WE BEAT OHIO STATE…HA HA HA….HA HA HA….). See you in the SUMMER, when I will write about many other serious issues and give timeless advice in the next newsletter, such as why it is never smart to eat a lot of fiber on the same morning that you expect to take a really, long and crowded Amtrak train ride that has bathrooms, but they are not available because of maintenance issues. I think you get where I am trying to go with this…oh and by the way….WE BEAT OHIO STATE IN FOOTBALL….HA, HA, HA…….!!

RADIUM-223: A NOVEL RADIOPHARMACEUTICAL THAT PROLONGS SURVIVAL IN ADVANCED PROSTATE CANCER

BY OLIVER SARTOR, M.D.

INTRODUCTION

It is now abundantly clear that the disease we call metastatic prostate cancer is a genetically complex disease. At this point determining which patient has which type of genetic alteration is beyond the capability of routine testing, and more importantly even if the specific genetic alteration were clearly defined, we lack the specific therapies necessary to successfully treat the vast majority of genetic alterations identified to date.

How to address this conundrum? Is it possible to devise a strategy that is successful despite multiple underlying genetic variations?

The answer is yes! For well over a century we have known that radiation is fully capable of killing cancer cells of many varying types. More recently we have come to understand that radiation is capable of killing cells that are highly heterogeneous in their genetic makeup. There are, of course, many limitations to radiation, as will be pointed out below.

Radiation today consists in three primary forms: external beam, brachytherapy (radioactive seeds), or injectable radiopharmaceuticals. External beam radiation is commonly used in both curative and palliative settings. Its strength is in its ability to deliver highly focused beams at relatively high doses. The limitation of external beam is simple; it only goes where you aim it and if cancer cells are outside the “field” then they are not affected. Radiation “fields” are limited by normal tissue “tolerance.” At some point, radiation will irreversibly damage anything in its path including normal cells, so consequently external beam radiation is always limited in scope.

Brachytherapy, or radioactive seed therapy, is similar in strengths and weaknesses to external beam. It is great for focal lesions and completely ineffective in disease that has spread beyond where the seeds are placed. It is good for small localized lesions and ineffective in disseminated cancers.

Injectable forms of radiation have long been used (since the 1950s) to treat patients with bone metastases. Three main forms of injectable radiation have been used in prostate cancer patients, phosphorus-32 (P-32), strontium-89 (Sr-89) and samarium-153 (Sm-153)-EDTMP. Each of these compounds are specific isotopes that emit radiation in the form of an electron (also called a beta-particle). Isotopes have an inherent defined half-life; meaning that half of the atoms decay over a set amount of time. P-32, Sr-89, and Sm-153 have half-lives of approximately 14, 50, and 2 days respectively.

INJECTABLE FORMS OF RADIATION THERAPY

How do injectable forms of radiation work? How do they localize to areas of bone metastases? Prostate cancer bone metastases are not comprised of normal bone. The cancer cells themselves are often “osteoblastic” or “bone-forming.” As such, the regions surrounding the cancer cells contain increased amounts of calcium and phosphate in the bone micro-environment. The process of forming osteoblastic lesions remains poorly understood, but that does not mean that physicians cannot therapeutically exploit the underlying differences between osteoblastic lesions and normal bone.

P-32 localizes to areas of phosphate deposition, which are enriched in osteoblastic lesions, and was the first systemic
isotope used to treat bone metastatic prostate cancer. Sr-89, though on surface very different from calcium, actually behaves quite similar to calcium in biologic systems. Both strontium and calcium are part of a group of elements in the periodic table termed “alkali earth metals.” Sm-153 does not bind to osteoblastic metastases itself. Instead it is molecularly bound to a molecule called EDTMP which is capable of binding to both Sm-153 and to the highly calcified portion of the bone inorganic microenvironment that is found surrounding the cancer cells. Uptake of Sm-153 EDTMP in bone is similar to that seen in a conventional bone scan for patients with osteoblastic metastatic disease (see Figure 1 for a comparison of uptake between a regular bone scan (using Tc-99-MDP and Sm-153 EDTMP).

**FIGURE 1.**

P-32, Sr-89, and Sm-153 EDTMP are all “beta” particle emitting isotopes that have been shown in clinical studies to relieve pain. The good news is that the molecules can help patients live better by relieving pain associated with bone metastases (1). The bad news is these agents do not help patients live longer. It is important to point out that these isotopes target only bone lesions that have enhanced uptake of calcium and phosphate. Patients with metastases in the liver or lymph nodes will not have those lesions treated by an intravenously administered bone-targeted isotope.

**RADIUM-223**

Recently a new form of injectable radiation has been introduced. This compound, radium-223 (Rad-223), has both similarities and distinctions as compared to the other injectable isotopes. For instance, Rad-223 is an alkali earth metal similar to Sr-89. Rad-223 tracks like calcium to lesions in bone that contain an excess of that element (osteoblastic metastases). It has a physical half-life of a little over 11 days. Rad-223 is different than the previous injectable isotopes in that it is an alpha-emitter. Alpha particles are comprised of two protons and two neutrons and are over 7000 times larger than beta-particles. Alpha particles, by virtue of their size alone, are highly energetic and quite destructive to cells.

Calculations indicate that only 1-10 “hits” per cell are lethal as compared to the many thousands of hits required for beta-particle induced cellular lethality. See Figure 2 for a summary of differences between alpha and beta particles.

Interestingly, despite their high energy, alpha particles do not travel far in tissue. In fact typically the alpha particles, because of their large size, interact abundantly with cells very close to their place of origin and come to a rest within less than one ten thousandth of centimeter from where they started. Beta particles travel much farther in human tissues, going about one tenth of a centimeter from their place of origin. The exact distance travelled by a beta-particle is dependent on the energy of the beta emission).

This ability of alpha particles to travel only a short distance from the site of origin, combined with their highly destructive cellular effects, results in a maximum amount of cellular killing in regions adjacent to their deposition and a minimal amount of damage less than a small fraction of a centimeter away. Thus, the side effects of alpha particle radiation are minimal because the particle has minimal effects on normal tissues. Only the tumor cells in close proximity to the osteoblastic metastatic lesion are radiated. In summary the bone-metastatic tumor and the tumor microenvironment are altered by Rad-223 alpha particle emissions but the adjacent normal tissue is relatively unaltered.

**CLINICAL DATA WITH RAD-223**

Though the theoretical advantages of alpha-particle radiation targeted to osteoblastic metastatic lesions are considerable, the proof of such a concept lies in the data derived from studies conducted in patients. Initial studies of Rad-223 in patients with prostate cancer established that the agent was able to effectively target osteoblastic bone metastases. Subsequently safe dosing ranges were established and pain relief was documented. Then a small randomized trial was performed in 64 patients (2) with bone-metastatic and “castrate-resistant” prostate cancer and somewhat
surprisingly patients were found to live longer (see Figure 3). That is surprising because small trials rarely give positive survival results.

To digress for a moment, patients that have failed initial hormonal manipulations such as Lupron, Eligard, Zoladex, or Trelstar, or surgical removal of the testicles, are referred to as having castrate-resistant prostate cancer or CRPC. Based on the survival advantage in the small randomized trial, a larger randomized trial (the ALSYMPCA trial) with over 900 patients was designed with a primary endpoint of survival. This trial enrolled symptomatic patients with bone metastatic CRPC who lacked liver or lung involvement. No lymph nodes larger than three centimeters were allowed. This was done to minimize the enrollment of patients with disease outside of the bone, a population unlikely to benefit from Rad-223. Patients had to have been treated with docetaxel or be considered by their physician to be “unfit” for docetaxel. A few patients refused to receive docetaxel (which is standard first-line chemotherapy for metastatic CRPC). Blood counts and metabolic parameters had to be either normal or close to normal. Patients were randomized to receive 6 intravenous doses (4 weeks apart) of Rad-223 plus best supportive care, or placebo injections plus best supportive care. Best supportive basically included a variety of secondary hormonal manipulations but no chemotherapy was allowed and no other intravenous radio-isotopes were allowed. All patients continued on their Lupron, Eligard, Zoladex, Trelstar type drugs so as to avoid a rise in testosterone (which is associated with disease progression in CRPC).

Over 900 patients were enrolled in the ALSYMPCA trial but an early “interim” analysis was performed to ensure that safety and ethical issues were appropriate for trial continuation. Surprisingly, this interim analysis (performed after 314 deaths) demonstrated a strong and positive survival advantage for those treated with the Rad-223 (3). The patients in the placebo group lived a median of 11.2 months while the patients in the Rad-22 group lived a median of 14.0 months. This compares favorably with other trials performed predominately in patients previously treated with docetaxel. The probability of this result being due to chance was less than 2 in a 1000.

The positive survival results lead to the trial being stopped at the interim analysis. It was considered unethical to continue to treat people with placebo given the extent of the survival advantage with Rad-223. In addition to survival being improved, the overall safety profile of the Rad-223 was excellent. Bone marrow suppression, though a potential significant toxicity, was relatively rare (less than 5% of patients).

**SUMMARY**

Rad-223 is anticipated to be reviewed by the FDA in 2012. If the FDA approves the drug, it should be available shortly thereafter. An “expanded access trial” has been approved by the FDA in accordance with strict guidelines. This expanded access trial should be open in the spring of 2012. Exact dates depend on the approval by local Institutional Review Boards and other regulatory agencies.

Combining Rad-223 with other therapies known to be effective in prolonging survival in metastatic CRPC is a strategy that is now attracting considerable attention (4). Trials with docetaxel are ongoing and these trials will need to be completed before safety concerns can be addressed.

Rad-223 may be the first step in a whole new therapeutic field. Now we know that alpha particles will prolong survival when properly targeted, there are many potential ways to improve targeting to include those patients with non-bone disease. Various antibodies and alpha-emitters may be conjugated together to form targeted forms of radiation therapy. Such concepts are now being explored in a number of laboratories and clinical trials using a variety of targeted alpha-particle's, which might be anticipated in the not too distant future.

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In the U.S.A. during the wide-spread use of the PSA (Prostate Specific Antigen) blood test and current prostate biopsy practice with the sampling of increased core numbers of biopsy tissues, men with elevated PSA have been subject to under-diagnosis of clinically important cancer and over-diagnosis and over-treatment of early prostate cancer, unnecessarily exposing them to treatment-related side effects and financial costs [Welch 2009]. The search for the optimal prostate biopsy technique still continues in accounting the balance between the benefits and harms of prostate cancer detection, debating various issues including the indication of initial screening biopsy, the indication of repeat biopsy after a previous negative biopsy, the intra-prostatic location of biopsy sampling, anesthesia technique, the optimal number of biopsy samples, image-guidance, biopsy-related complications and anxiety, and cost.

Prostate biopsy is generally performed transrectally by TRUS (transrectal ultrasound) guidance. Since the 1980s, the introduction of TRUS guidance for needle delivery into the prostate substantially improved the accuracy of prostate biopsy [Lee 1986]. Importantly, researchers reported that even in the current PSA era, the image-targeted biopsy (taken from abnormal TRUS findings) can provide the specimens with a significantly greater percentage of cancer involvement as well as higher grade cancer, in comparison to systematic random biopsy (taken from normal TRUS findings). Therefore, image-guided targeted biopsy-proven cancers from TRUS-visible-lesions are more clinically significant to better characterize the cancer [Toi 2007]. Emerging image-targeted biopsy (using the novel techniques of Doppler ultrasound, elastosonography, enhanced ultrasound, or Magnetic Resonance Imaging) could also duplicate significantly better performances of image-guided targeting. These result in better characterization of the biopsy-proven cancer, to determine the higher-grade and greater-volume cancers as ‘important’, as well as the lower-grade and smaller-volume cancers as ‘indolent’ [Ukimura 2012].

Unfortunately, however, today’s prostate biopsies are likely ‘not’ to use image-based suspicious lesion-targeting techniques, but simply to deliver the needle toward the “rough” region of the so-called ‘sextant’ of the prostate. This may be called “image-blinded” biopsy because it involves no effort to precisely target and document the biopsy-proven cancer in the prostate. As such, if they are image-blinded, currently wide-spread prostate biopsy practices are unable to precisely determine the spatial localization of the cancer foci and also unable to characterize clinically important cancers very well.

We believe that the better characterization of the known cancer as well as intra-prostatic 3-dimensional (3D) localization/documentation (mapping) of the cancer foci seems a key in successful decision-making for undergoing novel therapeutic strategy options, such as the active surveillance of slow-growing/low-volume prostate cancer. Another potential option includes targeted focal therapy of the known cancer foci, which aims to cure or control the known cancer while minimizing the treatment-related side effects [Ukimura 2011, Ward 2012]. Targeted focal therapy of the known-cancer foci is contemporary strategy in the way that most other solid organ cancers are treated.

The majority of contemporary prostate cancer patients are classified as having a low- or intermediate-risk form of the disease. The long natural history of low-risk prostate cancer and the presence of competing risks in an otherwise elderly male population all contribute to the problem of over-treatment of primary prostate cancer. The high incidence of clinically occult prostate cancer discovered at autopsy, the side effects of radical therapies, and the low risk of progression following radical therapies has led to development of less aggressive treatment strategies. “Active surveillance” is an approach incorporating regular clinical follow-up without intervention for select low-risk sub-groups of prostate cancer patients [Bill-Axelson 2005, Klotz 2006]. The issue is how to appropriately select and how to appropriately follow-up using the ‘best technique for surveillance biopsy’ under active surveillance practice.
there are significant differences in how patients are deemed to have “progressed” from active surveillance, a general consensus has developed around factors such as pathologic progression in surveillance of biopsy specimens (indicating increases in Gleason score or number of cores involved with the cancer, or percentage cores involved with the cancer), rapid PSA progression, and/or clinical progression on digital rectal examination. However, if there was “no” documentation of the precise 3D mapping of the biopsy-proven cancer at the time of the previous positive biopsy session, to accurately re-visit the biopsy-proven cancer lesion foci only 1-2 mm in size to move towards appropriate decision-making seems similar to a game of chance. There exists a need to better define patients enrolled, by developing a “targeted active surveillance” strategy that incorporates monitoring on a “per lesion of the known cancer” basis, founded on sophisticated imaging as well as precise 3D-mapping/documentation of cancer location rather than the current image-blinded prostate biopsy approach [Hoeks 2011, Ukimura 2011, 2012, Baumann 2011, Natarajan 2011].

An approach using the ‘best technique for surveillance biopsy’ would possibly be based on spatially-directed 3D mapping biopsy techniques.

Real-time 3D ultrasound image-based mapping biopsy technique using MRI/TRUS fusion guided targeting

Geographical 3D locations of every single biopsy trajectory (green color-coded) are digitally recorded in a computer workstation in the USC clinic. The recorded biopsy trajectories can be superimposed on either 3dMRI volume data (left) or 3D TRUS volume data (right) to confirm the relation of biopsy with 3D image of the prostate. The yellow color-coded lesions represent MRI suspicious lesions, and the targeted biopsy (orange color-coded) precisely hits the center of the lesion. Since the coordinates of the distal end (x1,y1,z1) and proximal end (x2,y2,z2) of the biopsy trajectory are recorded in computer workstations, future revisiting intervention the the same location is possible.

We believe that, for patients with low-or-intermediate risk disease, a new paradigm centered around the concept of treatment on a precise “per-lesion in 3D space of the prostate” rather than a rough ‘whole gland of the prostate’ basis is attractive. Recent evidence suggests that a primary tumor focus, an “index lesion” (that is, a dominant cancer lesion with the highest grade and/or largest volume per patient), is present in most patients and ultimately drives the natural history of the prostate cancer in each individual [Ahmed 2009]. In most cases, this “index lesion” can be distinguished by its larger size (several-fold larger than secondary lesions) and the presence of aggressive pathologic features such as Gleason grade 4/5 or extra-prostatic extension or metastatic potential. If the index lesion contains a clone with metastatic potential, it could be targeted and destroyed to minimize the life-threatening risks. Conversely, cancerous areas which do not harbour these “lethal” clones (which are likely in lower-grade and smaller volume cancer foci) could potentially undergo surveillance without intervention. It seems clear that serial “per lesion” monitoring, based on geographically-mapped precise biopsies of cancer lesions could provide new insights.

We believe that the two main streams for optimizing prostate biopsy strategy to improve patient decision-making for contemporary treatment options for early prostate cancer are, first, to improve the accuracy of cancer visualization using emerging imaging techniques and, second, to enhance the precision of needle delivery using the geographical 3D mapping techniques for biopsy-proven cancer.

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WHICH TREATMENT IS THE ONE FOR ME?
When faced with this question, the traveler through this Strange Place will discover the greatest conundrum of the disease.

THERE IS NO AGREEMENT IN THE MEDICAL PROFESSION AS TO WHICH TREATMENT, OR COMBINATION OF TREATMENTS, IS BEST.

Relevant scientific data from randomized studies comparing the outcomes of various treatment options does not exist.

So – How can this be? This excerpt from a 1997 article in The New England Journal of Medicine, the prestigious American medical journal, sums up the position pretty clearly:

‘...we have no firm guidelines for advising our patients about which therapeutic option is best. This means that education is more important than ever, but the art of multidisciplinary counseling is hampered by rivalries that seem more common among prostate cancer specialists than in other cancer specialties. This must change...Close collaboration between surgeons, radiotherapists, and medical oncologists is mandatory for substantially improved control of prostate cancer.’

There is no sign of any great change since that was written more than ten years ago. In contrast to virtually every other cancer, where oncologists are directly involved in the choice of appropriate treatment, prostate cancer is still mainly treated by urologists, most of whom are surgeons. They will usually recommend surgery. If a second opinion is sought from a radiologist, radiation therapy may well be recommended for the same diagnosis. Both can quote statistics to support their position - how can both be right? Until this is resolved, the newcomer to this Strange Place must make up his own mind what is best for him and choose a course of treatment balancing risks versus reward as defined by his values - these generally include both survival and quality of life considerations.

Hopefully what follows will help him find his way through the uncertainty of this Desert of Doubt.

When asked, a doctor may present percentage figures or other data regarding the likelihood of being ‘cured,’ ‘continent,’ and ‘potent’ following the course of treatment being recommended. It is essential to make sure that the terms used are understood. Most men expect ‘cured’ to mean that the tumor has been removed and that they will have no sign of the disease again: they do not expect to have regular PSA checks for the rest of their lives to ensure that the treatment has not failed. They expect ‘continent’ to mean that they will not leak and will be able to urinate without problems: they do not expect to have to use pads to remain dry or a penile clamp to stop leaking. And they expect ‘potent’ to mean that they will be able

This document is supplied free of charge to those who need it. A donation will ensure that members of the YANA site for their generous donations that made this edition possible.

Acknowledgement is made, and thanks given, to Donna Pogliano; members of the Prostate Support Action (PSA) Group and the YANA - You Are Not Alone Now website and members of my family who assisted in the final editing of this booklet. And to members of the YANA site for their generous donations that made this edition possible.

This is a booklet being printed in a multi-part series. The next series will begin with CRYOTHERAPY and then BEYOND TREATMENT-THE PLAINS OF RECOVERY.

Terry Herbert, the author of this booklet, has no medical training. He was diagnosed as having prostate cancer in August 1996 and has learned something about the subject since then. In 1998, with colleagues Gregg and Kerry Morrison he established a website - YANA- You Are Not Alone Now at www.yananow.net. The stated mission of the site, which is still active, is:

“To provide comfort to any man diagnosed with prostate cancer, to offer thoughtful support to him and his family and to help them to decide how best to deal with the diagnosis by providing them with and guiding them to suitable information, being mindful at all times that it is the individual’s ultimate choice; that the path he decides to follow is his own and that of his family; based on his particular circumstances”

Terry Herbert has produced this booklet. It represents a significant input of the knowledge, skills and time of Terry Herbert. It is regarded as intellectual property owned by Terry Herbert and is subject to copyright.

Having assembled all the data available about the diagnosis, the next step is to decide what treatment to choose - if indeed treatment is required. It may sound like madness not to treat a disease diagnosed as cancer immediately. But not all cancers are equal and in many cases - probably the majority, prostate cancer is a slow growing or indolent disease which should be managed successfully as a chronic illness. Of course no one should ever ignore a potentially dangerous disease, but immediate action may not be essential. All treatments for prostate cancer have a risk of side effects (termed morbidity) which can, in many cases, significantly reduce the quality of life. It is important to ensure as far as possible that treatment is justified and that the most appropriate treatment is chosen.

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BEYOND DIAGNOSIS - THE DESERT OF DOUBT

A STRANGE
PLACE - PART IV
AN INFORMATION GUIDE TO PROSTATE CANCER

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This article is a booklet being printed in a multi-part series. The next series will begin with CRYOTHERAPY and then BEYOND TREATMENT-THE PLAINS OF RECOVERY.
to achieve erections at will, whenever required: not to have to rely on medications such as Viagra or injections or mechanical devices. Yet studies have definitions of ‘cured,’ ‘continent,’ and ‘potent’ that differ markedly from these expectations and actual outcomes of treatment may be worse than they are said to be because of this. It is also important to understand that published information will usually show the results achieved by very skilled and experienced practitioners. Their results will almost certainly be better than someone who does not share these traits.

**MORE LANGUAGE HINTS:**

Before moving onto the treatment choices it is important to understand that there are no standard definitions for words like ‘cured’ or ‘continent’ or ‘impotent’ - all very important issues in the decision making process. Much published information avoids stating definitions and outcomes directly and as a result, men misunderstand the odds when choosing treatment. To make the decision that he will not regret, a man should understand his risk of morbidity (side effects) as well as his likelihood of a “cure” and how these terms are defined and measured.

Men should be free to decide that they would rather live with the cancer than with the side effects of being treated for it. Men choosing treatment should not expect to be free of its side effects; men choosing Active Surveillance should expect eventual disease progression. These factors must be weighed against a man’s expected longevity and pre-treatment situation - for example many men develop erectile problems as they age, so loss of this function might not be a big issue for them; a man with severe urinary problems from BPH (Benign Prostate Hyperplasia) might welcome the relief of urinating freely again after surgery, and accept the possibility of a bit of leakage. A young man diagnosed with aggressive disease is in a much different situation from that of an older man with low to moderate risk disease. If the probability of the tumor having spread beyond the gland is high, the odds of a ‘cure’ may be so low as to be a deciding factor not to have aggressive treatment. Family history should also be considered: sharing genes with someone gravely affected by prostate cancer may mean genetics increases the risk of not being treated.

As long as the overall death rate from prostate cancer stays at about one in eight for those who have been diagnosed (regardless of stage and grade), the decision not to have immediate treatment, in suitable cases, should not be viewed as an illogical course.

**IMPORTANT INFORMATION REGARDING TREATMENT CHOICE**

1. **Be certain that immediate treatment is required.** Published studies in Europe and the U.S.A. demonstrate that the majority of treatment procedures carried out for prostate cancer are probably unnecessary - estimates vary widely between 25% and 80%.

2. **The choice of treatment may be less important than the choice of who does the procedure.** Published studies have shown that the experience of the person or team carrying out the chosen procedure is of utmost importance. The more experience, the lower the morbidity, the greater chance of remission. This may seem obvious, but many men only find out the hard way. It may be embarrassing to ask a surgeon or radiologist to provide evidence of their skill, but bearing in mind the consequences, this question should never be avoided. Those with a good record are happy to share it.

3. **It is important to be as certain as possible that the disease is contained within the prostate capsule before making any final treatment decision.** This is where the Partin Tables and other similar nomograms are very useful. The information obtained by using the Partin Tables is no guarantee of the actual situation for any individual. It does however provide some indication of what treatment options might achieve the best result, and which might be ruled out because of the possible extent of disease.

**TREATMENT OPTIONS**

Treatment options vary from country to country. The greatest variety available is in the United States of America where, it is said, there are at least fifteen, none of which are demonstrably better than each other. The main options and sub-sets are:

- **Surgery** - This is the most common procedure, technically referred to as RP (Radical Prostatectomy). The main sub-sets are “open” and “keyhole” or laparoscopic procedures. Open surgery may be retropubic or perineal: keyhole surgery may be manual or robotic. Men with advanced prostate cancer may have their testicles removed surgically. This is called an Orchietomy or an Orchidectomy, and although a surgical procedure, it is really a form of hormone treatment.
• **Radiation Therapy** - The most common form is EBRT (External Beam Radiation Therapy) with a number of sub-sets that refer to the method of delivering the radiation dose. Another form of radiation therapy – Brachytherapy - has radioactive ‘seeds’ introduced into the prostate gland on a permanent or temporary basis.

• **Androgen Deprivation Therapy** - This is referred to as ADT, but more commonly known as Hormone Treatment. There are many variations on this type of treatment, but essentially all involve using medication to suppress the hormonal mechanisms that help tumors to grow. Orchiectomy, surgical removal of the testicles, is an irreversible form of hormone treatment.

• **Active Surveillance** - AS is often referred to as “Watchful Waiting.” No conventional treatment is undertaken unless regular monitoring indicates disease progression. Men choosing AS often make changes to diet and lifestyle with the intention of boosting the immune system.

• **Cryotherapy** - The prostate gland is frozen in this therapy usually referred to as Cryo. The treatment is evolving and now includes focal cryotherapy aimed at targeting a tumor (like a lumpectomy in breast cancer) and thus reducing the probability of side effects. It is still regarded as somewhat experimental.

• **High Intensity Focused Ultrasound** - This procedure HIFU uses the heat generated by the ultrasound to focus on and destroy the tumor. Developed in China and used for some years in a few European countries, Mexico and Canada, it is still regarded as experimental in the United States of America.

• **Chemotherapy** - This treatment has not been used very much in dealing with prostate cancer except as a last resort if all else fails. New chemicals and protocols mainly developed in the U.S.A. seem to be proving more effective than those in the past.

There is a need now for a short diversion to the Partin Tables before getting back to the treatment choices.

**DIVERSION TO CONSIDER THE PARTIN TABLES:**

Alan W. Partin, M.D., Ph.D., and Patrick C. Walsh, M.D. at the James Brady Urological Institute in Boston, U.S.A. developed these tables which are based on the analysis of many biopsies. Their aim was to try to establish if there was any relationship between the various aspects of diagnosis and the likelihood of the disease having moved beyond the capsule. The tables are too complex to reproduce in this document, but essentially they look at the three main aspects of diagnosis - PSA (Prostate Specific Antigen), Gleason Score and Clinical Staging - and show, as a percentage, the statistical likelihood of the disease having escaped the capsule or being contained.

To take the example referred to above, where the man was diagnosed as PSA 7.2: GS 3+3=6: Stage T2bNXM0, and referring to the relevant section of the Partin Tables we would find the following chances of:

- **Organ-Confined Disease** - 55% / 68% (median 62%)
- **Capsular Penetration** - 26% / 38% (median 32%)
- **Seminal Vesicle Involvement** - 3% / 8% (median 5%)
- **Lymph Node Involvement** - 0% / 2% (median 1%)

To give some idea of how one item might change these percentages, and how important the Gleason Score is, if the diagnosis was PSA 7.2: **GS 4 + 4 = 8**: Stage T2bNXM0, then the chances above would change to:

- **Organ-Confined Disease** - 17% / 33% (median 24%)
- **Capsular Penetration** - 29% / 48% (median 38%)
- **Seminal Vesicle Involvement** - 16% / 39% (median 27%)
- **Lymph Node Involvement** - 3% / 20% (median 10%)

There is a lower probability of benefit from surgery or other local treatments, if there is a high probability of the disease having escaped from the organ.

**NOW, BACK TO TREATMENT CHOICES:**

**SURGERY**: This treatment is technically called RP (Radical Prostatectomy), and is often referred to as the “gold standard” treatment, implying it is the very best. It is the treatment most commonly prescribed for younger men or early stage prostate cancer. The traditional surgery was an “open” procedure but there is enormous and rapid growth in laparoscopic - ‘keyhole’ - surgery, especially the Da Vinci robotic procedure.

In open surgery, the prostate gland is reached either from the lower part of the front of the body - this is a retropubic procedure - or through the area between the anus and the scrotum - this is a perineal procedure. There are no studies that show either of these procedures to be superior to the other. In the past the operation involved a substantial loss of blood. There have been significant improvements in surgical techniques and it is now unusual for a transfusion to be required. Some surgeons recommend the drawing and storing of the patient’s own blood ahead of the operation as a precautionary measure.

Laparoscopic surgery on the other hand requires five small (five to 10 millimeters) incisions (or portholes), one just above or below the belly button and two each on both sides of the lower abdomen. Four arms are inserted into the
portholes, three hold instruments, the fourth holds the camera - this is the laparoscope which enables the surgeon to get pictures of the prostate on a video monitor. Carbon dioxide is passed into the abdominal cavity through a small tube placed into the incision below the belly button. This gas lifts the abdominal wall to give the surgeon a better view of the abdominal cavity once the laparoscope is in place. The arms are used by the surgeon to remove the gland, through one of the port holes and are manipulated manually, except where the procedure is robotic assisted - a procedure usually referred to as the Da Vinci procedure. The surgeon sits at the console and looks through two eye holes at a 3-D image of the procedure, meanwhile maneuvering the arms with two foot pedals and two hand controllers. The Da Vinci System translates the surgeon's hand movements into more precise micro-movements of the instruments. RP, whether open or laparoscopic is a major surgical procedure and will usually take 3 - 4 hours. Discharge from the hospital was normally within 3 to 5 days for the 'open' procedures but is now likely to be 3 or less. Laparoscopic surgery, on the other hand, is far less traumatic and men are usually discharged from the hospital in 24 hours. There is still a good deal of disagreement about the merits of the two procedures. Surgeons favoring open surgery say that they can feel the prostate and get a better idea of where the tumor might be and thus have more assurance of negative margins: doctors favoring laparoscopic surgery say that the better view obtained through the magnifying lens enables them to cut and stitch more accurately. As yet there are no long term studies to support either view. The incidence of initial morbidity are similar as are early failure rates. One thing has become clear - the learning curve for the laparoscopic procedure is a long one. One published study implies that it takes at least 250 procedures before the surgeon can be regarded as proficient.

In either case, a catheter will be in place, sometimes for some weeks. It normally takes about three months to regain control of the bladder function, although some men achieve this sooner. Recovery of erectile function will almost certainly take a good deal longer, many months and sometimes a year or more. Recovery of erectile function is dependent to a large extent on the ability of the surgeon to spare the erectile nerves, although this is not the only factor.

The main benefit of surgery is that it introduces an element of certainty. The prostate gland can be examined closely to establish the extent of the tumor, to verify the Gleason Score and to clarify the likelihood of the tumor being contained within the gland. If there has been no spread beyond the gland, then the removal of the prostate should, by definition, remove the tumor. For many men that is of utmost importance.

However, surgery may not be a good choice if the disease has metastasized - that is if the disease has spread to distant sites beyond the prostate. There is a view that, in such cases, the removal of the gland and the main tumor may accelerate the growth of the secondary, metastasized, tumors and make control of the disease much more difficult. Like many other aspects of prostate cancer, there is no consensus on this issue, which is the subject of some debate among physicians and researchers. Because it is so difficult to establish beyond doubt whether the disease has spread beyond the gland, there may be an element of risk in opting for surgery.

Success or “cure” is measured by taking PSA tests at intervals after the surgery. Ideally there should be no PSA measurement detectable with the normal PSA test. Ultra-sensitive PSA tests may show very low levels – well below 0.10 ng/ml. No formal studies have demonstrated the superiority of surgery over other forms of therapy, including Active Surveillance, in early stage cancer. There is a failure rate of about 30% - 35% over a period of 10 - 15 years for men undergoing surgery. Some failures have been reported at 20 years. In the event of recurrence or failure of the treatment, it is possible to use EBRT (External Beam Radiation Therapy) to treat recurrence thought to be confined
to the prostate bed, or to use ADT (Androgen Deprivation Therapy) as a secondary treatment for recurrence where the disease has spread into other areas of the body.

The main side effects of surgery are erectile dysfunction (the difficulty or inability to have an erection) and bladder incontinence (the inability to control the bladder). The man also becomes infertile, since there is no ejaculate following the removal of the gland. Men intending to father children should bank sperm before surgery.

The first of these problems - erectile dysfunction (ED) - comes about because the nerves controlling erections are embedded near the surface of the prostate gland; one on each side of it. There has been a reduction in the reported rates of erectile dysfunction following the development of what is referred to as the “nerve-sparing” technique and the use of pharmaceutical drugs such as Cialis, Levitra or Viagra or one of the injectable materials - MUSE, Tri-Mix and the like. However, the position of the tumor may affect the ability of even the best surgeon to spare one or both of the nerves while removing all the cancer. The ED rate is still high - probably over 50%, especially for men over the age of 50. Studies quoted with better rates should be examined very carefully, especially for definitions of potency or erectile function. These studies usually involve excellent surgeons and may not reflect the general outcome of surgeries carried out by surgeons with less experience.

Total bladder incontinence is reported in a small number of men - about 5% - but many men experience some leakage, particularly during sexual arousal or when lifting, coughing, sneezing or laughing. Again it is important to look at definitions when considering studies showing levels of continence after treatment. It is not uncommon for the use of only one or two pads a day to be regarded as fully continent in such studies. The outcomes of surgery carried out by urologists who do not have the experience of surgeons in a center of excellence are usually worse.

Another issue to be aware of is stricture from scar tissue, which can also cause urinary problems. If the man has a history of poor scarring (some reports suggest that if any scar on his body is more than 10 mm (about 3/8”) wide) then there is about an eightfold increase in urinary problems following RP (Radical Prostatectomy).

Penile shrinkage is also reported in a significant number of men, thought to be the result of maintaining the penis in the flaccid state during what can be many months of recovery of erectile function. It is thought that this can be counteracted by stimulating erections with drugs or manual devices as soon as post-surgical healing has taken place.

A final issue, rarely discussed, is that of Peyronie’s Disease or Peyronie’s Syndrome. This condition is one where the erect penis acquires a bend or deflection. The vast majority of Peyronie’s cases are very mild but others can cause severe problems. It seems unlikely that the condition is directly caused by a disease or that it has any direct link with prostate cancer. A common cause is thought to arise from accidents during sexual activities, especially if the penis is not fully erect.

RADIATION THERAPY - the most common form of Radiation Therapy is known as EBRT (External Beam Radiation Therapy). There are many other acronyms, such as RT (Radiation Therapy), IMRT (Intensity Modulated Radiation Therapy) and 3DRT. All refer to the procedure where photon radiation is directed at the site of the prostate gland from an external source. The variations usually refer to the different aiming techniques. A form of EBRT known as CyberKnife® delivers what are termed hypofractionated doses - fewer doses, very much larger than normal EBRT but, it is claimed, delivered more accurately and thus reducing the potential for collateral damage. A significantly different form of EBRT is PBT (Proton Beam Therapy). It is claimed that the proton beams can be directed more accurately than photon beams, again with less likelihood of collateral damage. PBT for prostate cancer is only done at a few sites, mostly in the US.

Another form of radiotherapy is Brachytherapy or SI (Seed Implants). Radioactive “seeds” are implanted directly into the prostate gland, where they remain. There is a variation of SI known as HDR (High Dose Rate Brachytherapy) where seeds are inserted repeatedly for a short time delivering hypofractionated doses and then removed.

Radiation therapy is intended to destroy the cancer cells while leaving healthy tissue intact and is often the recommendation for older men for whom surgery presents a health risk. EBRT is also used where it is felt that the tumor has spread just beyond the prostate gland itself and as a “salvage” treatment for failed surgery. EBRT used in conjunction with other treatments such as surgery or brachytherapy is known as adjuvant treatment. Radiation treatment is not recommended for men who have had urinary problems prior to treatment since the procedure will often exacerbate these problems.

EBRT takes place over a number of weeks - usually six or seven - with daily sessions of therapy, the exception being CyberKnife® which takes about five days. The effect of radiation is cumulative, so low doses given on a regular basis build up into high doses, lethal to the tumor cells. Most men tolerate the procedure very well, although as time goes by, they may feel fatigued and it may be desirable to rest during the day. The feeling of fatigue will usually disappear sometime after completion of the treatment.

Brachytherapy is usually considered as an alternative to surgery for men with a suitable diagnosis. SI is a relatively short procedure, taking two or three hours, after which the man can go home and carry on with his normal activities: HDR might
need an overnight stay in the hospital. There is sometimes a feeling of fatigue, as is the case with EBRT, but this usually recedes with time, as the dosage from the seeds reduces (they are only fully active for about six months). Brachytherapy is not a good option for a man who has previously had a TURP (Transurethral Resection of the Prostate).

Two aspects of SI are often raised as concerns. Firstly, the man is carrying radioactive seeds in his prostate and the question asked is whether those seeds can injure anyone close to the man - for example, a grandchild sitting on his lap. Studies have demonstrated this is not a risk. The second concern is seeds migrating from the prostate to other parts of the body, notably the lungs. This happens when seeds work their way out of the prostate before the glandular tissue heals and locks them in place, or where they have not been securely placed. It is said this does not present any significant problem for the patient.

Success or “cure” for radiation treatments is measured by a gradual reduction in PSA level in the months after treatment is completed. The aim is to achieve a nadir, or low point, of 0.200 ng/ml and to maintain that level. Some authorities feel a nadir of under 1.00 ng/ml is an acceptable level. Some men experience what is referred to as a “bump” about 18 months after radiation when the PSA rises and then falls again. No formal studies have demonstrated the superiority of radiation therapy over other forms of therapy, including Active Surveillance. There is a failure rate of about 30% - 35% over a period of 10 - 15 years for men undergoing radiation therapy. A leading U.S. institution claims better long-term freedom from disease using combined SI/EBRT therapy than EBRT alone. They term this treatment procedure as ProstRcision®.

In the event of recurrence or failure of radiation treatment, surgery is not a good option and is rarely successful because of the damage done to the tissue by the procedure. The usual option for further management is ADT (Androgen Deprivation Therapy) although Cryotherapy can also be used as a salvage treatment.

The side effects of radiation therapy are similar to surgery with the added complication of urinary urgency/frequency, difficulty in starting a urine stream and incontinence. Radiation can sometimes result in bowel incontinence as well as rectal bleeding. ("Incontinence" is the inability to control bladder or bowel). The reported incidence of incontinence is fairly low for EBRT and even lower for SI and PBT. There is a reported improvement in radiation treatment side effects with modern techniques. Erectile dysfunction is reported to occur in a substantial number of cases, more so for EBRT than SI, but at about the same level as surgery. In contrast to surgery, where an immediate loss of function can be followed by a gradual recovery, erectile dysfunction associated with radiation therapy of any kind tends to occur well after treatment and to gradually grow worse over time.

ADT (ANDROGEN DEPRIVATION THERAPY) generally known as Hormone Treatment. There are many variations of this treatment, all with different acronyms. The theory behind this treatment is that growth of prostate cancer cells is fueled by dihydrotestosterone (DHT) a derivative of testosterone, the male hormone steroid, which is an androgen. A reduction in the production of androgen will therefore theoretically deprive these cells of nutrition and they will die. There are four methods by which the cells are deprived of androgen.

- **Ablation.** The testes produce approximately 90% of the male body’s testosterone with the balance being produced by the adrenal glands. Thus a simple way to reduce testosterone production is the surgical removal of the testes by way of an orchietomy or orchidectomy (castration).
- **Additive.** Testosterone production is attacked by dosing the man with estrogen.
- **Inhibitive.** This involves the use of chemicals to block signals from the brain to the production centers so that no testosterone is produced.
- **Competitive.** The final method of treatment involves what are known as antiandrogens. These do not prevent the production of testosterone, but block the receptors on the prostate gland, preventing the androgen from being absorbed.

The last three treatments are sometimes used in unison, in which case the treatment is usually referred to as CHT (Combined Hormone Therapy) or ADT3. Treatment is
administered in a variety of forms, from pills to monthly or quarterly injections.

ADT was at one time only used to manage late stage prostate cancer, where the tumor had spread beyond the capsule and therefore could not be treated by surgery or radiation and/or as a “salvage” therapy for failed surgery or radiation treatment. There is however a growing use of this therapy as a precursor to other treatments. This is known as neo-adjuvant therapy. Many practitioners are opposed to this practice because studies do not show any significant advantage for the inevitable side effects and there are several disadvantages. Some leading practitioners of both surgery and brachytherapy in the U.S. will not treat men who have had this neo-adjuvant therapy.

The aim of ADT is to manage and control the disease, since it is extremely unlikely that this therapy will result in a permanent “cure.” The degree of success achieved is measured by the reduction of the PSA to as low a level as possible and keeping it there. In many cases the PSA level can be undetectable and there are reports of men treated with this therapy achieving mortality rates very similar to those of men without the disease. Failure of this treatment occurs when the tumor becomes androgen independent (AI). This condition is often referred to as Androgen-Independent Prostate Cancer (AIPC), or Hormone Refractory Prostate Cancer (HRPC). This means the tumor has found a way of growing without the androgen associated with testosterone. Management of the disease at such a stage is very difficult although some success has been reported with new chemotherapy drugs.

There are numerous, very variable, side effects associated with this form of treatment whether the treatment is being used as an adjuvant treatment for early stage tumors or as a palliative measure for advanced cancers. Many of the side effects are those that occur naturally as men age. Some men have severe side effects, others have none: some appear early, some only after a long period of treatment. The ones reported most frequently by men undergoing any of the ADT methods are erectile dysfunction, loss of libido (no interest in sexual activity), hot flushes, osteoporosis (loss of bone), loss of muscle tone, weight gain and mood swings, with depression being widely reported.

Individual methods have other side effects such as the development of breasts (gynecomastia), increased risk of thrombosis, and an initial rise in tumor activity, known as a “flare.” This last effect is usually of a temporary nature. A flare can be prevented by administering an anti-androgen one week prior to the first injection of the drug being used to inhibit testosterone production.

A list of potential side effects associated with ADT include:

- Alcohol intolerance (with Casodex and Eulexin);
- Anemia;
- Anxiety or depression;
- Arthritic symptoms;
- Appetite loss;
- Blood in urine;
- Breast swelling and tenderness (gynecomastia);
- Cholesterol and triglyceride increase;
- Constipation;
- Diarrhea (Eulexin);
- Disturbed sleep;
- Drowsiness;
- Dry mouth;
- Emotional instability (especially crying);
- Feet or lower legs, swelling of (peripheral edema);
- Flatulence;
- Flu syndrome;
- Hair: decrease in pubic and body hair; facial hair grows more slowly;
- Headache;
- High blood pressure (hypertension);
- Hot flushes;
- Hyperglycemia (high blood sugar);
- Impotence (during the period of treatment and some months after);
- Indigestion;
- Itching;
- Insomnia;
- Liver problems;
- Memory loss;
- Methemoglobinemia (a crystallization in the blood);
- Nausea;
- Nocturia (need to urinate frequently at night);
- Nervous and twitchy legs;
- Osteoporosis;
- Pain: abdominal, back, chest, in right side;
- Pressure - feeling of extreme pressure in head;
- Prickling sensation on the skin;
- Shortness of breath;
- Testicular atrophy (shrinking) and soreness;
- Sweating;
- Weight gain (weight gain may continue for a while after treatment);
- Weight loss.

The following symptoms may reflect serious problems and if they occur, medical attention should be sought immediately:

- Bluish lips, fingernails, or palms of hands;
- Dizziness (extreme) or fainting;
- Fatigue, weakness;
- Pain: bone, joints, pelvic;
- Numbness, coldness, or tingling of hands or feet;
- Infections;
- Rash;
- Urinary incontinence;
- Urinary tract infection;
- Vomiting;
- Weak and fast heartbeat;
- Yellow eyes or skin.

A recent development has been towards “pulse” therapy known as IHT (Intermittent Hormone Treatment) or IHB (Intermittent Hormone Blockade). Some studies indicate that stopping the ADT once the PSA count has been reduced and reintroducing the therapy if the PSA count rises again might produce some benefit. The duration of the side effects of ADT are reduced and it appears the possibility of the disease becoming androgen-independent may also be lessened. In some very rare cases, the PSA does not rise again after the ADT is stopped and the man can be considered to be in remission. Men on ADT welcome the treatment “holidays” as many of the side effects disappear or diminish as the effect of the drugs wears off. In some cases some of the side effects are permanent.

This booklet is being printed in a multi-part series. The next series will continue with Treatment Options, starting with Cryotherapy.
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ACKNOWLEDGEMENTS OF CONTRIBUTIONS

October 1, 2011 Through December 31, 2011

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- New Jersey ....... 11
- New Mexico ....... 2
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- Ohio ................. 9
- Oklahoma .......... 2
- Oregon ............. 10
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- West Virginia .... 1
- Wisconsin ....... 5
- Canada .......... 1
- Luxembourg ....... 1
FINANCIAL SUMMARY REPORT  
(JANUARY 1, 2011 THROUGH DECEMBER 31, 2011)

**GENERAL FUND**

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