One year has passed since that sad day,
When one we loved was called away.
God took her home. It was His will,
But in our hearts she liveth still.
TABLE OF CONTENTS

Letter to PAAct, Bob Leibowitz, MD .................................................................3
Treatment of Localized PCa w Intermittent Hormonal Blockade* Bob Leibowitz & Steven Tucker .................................................................4
Your Approach and Your Medical Team, Lonnie Silva ................................8
What is Prostatitis, Paul Song, MD .................................................................9
An Urologist With Newly Diagnosed Prostate Cancer, Anonymous ....11
The Case Against Active Surveillance or Watchful Waiting for PC Robert Pugach, MD ......................................................................................14
Prostate Adenocarcinoma – 21 Year Journey, WS ......................................16
Color Doppler Ultrasound and Targeted Biopsy, Duke Bahn, MD ........18
Prostate or Bladder Infection? (Men), Dr. Bruce West DC .......................21
Changing Paradigm in PC Diagnosis: The Role of MR Imaging Aytekin Oto, MD, et al. ..........................................................22
Update: Overview of PET/CT Imaging in Recurrent PC Current & Emerging Techniques
Fabio Almeida, MD ......................................................................................26
What is the Best Treatment for PC?, Mark Scholz, MD & Elizabeth Graves .........................................................30
Solving the Prostate Cancer Puzzle, Michael Dattoli, MD & Ginya Carnahan ......................................................................................32
Cancer Lessons, Jim Hunter .........................................................................36
What the Heck…, Mark Moyad, MD, MPH ................................................37
Is Testosterone the New Therapy for Prostate Cancer? Jeffrey Turner, MD ......................................................................................45
Prostatepedia PC Treatment
Side Effects Aren't Side Issues When They Happen to You .................46
Chairman LAC-PAAct Update, Greg Teufel, Esq ......................................47
Chairman NY Health Insurers Required to Cover PSA Blood Test Greg Teufel, Esq ..............................................................48
Sexual Function after Prostate Cancer Surgery, Mohit Khera, MD ....49
Cyberknife Stereotactic Radiosurgery for Prostate Cancer
V Elayne Arterbery, MD ..............................................................................51
Making Prostate Cancer a Chronic Disease, Betrand Tombal, MD ..........52
IPCSG Support Group Meeting Notes on Proton Therapy ....................56
PCRI Blog Proton Therapy - Carl Rossi, MD ............................................59
Between the Sheets, US TOO ...................................................................60
How to Keep Your Sex Life Alive Now that Cancer has Entered the Picture
Dr. Chelsea Holland, DHS, LPC, MS ..........................................................62
The Promise of a Personalized Cancer Vaccine, David Bostwick, MD ....64
When to use Zytiga, Xtandi, and Erleada?, Mario Eisenberger, MD ....66
Alzheimer’s and Brain Plaque, Dr. Bruce West, DC ...............................69
O is for Orgasm: Your Guide to Orgasm in Relationship
Dr. Chelsea Holland, DHS, LPC, MS ..........................................................72
The Abscopal Effect: What You Need to Know Before You Choose a Treatment, Israel Barken, MD .........................................................74
Letters to the Editor ....................................................................................76
Grant Information .....................................................................................79
Dear Rick,

It was so nice hearing from you. I, too, very much miss speaking with you. We have traveled so many paths, roads, highways and super highways covering the past 35 years exploring the frontiers of prostate cancer therapies. Exploring and creating treatments to help patients achieve prostate cancer remissions.

I can remember my discussions with the Pioneer himself … Lloyd Ney. I was one of the speakers at a PAACT conference taking place in Grand Rapids, Michigan in the mid 1980's. At that time, I first learned my reputation for being the Ultimate Pioneer – the ultimate insane, dangerous pioneer. None of the other speakers thought that my therapeutic approach could possibly be successful at controlling prostate cancer. In fact, the moderator of the conference, Dr. Stephen Strum, had assigned the topics of discussion to the speakers. I do not even remember which topic he chose for my lecture. It didn't matter to me because I chose my own topic…Triple Hormone Blockade®. I knew that this was the subject that the audience wanted to learn about; an effective, non-invasive treatment for prostate cancer that did not require surgery or Radical Radiation Therapy. After just 13 months of a 3 drug treatment, men were maintained on one finasteride pill per day. Fewer than 5% of the men had any lasting side effects and in men with normal baseline levels of testosterone, it was rare to have lasting suppression. In fact, the average patient had testosterone recovery within 3-4 months after stopping hormone blockade. Men older than 75-80 sometimes took longer to recover.

The night before the conference started, Dr. Strum asked to review my slides with him. Dr. Strum and I had incredible mutual respect for each other as well as admiration for our ability to keep up with evolving knowledge in prostate cancer often each contributing to the prostate cancer field; we also had tremendous respect for each other as clinicians.

We belonged, as an old song stated to a “mutual admiration society.” With one notable exception … oops. As a junior in high school in Chicago, Illinois back in the early 1960’s, we underwent city wide testing. The first day tested I.Q. and I did ok. The second day, they tested for mechanical aptitude. At that time, in Chicago, approximately 20% of high school students were functionally illiterate. In spite of my advantage of being literate, I still scored in the lowest percentile at 3% of Chicago high school students for mechanical aptitude.

At the time of PAAC’Ts inaugural prostate cancer conference, in Grand Rapids, Michigan, almost all of the speakers used power point slides that they created. Almost, but not all - because I didn't know how to make any kind of slide, let alone a power point slide. I went to the Richard Grossman Burn Center across the way from my office and begged and bribed the burn photographer to help me with the slides. When I read medical articles, I underlined the important information using yellow highlighter – freehand. There were no straight yellow lines. The slides displayed the information correctly but, oh, my, what a mess!! When Dr. Strum first saw these slides, I thought that he was either going to cry or do great bodily harm to me. Instead, he began to make some power point slides from my mess but, alas, he had to stop and get some sleep.

When he introduced me the next morning, he apologized profusely to the audience for the lack of professionalism and hoped the audience might still be able to salvage something from my apparent catastrophe.

My girlfriend was in the audience that day; the lights were quite bright and I was unable to see past the first rows during my lecture on Triple Hormone Blockade® as a sole treatment of prostate cancer. As I finished, I saw Dr. Strum approaching the lectern, questions were not permitted until later in the day. As I walked off the stage, I heard extremely enthusiastic applause but it was not until I reached my girlfriend's side and heard her say, “Bob, look. You are the only speaker who received a standing ovation.” Only then, did I look over the audience and confirm what she had said.

And, finally I also heard Dr. Strum requesting the audience to stop applauding; to sit down; and to realize that until other investigators reproduce my results or until I publish my results in a peer reviewed journal, that the audience should reserve judgment. I published the results in the well- respected, Peer Reviewed journal “The Oncologist” in 2001, reporting my results on the first 110 men treated with Triple Hormone Blockade®.

Be well,

Dr. Bob

*Triple Hormone Blockade; Triple Androgen Blockade; and Finasteride Maintenance Therapy are all Registered Trademark of Dr. Robert L. Leibowitz.
ABSTRACT

Objectives. To determine the effectiveness of triple androgen blockade as an alternative to watchful waiting, radical prostatectomy or radiation therapy in the management of patients with clinical stage T1 to T3 prostate cancer.

METHODS. The records of 110 consecutive patients were retrospectively evaluated. Patients were treated with a three-drug androgen blockade regimen, consisting of a luteinizing hormone-releasing hormone agonist (leuprolide or goserelin) plus an antiandrogen (flutamide or bicalutamide) plus finasteride (a 5-alpha-reductase inhibitor), followed by finasteride maintenance therapy, as the sole intervention. All patients refused local therapy and had their prostates intact. Determinants of efficacy included serum prostate-specific antigen (PSA) levels and disease-specific survival.

RESULTS. Patients were treated for a median of 13 months with triple androgen blockade. At baseline, mean PSA level was 13.2 ± 1.2 ng/ml (range, 0.39-100 ng/ml), and mean Gleason score was 6.6 ± 0.1 (range, 4-10). During treatment, PSA levels declined to ≤0.1 ng/ml in all patients, with a median time of 3 months. After a median follow-up of 36 months since initiation of treatment, PSA levels have remained stable in 105 of 110 patients (95.5%). At a median follow-up of 55 months (range, 38-125 months), the mean PSA level for the first 57 patients treated in this series is 1.88 ± 0.1 (range, 0.11 ng/ml). Only 9 of 110 (8.1%) patients have a PSA level ≥4.0 ng/ml. To date, no patient has received a second cycle of hormone blockade.

CONCLUSIONS. Although median follow-up is short, triple androgen blockade therapy followed by finasteride maintenance appears to be a promising alternative for the management of patients with clinically localized or locally advanced prostate cancer. Further study of this approach is warranted. The Oncologist 2001:6:177-182

INTRODUCTION

Current treatment options for clinically localized or locally advanced cancer of the prostate include radical prostatectomy, radiation therapy, brachytherapy, cryotherapy, or “watchful waiting” (i.e., surveillance). Approximately two-thirds of patients are treated with either prostatectomy or radiotherapy. Although local therapies are potentially curative, they are associated with long-term, often permanent, side effects, and to date none have been demonstrated to provide a statistically significant survival benefit compared with surveillance in prospectively randomized trials. In the only prospective randomized trial comparing placebo to radical prostatectomy plus placebo, the Veterans Administration Cooperative Urological Research Group failed to demonstrate an overall survival benefit with a median follow-up of 23 years for patients undergoing prostatectomy compared to patients receiving no initial treatment [1, 2]. Moreover, reported 10-year disease-specific survival rates for prostatectomy (88% to 93%) and external beam radiotherapy (66% to 86%) are not different from those reported for surveillance (84% to 85%) [3, 4]. The curative potential of surgery or radiation has been further called into question by measurements of prostate-specific antigen (PSA), which indicate persistent or recurrent disease in up to 27% to 53% of patients treated for clinically localized prostate cancer [5-7]. This implies that only a limited number of patients treated with local therapy will enjoy long-term PSA failure-free survival. For men presenting with known adverse risk factors such as Gleason scores [8-10], PSA values greater than 10 ng/ml, or locally advanced disease and treated with radical prostatectomy or radiotherapy, the 5-year PSA biochemical failure-free survival is only between 21% and 32% [7-9]. Sensitive PSA assays, including reverse-transcriptase polymerase chain reaction for PSA, suggest that a large proportion of patients with clinically localized disease have occult micrometastatic disease in peripheral blood, lymph nodes, and/or bone marrow prior to prostatectomy [10-14]. Given these data and the well-documented morbidity associated with surgery and radiation, including impotence and urinary incontinence, the clinical benefit of local therapy for prostate cancer continues to be debated.

Combination hormone blockade has been suggested as an option in the management of patients with clinically localized or locally advanced prostate cancer. The combination of the 5-alpha-reductase inhibitor finasteride and a pure antiandrogen such as flutamide (Eulexin®, ScheringPlough Corporation; Kenilworth, NJ) is an effective form of androgen blockade. Finasteride inhibits the intraprostatic conversion of testosterone to 5-alpha-dihydrotestosterone, whereas flutamide blocks the interaction of androgens with their cytoplasmic receptors [5]. The advantage of this combination over traditional hormone therapy (e.g., chemical or surgical orchietomy) is that it does not affect plasma concentrations of testosterone, thereby maintaining potency and quality of life. Long-term treatment (i.e., four years) with finasteride monotherapy has been shown to produce continuous improvement in PSA over time in patients with benign prostatic hyperplasia in the PLESS Study Group trial [15], and finasteride in combination with flutamide has been shown to substantially decrease PSA levels in patients with metastatic prostate cancer [16].

Antiandrogens are typically used in combination with luteinizing hormone-releasing hormone (LHRH) super-agonists such as leuprolide or goserelin. This combination has been shown to provide a substantial survival benefit in patients with metastatic prostate cancer compared with an LHRH agonist or orchietomy alone [17-19]. While these studies suggest a benefit for combined androgen blockade, other well-designed studies dispute the benefit including four large meta-analyses [17, 20-24]. Some authors suggest that patients with minimal disease burden receive a more pronounced survival benefit with combined androgen ablation [19, 25, 26]. In patients with localized or locally advanced prostate cancer, long-term treatment with flutamide plus an LHRH agonist reduced PSA to undetectable levels in 39 of 46 (85%) patients.
with stage T2 and T3 disease who were treated continuously for a median of 7.2 and 9.9 years, respectively [27].

The triple combination of an LHRH agonist, an antiandrogen, and finasteride has also recently been studied in patients with localized prostate cancer [28, 29]. In this trial, 59 patients were randomized to an LHRH agonist plus an antiandrogen with or without the addition of finasteride. Finasteride was added both as part of the three-drug induction regimen and maintenance therapy. Patients who received the three-drug combination plus finasteride maintenance had a significantly shorter median time to undetectable PSA (three versus five months; p = .0095) and a significantly longer median time to relapse, defined as PSA increase to ≥2.5 ng/ml (34 versus 19 months; p = .013). These data suggest that this three-drug combination androgen-blockade regimen may be a highly effective alternative to prostatectomy, radiotherapy, or watchful waiting for the treatment of localized prostate cancer.

We have treated 110 consecutive patients who presented with clinical stage T1 to T3 prostate cancer and refused local therapy with this three-drug combination androgen-blockade regimen in a community-based medical oncology practice. Preliminary results suggest that the majority of patients maintain long-term, stable, low PSA levels following triple androgen blockade therapy with finasteride maintenance.

**MATERIALS AND METHODS**

**PATIENTS**

The records of 110 consecutive patients presenting with clinical stage T1 to T3 prostate cancer and treated between June 1990 and June 1999 were retrospectively reviewed. All patients had biopsy-proven adenocarcinoma of the prostate; biopsies were performed and interpreted at each patient's local institution. Routine staging with bone scans, magnetic resonance imaging, computer tomography, and/or indium-111 capromab pendetide (ProstaScint®; Cytogen Corporation; Princeton, NJ) was not performed. Any patient with clinical evidence of metastatic disease was excluded from study. Patients were not surgically staged to differentiate clinically localized (stage T1 and T2) from locally advanced (stage T3) disease, nor were baseline scans routinely ordered. No patient had undergone any form of local therapy. All patients, in fact, refused local therapy and were offered triple androgen blockade therapy. Patients were informed of the risks, benefits, and alternatives to hormone blockade before therapy was initiated.

**TREATMENT**

Patients were treated with an LHRH agonist (either leuprolide acetate [7.5 mg] or goserelin acetate [3.6 mg] every 28 days) plus an antiandrogen (either flutamide [750 mg] or bicalutamide [150 mg] daily) plus finasteride (5 mg daily) for a median of 13 months [30]. Induction therapy was followed by maintenance therapy with finasteride (5 mg daily) for an indefinite period.

Efficacy variables included: A) PSA levels; B) time to achieve undetectable PSA level (defined as ≤0.1 ng/ml), and C) disease-specific survival. Measurements of PSA were made at 3-month intervals or less during treatment with triple androgen blockade and at approximately 3-month intervals during maintenance therapy. Blood samples were assayed for PSA at our clinic or by local community laboratories. The AIA® 600 immunoassay analyzer (Tosoh Medics, Inc.; South San Francisco, CA) was used at our clinic, which employed a two-site immunoenzymetric assay and Tosoh AIA-PACK methodology. Baseline and follow-up testosterone levels were also measured at 3-month intervals until testosterone levels reached baseline levels or a plateau. Testosterone was also measured during finasteride maintenance to assess androgen recovery.

At the majority of patient visits, clinical symptoms and adverse effects were recorded. In addition, complete blood counts and comprehensive chemistry panels including liver function tests were performed.

**RESULTS**

**Patients**

Baseline patient characteristics are shown in Table 1 for 110 consecutive patients who completed treatment by May 2000. The median age was 67 years (range, 51 to 86 years), and the mean Gleason score was 6.6 ± 0.1 (range, 4-10). The mean baseline PSA level was 13.2 ± 1.2 ng/ml (range, 0.39-100 ng/ml). Mean baseline serum testosterone level was available in 54 patients and was 373 ng/dl (range, 154-819 ng/dl). Table 2 summarizes the Gleason score, clinical stage, and PSA risk group (PSA <10, 10-20, and >20 ng/ml) for men receiving triple androgen blockade. Forty-four percent of patients had clinical stage T1c and 40% of patients had clinical stage T2a. Patients with higher stages (T2b/T3) comprised 16% of the study population. Fifteen patients had Gleason scores of 8 to 10; 25 patients had PSA 10-20; and 20 patients had a baseline PSA >20. The mean PSA for patients presenting with a baseline PSA greater than 20 was 35 ng/ml.

<table>
<thead>
<tr>
<th>TABLE 1. BASELINE PATIENT DEMOGRAPHICS</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGE (YEARS)</td>
</tr>
<tr>
<td>MEAN: 67.0</td>
</tr>
<tr>
<td>GLEASON SCORE</td>
</tr>
<tr>
<td>MEAN: 6.6</td>
</tr>
<tr>
<td>SERUM PSA (NG/ML)</td>
</tr>
<tr>
<td>MEAN: 13.2</td>
</tr>
<tr>
<td>SERUM TESTOSTERONE (NG/DL)</td>
</tr>
<tr>
<td>MEAN: 373.0</td>
</tr>
</tbody>
</table>

**EFFICACY**

The median duration of triple androgen blockade therapy was 13 months. All 110 patients in this series achieved undetectable PSA levels (≤0.1 ng/ml). The median time to achieve undetectable PSA was 3 months (range, 1-10 months).

With a median follow-up of 36 months from the start of hormone blockade therapy, the majority of patients have maintained low PSA levels. As shown in Table 3, the mean PSA level for the entire cohort is 1.3 ± 0.1 ng/ml (range, 0-11.0 ng/ml). Eighty-five patients have now been off triple hormone blockade therapy for ≥12 months and have a mean PSA level of 1.6 ± 0.1 ng/ml. These men continue to receive finasteride...
The advantage of finasteride maintenance is that it may prolong and maintain stable low PSA levels with finasteride maintenance. Undetectable PSA levels with short-term triple androgen blockade clinically localized or locally advanced prostate cancer can achieve the results observed in this series indicate that patients with hormone blockade should be considered. Patients with PSA levels and his PSA was at or above pretreatment levels, retreatment is expected to have prolonged survival with the early use of hormone blockade and supports the rationale for use in localized disease.

**SAFETY AND TOXICITY**

Nearly all patients reported adverse events typically associated with hormone blockade therapy, including hot flashes, loss of libido, and loss of potency; however, these side effects resolved in nearly all patients on discontinuation of hormone blockade. No unexpected adverse events were reported. Return of testosterone to greater than 180 was attained by all men who had a normal baseline testosterone level; the mean post-treatment testosterone level was 412 ng/dl (range, 9-942 ng/dl; n = 91) among patients who have been off treatment for ≥12 months. Available testosterone data are summarized in Table 4.

Disease-specific survival is 100%. Although 10 patients have died, none of these deaths were considered to have resulted from prostate cancer or a treatment-related complication. In each case, prostate cancer was reported by the local attending physician to be controlled and in remission.

**TABLE 2. CLINICAL CHARACTERISTICS OF 100 MEN TREATED WITH TRIPLE ANDROGEN BLOCKADE**

<table>
<thead>
<tr>
<th>CLINICAL STAGE</th>
<th>GLEASON SCORE</th>
<th>PSA RISK GROUP</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1c</td>
<td>4-6</td>
<td>&lt;10</td>
</tr>
<tr>
<td>T2a</td>
<td>7</td>
<td>10-20</td>
</tr>
<tr>
<td>T2a/T3</td>
<td>8-10</td>
<td>&gt;20</td>
</tr>
</tbody>
</table>

**TABLE 3. POST-TREATMENT PSA LEVELS**

<table>
<thead>
<tr>
<th>MEAN PSA (NG/ML)</th>
<th>STANDARD ERROR</th>
<th>RANGE (NG/ML)</th>
<th>MEDIAN FOLLOW-UP (MONTHS)</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALL PATIENTS OFF TREATMENT</td>
<td>1.30</td>
<td>0.1</td>
<td>0-11.0</td>
<td>36</td>
</tr>
<tr>
<td>PATIENTS OFF TREATMENT ≥12 MONTHS</td>
<td>1.60</td>
<td>0.1</td>
<td>0-11.0</td>
<td>42</td>
</tr>
<tr>
<td>PATIENTS OFF TREATMENT ≥24 MONTHS</td>
<td>1.88</td>
<td>0.1</td>
<td>0-11.0</td>
<td>55</td>
</tr>
</tbody>
</table>

**TABLE 4. BASELINE AND POST-TREATMENT TESTOSTERONE VALUES**

<table>
<thead>
<tr>
<th>TESTOSTERONE</th>
<th>RANGE</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>BASELINE</td>
<td>373</td>
<td>154-819</td>
</tr>
<tr>
<td>PATIENTS OFF TREATMENT ≥12 MONTHS</td>
<td>412</td>
<td>9-942</td>
</tr>
</tbody>
</table>

**DISCUSSION**

The results observed in this series indicate that patients with clinically localized or locally advanced prostate cancer can achieve undetectable PSA levels with short-term triple androgen blockade and maintain stable low PSA levels with finasteride maintenance. The advantage of finasteride maintenance is that it may prolong time to relapse [29]. Despite the retrospective nature of this study and the relatively short duration of follow-up, these results are provocative and, in conjunction with other published reports, support a reassessment of currently accepted approaches to the treatment of localized prostate cancer.

The clinical benefits of androgen blockade therapy appear to be greatest when patients are treated early. This conclusion is supported by a study in patients with locally advanced or asymptomatic metastatic disease that showed early intervention with hormone blockade was more effective than deferred intervention [31]. Messing et al. [32] also reported that immediate hormone blockade therapy following radical prostatectomy in pathologically node-positive patients significantly prolongs survival compared with either observation or delayed hormone therapy. This suggests that men with low tumor burden might be expected to have prolonged survival with the early use of hormone blockade and supports the rationale for use in localized disease.

Labrie has reported that combined hormone blockade is highly effective in controlling clinically localized or locally advanced prostate cancer [27]. In 46 patients with stage T2 to T3 prostate cancer treated only with an LH-RH agonist plus flutamide for a median of 7 to 10 years, all patients achieved and maintained undetectable PSA levels; PSA failure occurred in only seven (15%) patients (two patients with stage T2 disease and five patients with T3 disease) after a median of 3 years. Moreover, Strum et al. have recently reported that intermittent androgen deprivation with an antiandrogen, an LH-RH agonist, and finasteride (given during induction therapy and as maintenance) resulted in significantly prolonged time off intermittent androgen blockade in patients with clinically localized prostate cancer; only 5 of 27 (19%) patients required retreatment after a median of 36 months [28, 29].

Unlike the regimen described by Strum et al., we have used triple androgen blockade with finasteride maintenance for all our patients. Additionally we recommend utilizing “high-dose” bicalutamide, 150 mg orally all at one time daily, rather than the 50 mg daily as used by Strum. Pharmacodynamic studies of bicalutamide demonstrate an increasing PSA response with higher dosing [33]. Studies suggest bicalutamide monotherapy at 150 mg daily may be equivalent to surgical castration or dual androgen blockade, and is associated with fewer side effects such as hot flashes, sexual interest, and physical capacity [34-36].

Thus far, none of our patients treated with this regimen have required retreatment with hormone blockade. Recurrences to PSA ≥ 4.0 ng/ml have occurred in 8% of patients (9/110), consistent with what others have observed [27, 29]. Follow-up PSA levels appear to have reached a stable PSA plateau in the majority of patients. However, if a patient experienced a progressive increase in PSA levels and his PSA was at or above pretreatment levels, retreatment with hormone blockade should be considered. Patients with PSA levels greater than 10 ng/ml may be candidates for further therapy.

Although PSA levels increased in nearly all patients when hormone blockade therapy was discontinued, one cannot assume that the relatively low levels of PSA observed in these patients...
result from residual or occult metastatic prostate cancer cells. At least some of this PSA is likely to originate from normal prostate-gland cells, as all of the men in this series still have their prostate glands intact. Therefore, as testosterone levels recover, as was the case in nearly all patients, normal prostate-gland cells will be stimulated to produce PSA. Remarkably, 18 patients (16%) in this series continue to have PSA levels less than 0.1 ng/mL, and seven of these patients have documented testosterone recovery to normal levels.

A particular benefit of the approach described here is its tolerability. The morbidities associated with radical prostatectomy or other forms of local treatment can substantially affect quality of life and are often permanent. While on treatment, most men reported loss of libido and potency as well as the occurrence of hot flashes. Surprisingly, six men in this series remained sexually active throughout the entire treatment period. No patients developed urinary incontinence or leakage. Approximately 25% of patients complained of some or all of the so-called “androgen deprivation syndrome” symptoms [37], including hot flushes, mood swings, mild arthralgias, and mild gynecomastia. Mild to moderate reductions in maximal athletic stamina were subjectively reported in our patients. These androgen deprivation symptoms generally resolved within a few months of testosterone recovery. With recovery of androgen production, patients reported an improved overall sense of well-being. Approximately 5% of patients reported persistent loss of libido and/or potency. While on therapy and during the testosterone recovery period, the use of Viagra® often improved sexual function and restored potency.

CONCLUSION

The current series has demonstrated that a single cycle of 13 months of triple androgen blockade followed by finasteride maintenance therapy yielded promising preliminary results. Since the median follow-up is short, it is premature to form definitive conclusions about triple androgen blockade with finasteride maintenance as primary therapy for localized prostate cancer. Nevertheless, 57 patients have now been followed for a median of 55 months without requiring a second cycle of androgen blockade. If these results can be confirmed in prospective randomized clinical trials, it may suggest a new paradigm for the treatment of clinically localized or locally advanced prostate cancer.

ACKNOWLEDGMENT

We would like to express our gratitude to Joni and Howard Miller for their assistance in data management and preparation of this manuscript.

REFERENCES

If this is your first time being diagnosed with prostate cancer, it’s best to set-up a plan of action from the onset of your diagnosis. Once you have received your diagnosis, I highly recommend conducting your own Internet research using reputable sites to gather as much information and resource tools as possible. There are many reputable prostate cancer patient information sites on the Internet such as; Mayo Clinic, Johns Hopkins University, UCSE, Stanford University, University of Michigan Health System (a top-ranked medical school), PAACT, PCRI, Health Alert and US-TOO to name a few to jump start your research. Arming yourself with as much knowledge, information, and resources, immediately after your diagnosis will help you make better & more informed decisions, as well as help you to understand the various medical terms that will be thrown at you at future appointments. You need to gain perspective for this new area of your life that you are entering.

First and most important, you will need a back-up plan that includes bringing someone with you to your initial appointment such as your spouse or significant other. When you are first informed that you have prostate cancer, it will hit you like a brick, to put it mildly. Half the things that you’re going to be told at your diagnosis appointment you won’t remember due to the imminent news you will receive, which is why I strongly recommend bringing a trusted companion along. That person can play a significant role at your meeting by just being there for support, but also asking questions and taking notes to help gather important information. In some medical establishments, you may be allowed to record the appointment via a Smart phone or recording device (provided you get advanced permission). Recording your conversation with your physician can serve as a meaningful tool that will enable you, your family & significant others in your life, to hear what was discussed and shared at your initial appointment in case you are unable to relay the information to them. An audio file can be sent to them via text or Email by you at any time after the appointment. This is also a good resource tool for you to have if you opt to see a physician outside your medical group or have a need to relay this first appointment to a specialist. This audio tool particularly works well when significant others or relatives live far away and can’t be there in person with you.

Establishing your medical team will consist of: 1) Your primary physician; 2) Your urologist; 3) Your medical radiologist; and 4) Your medical oncologist. I would suggest very strongly that you get opinions from ALL of these specialists in order to come to a conclusion and decision of what course you want to take and how you are going to proceed. And above all, YOU must be the one who makes the final decision, because YOU are the person that will pay for it in body damage, that is damage from the side effects from any treatment, procedure, surgery, or medication you choose to undergo. You only have one body and one time to make the most informed decision you can with the facts given to you by your physician. There is no redo or do over when it comes to your physical health. You need to remain in the driver’s seat by being proactive while doing your research, understanding your disease, and finding out the latest, innovative procedures available. Support groups are a great opportunity to talk to other men (and significant others as well) who have undergone similar procedures, or chose not to undergo treatment and why. The positive side about doing research, as well as talking to other prostate cancer patients is enlightening. It will show that medical procedures and technology have greatly advanced in the last one to two decades and now promote less down time, quicker healing, and advancing your physical life to its fullest potential.

The most important thing is to minimize what you will have to endure. It’s ideal to undergo a one-time treatment, but unfortunately, this does not exist. For this reason, it’s very important for you to gain knowledge and to understand the various procedures and their side effects that you most likely will have to endure the rest of your life. A small amount of information will help you in the long run to make the best medical decision about treatment options available to you.

Always remember **this is your life.** You are not in it alone - you have the medical community, support groups, and your family and friends along with you on this journey. You may ignore prostate cancer, but it WILL not ignore you so LEARN and LIVE. And, don't give into prostate cancer without RESEARCHING, LEARNING, and LIVING.
Prostatitis is a complex condition affecting many men of all ages. There are several types of prostatitis and many different causes. Prostatitis can cause significant discomfort and pain. It can affect a man’s sexual health, with research showing that 73% of patients reporting some kind of sexual dysfunction related to their prostatitis. It can also cause urinary and other related problems. Some types of prostatitis are caused by bacteria, but most prostatitis sufferers have a more chronic type of prostatitis known as “chronic pelvic pain syndrome” (CPPS), which can be caused by a multitude of factors that include stress, anxiety, tension, diet, and lifestyle. Knowing this is key in understanding prostatitis and can help in finding treatment. Long-term chronic prostatitis can be a troubling and bewildering condition for doctors and urologists to explain and treat.

Affecting 95% of prostatitis patients, CPPS is the most common prostatitis disorder. Traditionally CPPS treatment has been focused on treating the prostate itself and giving antibiotics even when no bacteria are present. Doctors and urologists today are finding more success in applying multimodal (using many different methods) “whole body” approaches to dealing with this difficult health problem. This treatment model combines naturopathic treatments, traditional medicine, and alternative treatments. Despite this, there are still many physicians who continue to refer to pelvic pain as prostatitis and treat men’s complaints of pelvic pain and urinary dysfunction as if the symptoms are caused by an infection or inflammation of the prostate.

It is baffling to many men and their doctors that most diagnosed cases of CPPS have nothing wrong with the prostate gland itself. In careful studies conducted over the past decades of treating the prostate, the majority of men treated with antibiotics or anti-inflammatory drugs aimed at treating the prostate gland derive no lasting relief from treatment.

Most cases of CPPS are caused by problems due to chronically tightened pelvic muscles. Basically, it is like having a “charley horse” up inside the pelvis. That can be the result of chronic stress, anxiety, or even weaknesses or tightness in the muscles. Much research has shown that approximately 90–95% of the men who seek help for pelvic pain have no prostate pathology and no infection found when cultured. Even inflammation is not the sole cause of symptoms because the men who have inflammation (evidence of white cells found in the prostatic fluid) still have their symptoms remain even after the inflammation is removed.

When you see “-itis” at the end of a condition, it usually refers to an inflammatory disease, but not in the case of prostatitis. The majority of symptoms that get diagnosed as “prostatitis” really have nothing to do with an “itis” of the prostate. Recognizing this is key to beginning to understand this complex condition and is one of the reasons why traditional treatments (like antibiotics and anti-inflammatory drugs) do not work.

Prostatitis can cause discomfort and problems that are related to the genital, rectal, and perineal areas. It can lead to urinary symptoms and can even make sitting very difficult. Some men feel as if they are sitting on a golf ball. All of these pains and symptoms can have nothing to do with the prostate gland in many prostatitis suffers.

Prostatitis is more common than you think, as half of all men experience prostatitis at some point. But not all men talk about it or are too embarrassed to discuss it, so many men do not know how common it is or know where to go for help. Unlike an enlarged prostate, which occurs in older men, prostatitis is more common in younger and middle-aged men.

Even if you do not currently have prostatitis, you could have it in the future because prostatitis might be the most common prostate-related disease. That is why it is important to learn as much as you can about male health, the prostate gland itself, and understanding prostatitis so you can help prevent it and learn the best ways to manage and treat the condition. The more you understand it, the better your chance of preventing it or keeping it from coming back.

Even though it can be confusing and difficult to treat, learning about its prevention, symptoms, causes, and many treatments can assist you in seeking help. The more you know, the better you can prepare for managing symptoms and living with it. Prostatitis does not have to be confusing or debilitating. Knowing how to fight it can help you take control of your pelvic health long-term.

continued
The prostate gland is a walnut-sized structure that sits beneath the bladder and in front of the rectum. This part of the male reproductive system wraps around the urethra, kind of like a tight donut, with the urethra going through it. The urethra is the tube that transports fluids such as urine and semen out of the body through the end of the penis. That is why an inflamed prostate can squeeze the urethra, restricting urine flow and causing urinary symptoms. Men with prostatitis often experience urinary symptoms as well as pelvic pain and sexual discomfort.

All boys are born with a prostate gland, but this reproductive gland does not become active until they reach puberty. At puberty, the gland grows to its normal and healthy size, weighing one ounce and reaching the size of a walnut shell.

The prostate begins to function in puberty. What does the prostate do? Its main function is to secrete a fluid that becomes part of the seminal fluid, which carries sperm. When a man has an orgasm, the muscles in the prostate contract which moves the prostate fluid and sperm into the urethra. The semen moves through the urethra and out of the body through the head of the penis during ejaculation.

Now you know what the prostate does, but what do you do if you have a problem? You need to see an urologist or specialist if you are suffering from urinary problems or other pelvic and sexual pain. The doctor may diagnose you with some form of prostatitis, but you could have other reasons for the inflammation and urinary symptoms such as benign prostatic hyperplasia (BPH). They will perform various tests for prostatitis and test for the presence of bacteria.

If you have prostatitis, know that it could be one of four types of prostatitis. Three types of prostatitis present with similar symptoms that have some slight differences from each other. One type of prostatitis—**asymptomatic prostatitis**—does not have any symptoms. Your lifestyle can be responsible for causing symptoms or many of the factors that can inflame your prostate. That is why you need to take steps in your life to help prevent this from happening and prevent prostatitis.

Last of all, even though the tiny prostate gland takes the heat for common male urinary and pelvic health symptoms, medical doctors and naturopaths are now recognizing that lifestyle plays a large role in these problems, the focus is shifting to look at neuromuscular tension-related causes of prostatitis, especially in cases of long-term chronic pelvic pain syndrome (CPPS).

When doctors and patients recognize that other factors like stress, anxiety, foods, and lifestyle lead to pain and discomfort, it can lead to successful management of the disorder, providing relief from the pain and symptoms. Applying a multimodal therapy when dealing with CPPS—including medications, changes in lifestyle, and other natural and alternative treatments (such as acupuncture, phytotherapy, supplements, psychological treatments, and pelvic trigger point therapy)—can provide a complete overall approach to treatment. It is more successful than simply prescribing ineffective antibiotics over and over.

There are four main types of prostatitis—**Acute Bacterial, Chronic Bacterial, Chronic Pelvic Pain Syndrome (CPPS) and Asymptomatic**. Prostatitis is more of a blanket term for a group of different but related conditions involving the prostate gland and pelvic area. Some of the types—in fact, the most common type of prostatitis (CPPS)—do not even involve the prostate gland itself.

**THE 4 TYPES OF PROSTATITIS**

1. **Acute bacterial prostatitis**: This bacterial infection of the prostate gland is actually the least common type of prostatitis. It is caused by several types of bacteria, but most commonly Escherichia coli (E. coli).

2. **Chronic bacterial prostatitis**: This recurrent bacterial infection of the prostate gland is not common. It is also caused by bacteria, but it lasts longer (three months or longer) than acute bacterial prostatitis and can be more difficult to treat.

3. **Chronic pelvic pain syndrome (CPPS)**: The majority of men with symptoms have this—the most common type of prostatitis, also known as chronic nonbacterial prostatitis. There is no infection found. The prostate itself may not be involved. There are two subgroups of CPPS:
Inflammatory chronic pain syndrome: White blood cells found in semen or static secretions.

Non-inflammatory chronic pelvic pain syndrome: No white blood cells found in semen or static secretions.

CPPS is a debilitating and distressing disorder for men and the hardest type of prostatitis to treat. The thing that is most challenging about treating CPPS is that it is usually caused by problems outside of the prostate. There is often tension in the pelvic muscles outside of the prostate. While antibiotics can usually treat bacterial prostatitis, they do not work for CPPS. Men with CPPS usually have to experiment with several natural therapies and alternative treatments to manage their disorder. A number of these natural and alternative therapies have been proven in studies to provide relief when they are used in a holistic multimodal treatment program.

4. Asymptomatic prostatitis: This is an uncommon type of prostatitis in which there are no symptoms typical of other forms of prostatitis. The prostate may be inflamed but without causing symptoms. It is usually found when a doctor finds white blood cells in prostatic secretions or prostate tissue when evaluating other disorders.

The first three types of prostatitis present with similar symptoms. Men who experience the following symptoms should get evaluated for prostatitis:

- dribbling when urinating
- difficulty starting the urinary flow
- weak urinary stream
- getting up during the night to urinate
- painful urination
- frequent urgent need to urinate
- pain when ejaculating
- pelvic pain

Only a healthcare professional can determine whether a patient has prostatitis and what type of prostatitis it is. A doctor can rule out other prostate conditions with some similar symptoms such as benign prostatic hyperplasia (BPH). If the patient is diagnosed with prostatitis after conducting an examination and doing any necessary tests, the doctor and patient should discuss treatment. A multimodal treatment approach can maximize chances of recovery.

Sometimes prostatitis can be a serious medical condition, especially in the case of acute bacterial prostatitis. Even though prostatitis is not contagious and is not transmitted sexually, it is important to discuss treatment options with your healthcare provider as soon as possible. Even if it does not seem like a serious case, it is important to start treatment to help alleviate discomfort, prevent complications from developing, and prevent long-term health problems. Some CPPS treatments do take a long time to get results, so embarking on treatment is making a big commitment to getting better.

AN UROLOGIST WITH NEWLY DIAGNOSED PROSTATE CANCER: WELCOME TO MY JOURNEY!

Anonymous

I am writing from a most unusual “position.” I am an urologist who has been in practice for 38 years with recently diagnosed prostate cancer. I envision a 4 part “installment” of communication related to my personal battle with this disease. These four “installments” will cover: 1) preoperative considerations and decision making (see below), 2) my experience with the surgery to remove the prostate (robotic radical prostatectomy performed early February 2019 – see below), 3) my recovery within the first few months after surgery (see below), and 4) long-term issues after initial treatment. I truly hope that my experience may help other men who are dealing with a recent diagnosis of prostate cancer.

PART 1 - I THINK IT MIGHT BE USEFUL FOR OTHERS TO UNDERSTAND MY PROSPECTIVE ON THE DIAGNOSIS AND FUTURE TREATMENT OPTIONS THAT I HAVE BEEN DEALING WITH.

My father had a history of prostate cancer, so I always felt there was a strong possibility that I would develop prostate cancer as well. For this reason, I have checked my PSA annually and noted a slow rise in the PSA over the last 4 years. My current PSA is 5.5. At this level of PSA, along with my positive family history, I was fairly sure I had prostate cancer. The questions that I struggled with included:
1) WOULD MY QUALITY OF LIFE BE BETTER IF I AVOIDED DEFINITE DIAGNOSIS AND TREATMENT?
For me the answer is no! Making a diagnosis at a potentially curable stage and getting appropriate treatment with the goal of potential cure is the best option for me. Avoiding diagnosis and treatment and potentially developing metastatic disease is a big “motivator” to deal with my situation now!

2) AT AGE 68, IS IT IMPORTANT FOR ME TO TRY TO MAXIMIZE MY LIFE SPAN?
The answer is yes, especially when I consider seeing my grandchildren grow up!

3) WHAT PROSTATE CANCER TREATMENT IS BEST FOR ME?
I can only address my own personal situation. My prostate MRI showed two highly suspicious areas on the right and left side of my prostate. There is a relatively new prostate biopsy technique called Uronav that allows the urologist to superimpose the MRI image with abnormal areas clearly marked as “targets” with the live transrectal ultrasound. With this technology, the urologist can clearly sample the target areas seen on the MRI, as well as obtain other random samples of the prostate gland. My biopsy was performed in the office with local anesthesia. Although it was uncomfortable, I was easily able to tolerate the procedure with no major problems following the biopsy. My pathology report showed 7/17 biopsy samples (from both sides of the prostate) were positive of Gleason 3+3=6 prostate cancer. I knew the biopsy would be positive, but I was surprised that the cancer was as extensive as demonstrated by the pathology report. There were multiple areas of the prostate that looked normal on both the MRI and ultrasound that were positive for cancer. To me, this is very important since there are a number of potential treatment options (like HIFU and radiation therapy), that supposedly target the prostate cancer with minimal side effects. With the extensive cancer that I have on both sides of the prostate, I am very concerned that any treatment that treats less than the entire prostate will not be successful. I am also fortunate that my Gleason grade of the cancer is “mid-range” of 3+3 (total of 6). Cancers with a higher Gleason score (greater than 6), tend to be more aggressive with a high risk for spread (metastasis). Currently, although my cancer is bilaterally extensive in the prostate gland, it appears to be localized with a favorable Gleason score. For this reason, I plan to have a robotic radical prostatectomy early in February 2019. I believe that the surgical removal of my prostate offers the best chance for cure. Also, over the last few years I have noted some decrease in the strength of my urinary stream and a feeling of not always emptying my bladder completely. These are signs of the prostate causing some blockage to the flow of urine. Removing the prostate will eliminate this problem. Other treatments, like radiation therapy, will cause the prostate to “swell” and make this problem worse. Also, with aging, the prostate may continue to grow causing increasing problems with weak stream and bladder emptying.

4) WHAT CONCERNS DO I HAVE REGARDING REMOVAL OF THE PROSTATE?
A) Being Cured of Prostate Cancer: With current robotic techniques in the hands of an experienced surgeon, the procedure usually is accomplished with few complications and good control of the cancer. Obviously, the goal is to remove all the prostate cancer from the body (which is hopefully confined within the prostate gland) and to have negative margins at the edges of the resection. When the margins of the resection show evidence of cancer, further treatment, such as radiation therapy, may be required.

B) Urinary Control Issues after surgery: Concerns relate to the preservation of the valve muscle (i.e. external sphincter) which is adjacent to the front of the prostate. When this sphincter is damaged, stress incontinence (either temporary or rarely permanent) may result after surgery. Significant incontinence after prostate cancer surgery creates a major quality of life issue. Approximately 3% of men will have significant bladder control issues following prostate removal. The good news is that this problem is rare and it is treatable. It is my impression, that the current advanced robotic surgical techniques have dramatically decreased the risk of damage to the valve muscle (sphincter) in front of the prostate. Also, should sphincter damage occur (which is rare), the bladder control problem can usually be corrected. Personally, the goal of cure of localized prostate cancer with removal of the prostate, far outweighs the small risk of erectile dysfunction and incontinence (both of which are treatable).

C) Sexual Function after surgery: The nerves that control erection are adjacent to the prostate and these nerves may be damaged at the time of prostate removal, resulting in postoperative impotence. In men that have normal erectile function before radical prostatectomy, approximately 50% will have issues with postoperative erectile dysfunction. Erection problems can be corrected with oral medications, injection therapy, or possibly a penile implant. The ability to ejaculate is permanently lost after prostate removal.

5) WHAT ABOUT HIFU, RADIATION THERAPY OR CRYO-ABLATION OF THE PROSTATE?
As an urologist, I realize that the most important decision one must make is choosing the “best” first-line therapy! In my mind, that therapy should have the best chance of permanent cure. When the cancer is localized to the prostate, the best chance to remove all the prostate cancer from the body is to surgically remove the prostate. Other therapies, such as HIFU, radiation therapy, or cryo-ablation may kill cancer cells for a period of time until the PSA either becomes detectable or starts to rise! At this point, curative therapy is no longer possible. At this early stage of my disease, I have decided to choose the treatment that gives me the best chance for cure with minimal potential side effects, i.e., surgical removal of the prostate gland.

6) CAN WE REALLY “LOCALIZE” THE EXACT LOCATION OF THE CANCER WITHIN THE PROSTATE GLAND BY USING MRI OR ULTRASOUND?
We know that prostate cancer is a “multifocal disease,” meaning that the cancer is usually present in multiple areas of the prostate and rarely localized to one or two “spots” within the prostate gland. It would be great if either MRI or prostate ultrasound could truly localize the cancer within the prostate and define the true extent of the disease. In my case, this is clearly not the case. Two suspicious areas were seen on my prostate MRI. Both areas were biopsied and were positive for prostate cancer. However,
there were multiple other areas of the prostate that looked entirely normal on both MRI and Ultrasound that were biopsy positive Gleason 3+3 prostate cancer. These findings demonstrate to me the fallacy of selecting “localized treatment” to treat only the “cancer areas” of the prostate with HIFU or radiation therapy. When my prostate is removed and the pathologist carefully sections the prostate and examines the entire gland, I am sure the multifocal nature of the cancer will be confirmed. More information to follow after my surgery!

7) WHEN A MAN Chooses “NON-SURGICAL” TREATMENT AS THE PRIMARY TREATMENT FOR LOCALIZED PROSTATE CANCER, CAN “SALVAGE SURGERY” BE PERFORMED LATER WHEN THE PSA STARTS TO RISE?

When PSA starts to rise after radiation therapy, HIFU, or cryotherapy surgical treatment becomes much more risky. All of these therapies can cause significant scarring in and around the prostate gland that may make “salvage” surgical removal extremely difficult. Frequently, “salvage” surgery carries a high risk of damage to adjacent structures such as the rectum, sphincter or valve muscle in front of the prostate, and the nerves adjacent to the prostate that facilitate erection. When damage occurs to these adjacent critical structures, the patient may end up with a colostomy bag, in diapers with severe urinary incontinence day and night, and impotence. Also, because the disease has frequently progressed by the time surgery is considered, the chance for “cure” from the prostate cancer is significantly diminished.

Quality of life issues certainly play a major role in our treatment decision making process. These quality of life issues must be balanced with the best chance for prostate cancer cure. Personally, my main goal is being cured by cancer removal from my body. I can live with minor incontinence issues, erection issues (which can be treated), lack of ejaculation, and other hopefully minor post-operative complications. Many men look back at their initial treatment choice and comment: “If only I knew then what I know now, I would have chosen a different initial treatment.” There are no right or wrong answers that apply to everyone, but I hope that as I embark on this personal journey, that others may benefit from my experience.

PART 2 - PREPARATION FOR SURGERY

The most important part of the preparation for my surgery, was taking the attitude of attacking and curing my prostate cancer at a stage and time when the tumor is potentially curable by removal of the prostate. All preoperative testing (MRI, biopsy tissue analysis, etc.) indicated an excellent chance for cure.

The next most important step is to choose the best surgeon. As a urologic surgeon myself, I know this is usually based upon the trust and communication essential to an ideal patient-physician relationship. The surgeon’s experience and results are obviously very important as well as the availability of the surgeon to handle any questions or complications that may arise after surgery. I was also very concerned about preservation of the nerves that allow erection to occur as well as the sphincter (valve) muscle that allows the man to have good bladder control after the catheter (drainage tube) is removed.

Robotic removal of the prostate is a very technical procedure that requires not only an excellent surgeon, but also significant support from the hospital to run a successful robotic surgery program. Specially trained staff, expensive equipment (i.e. the robot), ongoing maintenance, etc. are essential to a good surgical outcome. I was confident that my choice to have my surgery at Cedars-Sinai was the best option for me. Fortunately, the surgery was completed without complication with preservation of both the erection nerves and the sphincter muscle.

As a practicing surgeon for 39 years, I rarely get to see things from the patient’s perspective. Although I always realized how important the nursing staff is to postoperative patient care on the Urology Floor at the hospital, having a first-hand experience really opened my eyes! The nurses taking care of me after my surgery were amazing. They always responded in a timely fashion, they provided excellent care and never acted in anyway like I was “bothering” them. Again, choosing the right hospital is very important.

The combination of excellent preoperative preparation, good surgical technique, and wonderful postoperative care allowed me to be discharged home at 8am the morning after my surgery. I am fortunate that I live only 10 minutes from the hospital, so I felt very comfortable going home with my drainage catheter in place for the next 6 days. I am also very fortunate to have an excellent caregiver at home who was extremely helpful at each stage of my recovery.

PART 3 - POSTOPERATIVE RECOVERY

Although there was some postoperative abdominal pain, it was not severe. Most of the pain was managed with Tylenol and ibuprofen. I was very concerned that wearing a catheter (tube) to drain the bladder for 6 days following the surgery would be very uncomfortable. To my surprise, the catheter did not bother me at all and was only a minor inconvenience. Each day I would walk more and had less pain.

Six days after my surgery I had a CT cystogram. The is an X-ray study to check the healing at the prostate removal site before the catheter is removed. The bladder is filled with a special dye and a CT scan is performed to make sure that no dye is “leaking” at the site where the urethra is sewn to the opening of the bladder. Fortunately, my CT scan looked good and the catheter was removed. Now I got to urinate and check my bladder control.

After prostate removal for cancer, it usually takes 4-6 weeks to regain full bladder control. Rarely (less than 3%), men may have major bladder control issues that require further treatment. This was my biggest fear! Thankfully, my bladder control has been excellent, without the need for diapers or protective pads. Since the “blockage” from the prostate has been removed, I noticed that my urination stream is much stronger, and I empty my bladder better. It is still too early to know if preservation of my nerves will allow return of my sexual function. Some have suggested that taking a daily Cialis pill and using a vacuum erection device may facilitate successful return of the erection. Since I am only one week after surgery, I will consider these options (if needed) in the near future. Pathology Results: pT2
After the prostate is removed, the pathologist does a very careful sectioning and examination of the gland under the microscope. The surrounding tissues which are also removed are examined as well. Based on the microscopic pattern of the prostate cancer, a final “Gleason Score” is determined by the pathologist at this time.

The pathologist reported that my cancer had not spread outside the prostate, but cancer cells were close to the margin of the prostate capsule. All lymph nodes and surrounding tissues showed no sign of spread. At least 10% of the cancer cells showed a Gleason pattern of 3+4=7 (which is of more concern than the pre-surgical biopsy which showed only 3+3=6). It is very common that the final examination of the prostate after removal shows a greater volume of higher grade cancer. Thus, being lulled into a sense of security based only on the biopsy results may be a big mistake. Also, many areas of the prostate that contained cancer looked totally normal on my preoperative prostate MRI study.

**NEXT STEPS**

Given my pathology results, my PSA should go to zero in the next few months. Going forward, I will check my PSA every 3-6 months on an ongoing basis. No other treatment is planned at this point. Should the PSA become detectable at a later date, further treatment, such as radiation therapy, may be required.

Since I am doing very well with regard to my bladder control, fortunately, this is not an issue for me. Should urinary leakage be a major ongoing problem for some men, effective treatment is available.

It is still too early to know about my sexual function (my surgery was one week ago). I will continue Cialis 5 mg daily (or the generic equivalent) and consider the use of a VED (Vacuum Erection Device) or penile injection therapy later if required. I have also had a frank discussion with my two sons urging them to get a PSA and digital rectal examination annually starting at age 40. They have a strong family history of prostate cancer (both their father and grandfather), so they should have close monitoring at an earlier age.

**SUMMARY:**

The most important message that I want to convey to other men is that if your PSA and/or prostate examination is abnormal, do not delay further evaluation and treatment. For every man with prostate cancer, there is a “window of opportunity” for cure that exists for a finite period of time. Getting treatment (with the goal of cure) within this window is extremely important. Like my four year old grandson told me: “Grandpa had a monster growing in his prostate, and now the monster is gone!” I know I have done (and will do everything in my power) to get the best chance for cure from prostate cancer and I encourage you to do the same!

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**THE CASE AGAINST ACTIVE SURVEILLANCE OR WATCHFUL WAITING FOR PROSTATE CANCER**

Robert Pugach, MD

I write this article with two very interesting perspectives and viewpoints. Firstly, I am an urologist. I treat a lot of prostate cancer. In fact, I have one of the largest prostate cancer practices in the United States. I regularly see patients from all over our state, from other states and from countries throughout the world.

Secondly, I am a prostate cancer survivor. I was diagnosed with cancer late last year. In May of this year, I underwent an urethral sparing HIFU procedure and I am now cancer free.

For many years, there has been a movement to not treat all prostate cancers. The reason is that there are many men whose cancer will never grow to the point where it will metastasize (spread to other parts of the body) or cause death. The movement to not treat has now expanded to not even diagnosing prostate cancer. The result is that there are now potentially millions of men with prostate cancer who either don’t know they have it or are allowing it to grow and spread.

Why has the movement to not treat grown? The answer is, quite simply, that the results of the two traditional treatments – radical surgery or radiation – can have significant, life changing side
effects that negatively impact a person’s daily quality of life. The worst one is permanent urinary leakage that requires constant use of absorbent pads or diapers. This occurs in 35% - 50% of treated men. The second dreaded side effect is erectile dysfunction (ED). The incidence of this varies depending upon the extent of cancer in the prostate but it’s safe to say that at least 50% of men lose the ability to have spontaneous erections. The unfortunate truth is that the newest surgical technique – robotically assisted laparoscopic surgery – has not changed these statistics to a significant degree.

Radiation is available in many forms. The most common ones are Protons, radioactive seeds (brachytherapy), high dose radioactive rods, gamma knife, conformal therapy and IMRT. Most will give a good result for 5-6 years but that’s when the recurrences start. The sad truth is that estimates are - that up to 60% of patients will fail radiation treatment. A good example of this is our governor, Jerry Brown. Governor Brown’s prostate cancer was treated with radiation in 2012. Now, newspapers report his cancer has re-occurred. While reports say he’ll have more radiation, that won’t cure his cancer. Firstly, he cannot have a significant amount of radiation because he’s already received close to the maximum allowable dose. Secondly, why would he have the same treatment that has already failed?

With all of this as background, here are my thoughts about what a patient should do. They are not just words from a doctor; they are words from someone who did what I’m about to say.

We need to understand that prostate cancer is CANCER. It is not necessarily a slow growing tumor located in the prostate. It has the potential to spread locally and obstruct the ureters that carry urine from our kidneys to the bladder. It has the potential to grow into the bladder and cause significant bleeding. It has the potential to metastasize to other areas. The most common site of metastasis is to the bones. These metastases are extremely painful. If the vertebral bodies that surround the spinal cord are affected paralysis can result. Once again, prostate cancer is CANCER!

As with any cancer, early diagnosis is the key to a successful treatment outcome. That’s why PSA testing is so important. That’s how my cancer was diagnosed. My prostate examination was completely normal. So was an MRI of my prostate. But my PSA was abnormal. Actually, the total PSA level was normal at 1.1. But the free PSA fraction (that’s the part of PSA not tied to proteins in your blood stream) was low. It should be more than 25%; mine was 18%. **This is important – always request that your doctor order both a total and free PSA.** If I had not had a free PSA, my prostate cancer would not have been diagnosed and it would still be growing inside me.

The next step was a biopsy. Many people fear biopsies. It’s an uncomfortable procedure. There’s a chance of infection afterwards. But, with a properly done nerve block and proper antibiotic prophylaxis, the chance of pain or infection is minimal. Some men fear that a biopsy may spread cancer. While that’s never been documented after decades of biopsies of prostates and many other parts of our bodies (breast, lung, bone, lymph nodes, etc.), the obvious question is: what is the alternative? We cannot diagnose cancer without a biopsy. So, if you don’t have one, and you have cancer, you are allowing it to grow and spread. That makes no sense.

When my cancer was diagnosed, I wanted it treated in a way that would not leave me with serious side effects. I wanted to be “whole” afterwards. That’s why I chose HIFU – High Intensity Focused Ultrasound. With HIFU, we finally have a treatment that can cure cancer with a markedly reduced potential for the side effects seen with surgery and dramatically fewer recurrences than radiation. Instead of the 35% - 50% incidence of urinary incontinence seen after surgery, there is a 3% chance with HIFU. Instead of a 50% or greater likelihood of ED, HIFU has a 5% incidence.

In the weeks leading up to my treatment, I was surprisingly calm. I can honestly say that I never had a moment of fear, anger, panic or any of the other emotions that many of my patients have shared with me in over 30 years of treating this potentially lethal, terrible disease.

The reason for my attitude was that my cancer was diagnosed at the earliest possible stage. The odds were overwhelmingly likely that it would never return. That meant that I was in charge of my cancer instead of it being in charge of me. I was spared the fear that patients experience when they are diagnosed with advanced prostate cancer that can be extensive or aggressive and, potentially, not curable.

I was also calm because I had the utmost confidence in my doctor. Like me, he had been travelling to other countries for the past 10 years treating patients with HIFU. I knew he was experienced and that I was in good hands.

On Tuesday, May 9, I had my HIFU treatment. I had worked a full day in my office the day before. The anesthesiologist gave me some oxygen to breathe as I drifted off to sleep. My procedure lasted about 3 hours. My HIFU doctor told me that the procedure went perfectly. That evening, I was at a urology dinner meeting enjoying a steak and a glass of wine. Other than some discomfort from a urinary catheter, I had no pain.

I arrived for my HIFU treatment with prostate cancer. Several months later, my PSA is excellent and indicates that I am cancer free. I do not have the side effects of radical surgery. I did not go through weeks of radiation therapy wondering afterwards if I would be in the large group of men with recurrent cancer. I don't wake up each day worrying whether or not I should have treatment for my prostate cancer. I am whole and back to a normal life. In fact, I was back to normal activities 3 days after my procedure.

The key to successful treatment of prostate cancer is to have it diagnosed at its earliest stage so treatments like HIFU are a viable option. I can tell you now, from my personal experience, that it's the key to getting on with your life while leaving you whole.

Pacific Coast Urology Medical Center and Western States HIFU is one of the leading medical practices in the U.S. specializing in diagnosis and treatment of prostate cancer. Call 844-HIFU/DOC (443-8362) or visit: www.pacificcoasturology.com and www.hifuprostatecancermd.com
Please find enclosed my story dealing with prostate cancer for 21 years. It differs from other articles I’ve read in the PAACT magazine over the years, but aligns with PAACT articles by Dr Moyad concerning the importance of diet and exercise in fighting cancer. I’ve enclosed the various test results and analysis of the biopsies I have had over the 21 years. I’ve sent an envelope that was enclosed in the latest issue of the PAACT magazine which contains a membership form and a contribution of $1,050. I’ve been remiss in making the annual contribution for 20 years, even though I had intended to send my annual membership dues every time I received your publication. I appreciate the articles I’ve read over the years and hope that there will be many more years that I’ll have the pleasure of reading your informative articles.

May 15, 1997 changed my life in ways I could never imagine. It was the day I was told that my PSA value (5.54 ng/ml) exceeded the normal upper range and that a biopsy should be performed. I was 53 years old. The biopsy, performed on June 5th, only intensified my anxiety when it revealed that I had an adenocarcinoma of the prostate with a Gleason score of 3+4=7. My Kaiser urologist explained that given my age, I was strongly encouraged to have surgery to remove the prostate since my age and life expectancy meant that, in time, it was likely the cancer would spread beyond the capsule and metastasize. It is the day my anxiety about my life being cut short had never been higher.

The next 6 months were filled with my indecision about what to do. At that time, I found your PAACT magazine which opened my eyes to the range of possible treatment forms and allowed me to begin exploring ways to establish a treatment strategy. During this period of investigation, I discovered the analysis of the biopsies I have had over the 21 years. I’ve previously researched the Partin Tables which indicated, based on the biopsy results that I had a 50-50 chance of cancer being confined within the prostate, which didn’t account for perineural invasion. On consultation, I was informed that not only would I be given a series of proton beam treatments, but would also be given a required series of conventional radiation treatments to kill any cancer cells that were outside the capsule.

On July 11, 1997, I began the Triple Hormone Blockade® (THB), as prescribed by Dr. Bob, a systemic therapy consisting of Lupron®, Proscar® and Casodex®, which I continued for 13 months. On September 12, 1998, I stopped the medications, except that I continued Proscar maintenance. After starting the THB, Dr. Bob subsequently cautioned that THB should only be used once, because “Every time you are treated with another cycle of hormone blockade, your time on hormone blockade lengthens, and your time off hormone blockade shortens. You can recognize this pattern as evolving hormone resistant prostate cancer.” He offered another approach to follow THB, i.e. a “prostate cancer antiangiogenic cocktail,” consisting of Proscar, thalidomide, Celebrex®, Zometa® or Aredia®, and a specific form of shark cartilage. As can be imagined, my anxiety level increased markedly when I read his admonition. My PSA only slowly increased until the time I received the biopsy results. I decided to explore potential alternatives and arranged to meet the head of oncology at the Newport Beach Hoag Memorial Hospital, with the hope he might have some advice I wasn’t getting at Kaiser. He suggested another biopsy to determine what had happened during the 10 years since the last biopsy. On February 18, 2008, I had a prostate ultrasound of my prostate, followed on April 14th by a biopsy being performed, with the results like the first biopsy Gleason Score 3+4=7 with perineural invasion. In addition, an immunohistochemical analysis was performed on the biopsy cores with a result that my P-53 gene, which regulates the cell cycle and, hence, functions as a tumor suppressor, was normal. A tumor suppressor gene slows down cell division, repairs DNA mistakes, or tells cells when to die. I was told by Hoag’s head oncologist that, in his words, he couldn't offer any better advice than, given the results of the biopsy and immunohistochemical analysis results, I had discovered on my own.

Nov 28, 2008 – After researching the National Library of Medicine, I found that an extract of Rhubarb called Emodin
induced androgen sensitive prostate cancer cells to self-destruct (apoptosis). I initially tried 3 g/day of the Emodin extract and the next month the reading of my PSA dropped from 7.6 to 6.8 ng/ml. I increased the dose to 5 g/day, the second month, and the PSA dropped to 4.5 ng/ml. The third month, however, my PSA increased to 8 ng/ml, the fourth month it increased to 9.2 ng/ml, and I ended my Emodin experiment on March 3, 2009.

May 29, 2009 – After researching the National Library of Medicine, I found that Insulin-like Growth Factor (IGF) causes cells to proliferate, and, also, it prevents cell death, which is normally a needed function but not for persons with an active cancer. IGF comes from animal sources and is also produced by our liver to replace damaged cells. Exercise retards IGF production by our liver. Given this information, my wife and I began a whole plant-based diet and a daily hour-long strenuous exercise program. At the time, my PSA results had reached 11.5 ng/ml.

April 1, 2010 – My PSA was 11.4 ng/ml, nearly identical to a year earlier. I felt that starting a whole plant-based diet and exercise regimen and avoiding all forms of animal foods; including eggs, fish, meat and, especially, dairy, which contains the highest levels of IGF; had been and is beneficial. It made me regret having started on any form of treatment instead of focusing on diet and exercise. In fact, in October 2016, Nutritionfacts.org produced a video which demonstrated the power of diet and exercise in controlling the growth of cancer https://nutritionfacts.org/video/how-not-to-die-from-cancer/

May 21, 2010 – With my PSA at 12.6 ng/ml, I started a second round of THB systemic treatment but using a different combination of medications to possibly repeat the previous extended period of off treatment. I used Lupron, ketoconazole and Avodart, since they have been shown to successfully reduce the prostate cancer load. I remained on a whole plant-based diet with the thought that it might help in prolonging the off-treatment period.

April 20, 2011 – I completed the THB systemic treatment but continued Avodart for maintenance.

March 22, 2012 – My PSA was 4.71 ng/ml, I started a third round of THB systemic treatment, using yet a different combination of medications. This time I used Firmagon®, Zytiga®, prednisone, Avodart, and metformin, which dropped my PSA to undetectable levels in 3 months, but I continued the treatment for another 5 months (Nov 8, 2012) and then used Proscar and metformin for maintenance.

December 6, 2013 – My PSA at 7 ng/ml, I started a fourth round of THB+ systemic treatment but using still yet another different combination of medications. This time I used Lupron, Zytiga, prednisone, Avodart, and metformin which dropped my PSA to undetectable levels in 6 months, but I continued the treatment for another 5 months (Nov 5, 2014). I took no subsequent maintenance medication for 9 months.

October 29, 2015 – My PSA at 8.1 ng/ml, I started a combination of Avodart and Proscar for 3 months.

December 18, 2015 – My PSA at 5.4 ng/ml, I started the Gerson Therapy, consisting of very strict dietary requirements, including twelve 8-oz. glasses of vegetable juice/day and 4 coffee enemas/day. During the period on the Gerson Therapy, I used Xandi, (which doesn't require a chemical castration to be effective), starting on July 8, 2016 for 5 months, to increase the chance of success of the Gerson Therapy. I ended the Gerson Therapy on January 12, 2017 with a PSA at 0.5 ng/ml, having realized that the therapy was not preventing an increase in PSA.

The whole plant-based diet, however, has proven to be a life-prolonging decision. My maternal grandmother had a stroke that paralyzed her from the neck down for years. My mother was so frightened that she, too, would have a stroke, that she took blood pressure medicine for over forty years. She, however, had many small strokes called transient ischemic attacks (TIA), instead, where each TIA caused some damage until, before her death at 94 years; she was reduced to the same state as her mother. My two older brothers ignored my pleas to change their diets, subsequently they suffered from diabetes, heart disease (both took statins but still had heart surgeries – one had stents, the other bypass surgery), strokes (one brother mostly lost the use of his right arm and leg), and died from cancer (one brother from metastatic esophageal cancer, the other from red-blood-cell-leukemia).

August 2, 2018 – My PSA at 1.2 ng/ml, I have been using Xandi, Avodart, and Proscar for, at most, 7 days, once a month. My testosterone level has been steady at approximately 100 ng/dl. The low testosterone level has not impeded an active sex life or my use of circuit training exercises. There are no signs of arthritis, diabetes, cardiovascular disease, or osteoporosis. I also have a strongly-held belief that I didn't have any side effects from the combination of hormone-blocking treatments since changing to whole plant-based diet. Also researching in the National Library of Medicine, I discovered that raw garlic and capsaicin (cayenne pepper) have anti-cancer properties. I have been consuming 4 cloves of raw garlic/day, 3 grams of cayenne pepper capsules/day and two large salads/day for lunch and dinner consisting of organic vegetables, i.e., kale, chard, spinach, garlic, mushrooms, red onion, broccoli florets, red cabbage, cauliflower, sweet red pepper, zucchini, walnuts, raisins, flax oil and apple cider vinegar. For the dinner salad, in addition to the other ingredients, I add organic cucumber, cherry tomatoes and avocado. For breakfast, I eat a bowl of oatmeal; at lunch, only a salad; and for dinner, a salad plus a whole plant-based meal that my wife prepares. My weight remains the same as when I was in my 20's at 149 lbs (5’7” in height). I've used this regimen since ending the Gerson Therapy in January 2017. I strongly believe, if I had started the whole plant-based diet and the use of garlic and cayenne pepper, in combination with the described salads, I would not have had to do any form of localized or systemic treatments to address my prostate cancer. In addition, an article published in the 2014 journal Neurobiology of Aging, “Dietary and Lifestyle Guidelines for the Prevention of Alzheimer's Disease,” was: “Vegetables, legumes (beans, peas, and lentils), fruits, and whole grains should replace meats and dairy products as primary staples of the diet.” My wife and I both look forward to a long and healthful future.
Since the advent of PSA screening the rate of prostate cancer being diagnosed has more than doubled, mainly due to the indiscriminate random biopsies. Ironically though, this presents a dilemma for the patients and the clinicians. Although lives are saved by early diagnosis, many men are being diagnosed with “latent” or “insignificant” tumors that do not need treatment. Random biopsy in every man with slightly elevated PSA causes a high incidence of over-diagnosis and over-treatment. (1-3). As a result, the prevailing practice of PSA screening and subsequent biopsy has been called into question by the United States Preventive Task Force (4) which recommends that PSA testing only be offered after a careful discussion of the risks and benefits.

More precise ultrasound evaluation with color-Doppler, Tissue harmonic, and Elastography combined with targeted biopsy can provide a possible solution to the ongoing controversy about PSA screening. However, this type of enhanced imaging followed by targeted biopsy is only available in limited centers around the United States. This paper will expound the many advantages of using high-resolution color-Doppler ultrasound for the diagnosis and staging of prostate cancer.

PSA, GLAND VOLUME AND DIAGNOSIS
Absolute cut-off levels for PSA are too arbitrary to apply to all men. The prostate gland volume (and therefore the PSA) changes as men age. – I use a serum PSA threshold of >2.5 ng/mL as a trigger for a concern. However, in men at high-risk (family history of prostate cancer or African American) the cut-off point would be PSA > 2.0. I also use a PSA increase of 0.75 ng/mL in a year as an indication for further investigation. Once the prostate size is calculated the patient’s serum PSA takes on even greater meaning. If the patient’s serum PSA (blood test PSA) is greater than the “predicted” PSA (gland volume x 0.12), he is at high-risk for cancer.

ULTRASOUND ABNORMALITY AND PROPER TARGETED BIOPSY
Prostate cancer tissue is histologically different from normal prostate tissue. The cancer tissue shows a loss of glandular architecture, more compact in tissue density, and an increase of the microvascular density (hypervascularity). This difference can be visualized by ultrasound as a various degree of hypoechoic lesion (dark spot on gray scale ultrasound). Hypervascularity (increased blood flow) can only be appreciated with “Color” Doppler or contrast-enhanced Doppler evaluation. About 15% of cancers are not seen on gray scale ultrasound and are only visible on color-Doppler ultrasound.

High-resolution color-Doppler ultrasound can identify tumors greater than 5mm in size. The lesions visible on ultrasound are mostly clinically significant cancers. Clinically significant cancers are often hypervascular on the color-Doppler and typically have high Gleason scores (5). Targeted biopsy of such lesions can diagnose clinically significant cancer by taking fewer biopsy cores while reducing the chance of detecting clinically insignificant tumors.

UNDERSTANDING THE PROSTATE ANATOMY AND THE SITES OF ANATOMIC WEAK
Depending on tumor architecture, the degree of hypoechogenecity (darkness on gray scale ultrasound) ranges from obvious (nodular) to subtle (infiltrative) changes. It is incumbent upon the physician performing the examination to be familiar with the zonal anatomy and morphologic presentation of prostate cancer.

Cancers in the outer gland (peripheral zone and central zone) and inner gland (transition zone) have different sonographic appearances and biologic behavior, and our threshold that defines whether to biopsy varies depending on the lesion size, location and amount of excess PSA.

Outer gland (Peripheral Zone) cancers have a greater propensity than inner gland cancers for extracapsular spread because they can escape easily through the sites of anatomic weakness (entry of neurovascular bundle branches (NVB), seminal vesicles (SV), and apex). Fortunately, these tumors are easy to visualize because the background tissue is more homogeneous than that of inner gland tissue.

Most outer gland cancers develop in the lateral section of the prostate near the entrance of the neurovascular bundles. When targeting outer gland lesions, taking a sample from the lesion in the prostate and one from the adjacent neurovascular bundle enable us to assess the tumor extension outside the prostate (Extra Capsular Extension).

When outer gland tumors extend toward the midline, we take tissue samples from the confluence of seminal vesicle and/or trapezoid space of the apex. Hypoechoic lesions of the outer gland should be pursued vigorously because they can escape when they are relatively small. (See Figures 1 & 2)

Inner gland (Transition Zone) cancer detection is more difficult than outer gland tumors. They are usually poorly defined hypoechoic lesions. Cancers that are in the center portion of the prostate, the anterior apex and the bladder neck need to be watched carefully for possible extra-prostatic spread. Vascular evaluation with Color-Doppler is essential because most tumors larger than 1.0 cc have relatively abundant vascularity. Often, the increased blood flow may be the only clue for the presence of cancer. Recently developed Elastography can help to identify the inner gland tumor by measuring the tissue stiffness. (Figure 3)
Staging Biopsy Technique
The biopsy protocol should include taking one sample from the center of the lesion and additional samples from the routes of possible tumor escape based on the tumor location. Random biopsies only harvest samples from the prostate. Therefore, it cannot provide the staging information of the cancer, whether it is contained in the prostate or not. When a biopsy core is obtained, the rectal end of the tissue core is stained with blue ink before sending it to the laboratory. This helps the pathologist orientates the biopsy core in relation to the front and back of the prostate gland and evaluates the closeness of the cancer to the prostate capsule and the rectum.

INFORMATION PROVIDED BY COLOR DOPPLER AND TARGETED BIOPSY
- Where is the exact location of the tumor? Is it an inner gland or outer gland tumor? Is it in the base, mid or apical portion of the prostate?
- What is the tumor diameter in millimeters? Does the size of the lesion detected by imaging coincide with the length of cancer reported in the biopsy report by the pathologist?
- What is the Gleason grade? (If it is 7, is it 3+4 or 4+3, and the percentage of 4?)
- Is the tumor close to the neurovascular bundle (NVB) or seminal vesicle (SV), or the easily spread areas of the tumor outside of the gland, such as the apex tumor with external sphincter (ES) invasion?
- Is the tumor contained in the prostate or not (Stage T1 -2 or T3-4)?
- Is the tumor size or vascularity on sequential scanning increasing over time for men who are on active surveillance?

This information will help the physician and patients choose appropriately if further staging studies are needed and decide on the best treatment options.
STATE-OF-THE-ART ULTRASOUND EQUIPMENT
It is necessary to use state-of-the-art ultrasound equipment for an early detection and accurate staging biopsy. Power color-Doppler ultrasound demonstrates the blood flow patterns inside of the prostate. Usually, cancer tissue shows a higher blood flow (tumor neo-vascularity) than normal tissue. Color Doppler improves the detection of the cancer and the estimation of the cancer size.

Tissue Harmonic technology improves spatial resolution to permit visualization of smaller objects and improve contrast resolution to discern very subtle differences in grayscale. This is different from conventional ultrasound imaging, which sends out a burst of ultrasound and listens for that burst to back off structures in the body (an echo that is usually weak and distorted). In Tissue Harmonic technology, instead of listening of the same sound burst to return in the echo, it listens only for a sound burst at twice the transmitted frequency.

Another new technology is Elastography. Ultrasound Elastography quantifies the stiffness of tissue during the manual or mechanical compression of the gland by the transducer (tumors have increased stiffness compared to normal background tissue). Target biopsy of an area of abnormal stiffness has been shown to improve cancer detection compared to the systemic biopsy with fewer tissue cores taken (6).

Contrast-Enhanced Ultrasound is another exciting technology that is in use extensively in Europe and Asia. The contrast agents are composed of tiny bubbles of injectable gas contained within a supporting shell. The gas is a strong echoic material and the Doppler signal is greatly enhanced, particularly within areas of cancer. Contrast enhanced color-Doppler imaging will definitely improve the sensitivity of cancer detection and cancer extent. Unfortunately, it still waits for FDA approval here in the United States.

PROSTATE MRI AND ULTRASOUND FUSION AND BIOPSY.
Good ultrasound evaluation with staging (targeted and strategic) biopsy may eliminate an uncomfortable and costly MRI study (that is still an imaging study without tissue confirmation). However, an MRI study can be a good complement to TRUS in selective cases.

Recently, multiparametric magnetic resonance (MRI) imaging and ultrasound fusion biopsy technique has been developed. The MR images obtained before the biopsy procedure are superimposed to the ultrasound images obtained at a different setting. This fusion allows targeting suspicious lesions seen on the MRI for biopsy under real-time ultrasound. As an alternative, the ultrasound experts can cognitively fuse the MRI reported areas of abnormality on the real time ultrasound image for a target biopsy (cognitive fusion biopsy). Studies have shown that clinically significant tumors can be diagnosed this way in patients who had prior negative ultrasound biopsies (7).

THE ROLE OF ULTRASOUND-GUIDED TARGETED AND STAGING BIOPSY.
- Identification of the lesions enables a proper targeted biopsy rather than a blind, random systemic biopsy (Take less numbers of tissue cores and decrease the chance of complications).
- Increase the yield in cancer detection and minimize the diagnosis of “latent carcinoma.”
- Provide an accurate cancer location, volume (size), neovascularity and stage.
- Based on our published data, 26% of the stage T1-T2 (tumor contained within the prostate) cancers defined by systemic biopsy were upstaged to T3-T4 (non-confined) by our staging biopsy technique (8).
- The Gleason grade was higher in staging biopsy (8-9).
- The cancer invasion in the core (by %) was higher (8-9).
- The tumor size can be measured precisely and it can be monitored objectively along with the tumor vascularity changes. It is extremely important in an active surveillance management setting.
- Diagnosing unsuspected extracapsular extension of the cancer objectifies the prognosis and the choice of definitive treatment.

Conclusion
Recently diagnosed cancer patients are faced with the enormous task of understanding the disease and choosing the most appropriate treatment. The cancer characteristics and staging information based on blind systemic biopsy are often “guessimations.” Today’s patients seek answers through patient advocacy groups, internet, and through scientific literature. When a patient consults with a “specialist,” he quickly surmises their uncertainty and discovers to his consternation that the ball is in his court and he alone must make the elusive three-point shot.

Using of state-of-the-art ultrasound with color-Doppler, Tissue Harmonic and Elastography helps resolve the uncertainty of whether a cancer is organ-confined. Then, and only then, can a clinical decision be made that is based on accurate staging information.

References
Whenever men suddenly begin to have to pee all night long – 3-4-5-6 times a night, you almost always think about the prostate. And this is usually the cause of the problem. But sometimes, especially if the onset of peeing too often at night (nocturnal polyuria) is sudden, the problem may be a simple bladder infection. If this is you, there is a simple resolution – Digestive and Urinary Tonic (DUT).

If you suddenly have to get up all night long, perform this simple test and treatment. Drink two ounces of DUT on an empty stomach, followed by another two ounces on an empty stomach an hour later. Do the same thing later in the day, and use four more doses the following day. If you acquired a simple bladder infection, you will be amazed at how it just clears up, and you can get back to restful, uninterrupted sleep. If you have had a urine test and discovered bacteria, you can follow your treatment with another urine test to see if you have killed all the bacteria.

Although we have not always been able to differentiate between a bladder and prostate infection, we are finding that men with an apparent acute prostate infection can also get well quickly using this same treatment. These would be men who do not have an apparent bladder infection (no bacteria in the urine), but have the same symptoms. This most often indicates an acute prostate infection. Since DUT is effective, safe, and inexpensive no matter where your urinary tract infection resides, you should always treat for two days using my protocol before you start on antibiotics.

CYSTITIS AND UTIs IN WOMEN
This same treatment should be used with all women who suffer through the medically-incurable cases of cystitis, bladder infections, and/or UTIs. This should be done while they are on my protocol for women with these problems. This protocol can be found in my article “Cystitis and UTIs” on page 133 of your free book that came with your new subscription or renewal. This protocol can be a Godsend, ending years or lifelong urinary tract infections and problems. You can use the DUT treatment twice daily for a week alongside the protocol. After that, simply stay on the protocol of Arginex (6 daily), Cataplex E (6 daily), Cyruta-Plus (9 daily), Blue Ice Fermented Cod Liver Oil (3-4 daily) for as long as it takes to finally beat this miserable, dangerous, life-altering medically-incurable condition.

CHRONIC ENLARGED PROSTATE IN MEN
Men, if your urinary problems are caused by an enlarged prostate, remember, do not get talked into getting a TURP operation. This is an old, outdated, dangerous, and debilitating surgery that should be relegated to the medical scrap heap. Instead, try to beat, your problem with my protocol. It is in my article “Benign Prostatic Hyperplasia (BPH)” on page 130 of the free book that came with your subscription. It consists of Cataplex F (4-6 daily), Palmettoplex (3-4 daily), and Prostate PMG (3 daily).

Use this protocol for six months to see if you can beat BPH. You can use DUT therapy twice daily for the first week of your treatment period. If your prostate is just too large, you can have a Green Light Laser surgical procedure. This is a 30-minute outpatient procedure where a tiny laser is used to open any blockage in your urethra where it passes through your prostate. The expert in this field is Mahmood Hai, MD, in Detroit, Michigan. He has trained just about all American urologists in Green Light Laser surgery. Since this procedure could be dangerous when performed by someone who doesn’t not have lots of experience, if it were me, I would make an appointment and travel to Detroit to have it done by the expert. His number for appointments is 734-595-1166.

In all cases, always try to resolve this problem yourself using my protocols. Even Green Light Laser treatment is still surgery. And problems can occur even when your surgery is being performed by the best in the business. Most men with moderate BPH can get by using my protocol. DUT for a week can help with sudden-onset infection or worsening of symptoms. Otherwise, just use the nutritional protocol for up to a year to see if you can beat BPH naturally. Despite the glitzy ads you may see or hear about products that are more potent, that contain “100x the dose of the active ingredient” in other products, and that are “pure, pharmaceutical grade herbs,” nothing works better than my protocol.
INTRODUCTION
Prostate cancer is the second leading cause of cancer-related death among men in the United States (1). Clinical suspicion of prostate cancer may arise when a patient has an elevated prostate-specific antigen (PSA) level or abnormal digital rectal exam (DRE). Such patients are typically offered a blind, random but systematic transrectal ultrasonography-guided biopsy (TRUS-guided biopsy) of the prostate. The prostate biopsy not only determines the presence or absence of cancer, but also determines its Gleason score, which is the best current measure of prostate cancer aggressiveness. The Gleason score is a major determinant of the course of therapy that is recommended to the patient.

WHAT IS THE STANDARD BIOPSY?
Systematic TRUS-guided biopsy is currently the standard biopsy procedure for patients suspected to have prostate cancer. This procedure is commonly conducted in the urologist’s office. The patient lies on the exam room table and an ultrasound probe is inserted into his rectum. The urologist uses images from the ultrasound probe to guide the biopsy needle through the rectal wall and obtain 10-12 sample biopsy ‘cores’ from the prostate. Essentially, this approach is blind to the location of the cancer, and is prone to substantial undersampling of the prostate, and is associated with underdiagnosis of higher grade, clinically significant prostate cancer (2) and over-detection of low grade, clinically insignificant cancers that have virtually no risk of metastasis.

The standard transrectal US-guided approach is particularly poor at detecting cancers in the front and apical areas of the prostate. Accurate attribution of cancer risk is critical, however, a major limitation of TRUS-guided biopsy is that up to 40% of cases classified at the time of biopsy as low grade are found to be of higher grade disease after prostatectomy (3). Detection of low grade, clinically insignificant cancers and uncertainty of the biopsy results can lead to increased patient anxiety, compelling patients to elect unnecessary aggressive therapies with associated side effects, morbidity, decreased quality of life, and increased cost of care (4) (5) (6) (7).

A BETTER OPTION
Is there a better option or pathway that can bring the prostate cancer diagnosis algorithm into the 21st century? There is a clear need for an alternate test for prostate cancer that would not only be minimally invasive, but identify a higher proportion of men with high grade cancer who would benefit from treatment, yet minimize identification of those with low grade cancer in order to prevent overtreatment. Targeted biopsy of the prostate by using prebiopsy magnetic resonance imaging (MRI-targeted biopsy) appears to achieve these goals better than the traditional standard TRUS-guided biopsy.

In the past, prostate MRI was performed mainly for staging of known cases of intermediate-to-high risk prostate cancer (8). However, advances in MRI technology, increasing research, and the use of the Prostate Imaging Reporting and Data System (PI-RADS™) by radiologists have all contributed to the growing role of prebiopsy prostate MRI in cancer detection, biopsy guidance and risk assessment (9).

Prebiopsy prostate MRI and MRI-targeted biopsies tend to increase the detection of clinically significant prostate cancer while reducing the detection of inconsequential tumors (10) (11) (12). Thus, prebiopsy MRI could be used as triage to avoid a biopsy if the results were negative (11), while positive results could be used for targeting during prostate biopsy. Additionally, MRI-targeted biopsies have been shown to reduce upgrading of cancers at surgery, improving confidence in the biopsy results (13) (14).

The use of prebiopsy MRI has significantly increased in the U.S. per a recent study in the Medicare population (15). This study showed that in male Medicare patients’ prebiopsy MRI use increased from 0.1% in 2010 to 10.3% in 2015, a 10-fold growth. And in 2016, the American Urological Association (AUA) and the Society of Abdominal Radiology (SAR), in a joint statement, supported the role of prebiopsy prostate MRI and MRI-targeted biopsy in men with a prior negative prostate biopsy and persistent suspicion for prostate cancer (16).

WHAT IS PI-RADS™
In the not so distant past, the assessment of lesions noted on prostate MRI by radiologists posed a problem. These assessments were mainly subjective and not standardized across practices or institutions. This problem has now been largely addressed by the PI-RADS (Prostate Imaging Reporting and Data System) classification system (17) (18). Now on version 2 (PI-RADS v.2), this system standardized the challenge of reporting of prostate MRIs among radiologists around the world, although the evaluation still remains subjective. This system gives a specific score (1-5) to each lesion seen by a radiologist on a prostate MRI. A score of 1 or 2 means there is a very low risk that clinically significant cancer is present, and a score of 4 or 5 means there is a very high suspicion of clinically significant cancer. This score provides a highly standardized way to understand a patient’s risk, and has significantly contributed to the growth and usefulness of prebiopsy prostate MRI.

MRI-TARGETED BIOPSY: TYPES, DIFFERENCES AND PROCEDURE
MRI-targeted biopsy refers to any prostate biopsy in which a prebiopsy MRI is used to locate the biopsy target, whereas
MRI-guided biopsy assumes the use of MR imaging for needle guidance at the time of biopsy (19).

In all three types of MRI-targeted biopsies described below, a high-quality multiparametric MRI (MP-MRI) of the prostate is obtained prior to the biopsy. A radiologist locates suspicious targets on the MRI and assigns a score to them based on the PI-RADS version 2 (17) (18).

Figure 1: 50 year old patient with PSA of 4.8 ng/mL. Multi-parametric MRI showed a PI-RADS score 5 lesion. Apparent Diffusion coefficient (ADC) maps (~1.7 cm in size) and T2-weighted MRI (red arrows) and shows some early enhancement on dynamic contrast enhanced (DCE) MRI. A computer-aided diagnosis tool based on quantitative MRI (20) (21) shows risk associated, which predicts a cancerous lesion in the right posterior peripheral zone. The lesion was found to be a clinically significant (Gleason score 4+3) cancer on histology section after radical prostatectomy.

In-bore MRI-targeted prostate biopsy (aka MRI-guided biopsy) – this involves obtaining tissue samples under direct MRI guidance while the patient is in the MRI scanner, and allows the operator to see the target lesion and the biopsy needle at the same time. The patient is placed in the prone position (back facing up) on the MRI table. A disposable rectal needle sleeve, lubricated with lidocaine, is inserted into the patient’s rectum and MR images are obtained to make sure it is positioned appropriately. After adjustments are made to confirm the needle sleeve is in the optimal position, an MRI-compatible biopsy needle is inserted through this to obtain a sample. Although this method is most commonly done transrectally, transperineal and transgluteal approaches can also be used, especially in patients with limited or no rectal access due to previous surgery or radiation therapy.

The main advantage of MRI-guided biopsy compared with other MRI-targeted biopsies is improved targeting of the lesion and more accurate documentation of the location of the biopsied lesion. This is particularly valuable for small lesions. Additionally, because only the target lesion is biopsied rather than the entire prostate, fewer cores are obtained, which may minimize the risk of complications. Transperineal MRI-guided biopsy of the prostate can be the only approach for patients without a rectum. The transperineal route also has much lower rates of infection compared with transrectal (22).

Compared to systematic TRUS-guided biopsies, MRI-guided biopsies allow detection of more clinically significant cancer with fewer cores in patients with elevated PSA (23). Another important advantage of MRI-guided biopsy is that the determination of the lesion’s Gleason grade by this method is found to highly represent true tumor grade, exactly matching prostatectomy Gleason score in 88% of the cases (13) (24). In contrast, Gleason scores based on TRUS-guided biopsy undergrade up to 40% of tumors when compared with prostatectomy (3). Reported complications from MRI-guided biopsy are rare and usually mild, such as self-limiting hematuria, rectal bleeding and urinary tract infection (23) (25).

However, MRI-guided biopsy is not widely available. The procedure takes a long duration of time, about 30-45 minutes, and requires special MRI compatible equipment, there is no real-time feedback, and there is a steep learning curve for the operator. Additionally, this method is not compatible with urologists’ current workflow because the biopsy is performed in the MR imaging unit of the radiology department rather than an office setting.

Cognitive MRI-targeted Biopsy – Essentially, in this method the urologist performing the TRUS-guided biopsy reviews in detail the location of a target lesion identified by an MRI done prior to the biopsy. He then visually translates this location on the MRI to the anatomic site in the prostate gland to be targeted by TRUS-guided biopsy. Existing studies on the results of cognitive MRI-targeted biopsy suggest it is superior to systematic TRUS-guided prostate biopsy and potentially comparable to other fusion methods (18) (26) (27). Furthermore, there is no need for additional hardware or software.

Transrectal US-MRI Fusion Biopsy (TRUS-MRI fusion biopsy) – This method is becoming a highly utilized method for targeted biopsy of the prostate. TRUS-MRI fusion biopsy combines the superior lesion detection of MRI with the real-time capabilities of transrectal ultrasound (US). This technique
is performed by aligning (fusing) a prebiopsy MRI with real-time transrectal US to accurately direct the biopsy needle under US guidance. This allows the operator to target the lesions identified by MRI, but in an office setting outside the MRI scanner, which is the main advantage of this kind of MRI-targeted biopsy. Additionally, in a prospective study by Arsov, et al. combined systematic TRUS-MRI fusion-targeted biopsies were shown to require significantly less time (28 minutes vs. 42 minutes; \( P<.001 \)) and significantly less reported procedural pain than MRI-guided biopsies (28). Another advantage of this method is the fact that it can be combined with random 12-core systematic biopsies.

In 2015, a review paper published in European Urology compared results of MRI-TRUS fusion targeted biopsy with standard TRUS-guided biopsy (29). This review included papers published from 15 studies, totaling 2293 men who had either never had a biopsy, had previous negative TRUS biopsies, or previous positive TRUS biopsies. Across all studies, the median detection rate of higher risk clinically significant cancer was 23.6% for standard biopsy compared with 33% for MRI-TRUS fusion targeted biopsy. Not only was the fusion biopsy detection rate superior, it was achieved using far fewer biopsy cores (median 9.2 vs. 37.1) compared with standard biopsy, thus highlighting the efficiency of the MRI-US fusion targeted approach.

Several systems are now available that are designed specifically to fuse MRI and transrectal US for prostate biopsy, including, but not limited to, UroNav (Invivo), and Artemis (Eigen, Grass Valley, Calif).

**QUANTITATIVE APPROACH**

Computer-aided diagnosis and quantitative MRI tools (20) (21), where data from MP-MRI further improves the diagnosis of prostate cancer, have recently been investigated. In fact, our research group at the University of Chicago has developed and is currently testing, a novel model for automated computer-aided diagnosis of prostate cancer using MP-MRI. These methods are more sensitive to subtle changes, and their role might be even more critical in focal therapy planning, especially in determining the optimal treatment option by differentiating between clinically significant and non-significant cancers, and in determining the tumor volume to reduce the number of recurrences due to incomplete ablation of cancer tissue. Figure 1 shows a representative example of computer-aided diagnosis based on quantitative MRI.

**WHO SHOULD HAVE AN MR-TARGETED BIOPSY**

Any patient for whom a standard systematic TRUS-guided prostate biopsy would be indicated could also benefit from a MRI-targeted prostate biopsy. These would include patients suspected of having prostate cancer due to elevated PSA or an abnormal DRE, patients with elevated PSA and negative initial TRUS-guided biopsy, as well as patients with a known prostate cancer diagnosis, who may be undergoing biopsy for treatment planning, guidance of active surveillance (30), or detection of local recurrence after therapy. Which type of MRI-targeted biopsy is right for you? All three methods of MRI-targeted biopsy (cognitive, in-bore, and TRUS-MRI fusion biopsy) outperform standard systematic TRUS-guided biopsy in various measures of cancer detection. However, there is far less data available on how these methods compare with one another. Each has its strengths and weaknesses, but the ultimate decision on which method will achieve the best results for the patient likely rests on practical issues such as cost and ease of workflow.

**THE PRECISION TRIAL**

This PRECISION clinical trial, an international, multicenter, randomized clinical trial conducted in 11 countries, and partly funded by the NIH, aimed to evaluate whether prebiopsy MRI and MRI-targeted biopsy was as efficient as standard TRUS-guided biopsy in the detection of clinically significant prostate cancer in men suspected to have prostate cancer who had not previously undergone biopsy (31). The study enrolled 500 men who were randomly assigned to either the MRI group (with or without MRI-targeted biopsy) or the standard biopsy group. Clinically significant cancer was detected in 38% of men in the MRI-targeted biopsy group, as compared to 26% in the standard-biopsy group. Results, published in May 2018 in the New England Journal of Medicine, not only concluded that prebiopsy MRI was not only non-inferior to the standard TRUS-guided biopsy, but was, in fact, superior. Additionally fewer clinically insignificant cancers were identified in the MRI-targeted biopsy group than in the standard-biopsy group (9% vs 22%), and a greater percentage of cores were positive for cancer in the MRI-targeted group than in the standard-biopsy group (44% vs. 18%). Although both procedures were associated with similar immediate post-procedure levels of pain and discomfort, at 30 days the MRI-targeted group reported fewer complications than the standard biopsy group.

It is interesting to note that most of the investigators in this trial had modest experience with MRI-targeted biopsy. There is a low risk that clinically significant cancer may have been missed in men in this trial who did not undergo biopsy, but because systematic TRUS-guided biopsy was avoided, clinically insignificant cancer was detected in fewer men, which may have a substantial benefit in reducing the overtreatment of men with prostate cancer.

This trial concluded that the use of risk assessment with MRI before biopsy and MRI-targeted biopsy was superior to standard TRUS-guided biopsy in men at risk for prostate cancer who had not previously undergone biopsy.

**PROMIS CLINICAL TRIAL**

The PROMIS clinical trial studied whether a pathway with MR imaging used as a triage test may allow men to avoid unnecessary TRUS-guided biopsy and improve diagnostic accuracy (11). This prospective, multicenter, confirmatory study tested the accuracy of MP-MRI and TRUS-guided biopsy against a third test called TPM-biopsy (template prostate mapping biopsy). TPM-biopsy samples the entire prostate and is highly accurate as it samples the prostate every 5mm. The
trial enrolled 740 men with a suspicion of prostate cancer, but no prior biopsy. Of these, 576 underwent MP-MRI followed by both TRUS-guided and TPM-biopsy. Results, published in 2017, showed that using MP-MRI to triage men might allow 27% of patients to avoid a primary biopsy, and diagnosis of 5% fewer clinically insignificant cancers. MP-MRI, used as a triage test before first prostate biopsy, could reduce unnecessary biopsies, over-diagnosis of clinically insignificant cancer and improve detection of clinically significant cancer. This study provides a strong argument for recommending prebiopsy MRI as a triage test to all men with elevated PSA.

CHALLENGES

Despite the advantages, patients are not routinely offered prebiopsy MRIs in small community practices. The reasons are multifold, but barriers include access to advanced MRI technology and MRI-targeted biopsy capabilities, lack of expertise of local radiologists, urologist acceptance of the procedure and challenges to reimbursement of costs for both the patient and clinic. All these factors have limited the procedure to expert imaging centers, mostly associated with large academic institutions.

The paradigm is steadily changing, however reimbursement remains a problem. A recent paper published in the Journal of the American College of Radiology (32) assessed the current state of private insurance coverage nationwide for prostate MRI. This assessment revealed that prostate MRI coverage among private payers is highly variable and restrictive, fails to recognize the many clinical scenarios, and often does not reflect current clinical practices. Only 11.1% of payers cover prostate MRI in patients who are suspected to have prostate cancer but have not had a previous biopsy. The remaining 88.9% require a prior negative biopsy.

Although overall use of prebiopsy MRIs and MRI-targeted biopsies has increased, substantial racial and geographic variations still exist (15) likely due to difficulties in access. It is concerning that use in African American men is significantly lower than in Caucasian men, especially given the higher incidence, aggressiveness and mortality associated with prostate cancer in African American men (33). Pronounced geographic variations exist between states, likely due to the early development of prostate MRI at a limited number of academic medical centers. Use is much greater in the Northeast than in the Midwest.

CONCLUSION

In men suspected of having prostate cancer, accurate attribution of cancer risk is critical to avoid overtreatment and its detrimental impact, as well as undertreatment and the potential of missing clinically significant disease. The growing role of prebiopsy MRI and MRI-targeted biopsy in the treatment of men with known or suspected prostate cancer is now well recognized (34), and has grown 10 fold from 2010 to 2015.

A diagnostic pathway which includes a triage prebiopsy MRI, followed by an MRI-targeted biopsy has been noted to be superior to the current approach of standard random TRUS-guided biopsy. Not only is this approach minimally invasive with few side effects, it identifies more high grade clinically significant cancers using fewer cores than standard biopsy, while minimizing the identification of low grade tumors, thus preventing overtreatment. Additionally, there is more confidence in the results as fewer cancers are upgraded following prostatectomy.

A variety of methods have been developed for MRI-targeted biopsy, including in-bore, cognitive MRI-targeted biopsy, and TRUS-MRI fusion biopsy. However, a number of limitations to its widespread use remain including increased procedure time, high cost, expertise of the radiologist and urologist, incorporation into the current workflow, and reimbursement of costs from insurance. Overall, private insurance coverage has not kept pace with evolving clinical practice, creating challenges and uncertainty for patients, radiologists and referring physicians seeking access to prebiopsy MRI and MR-targeted biopsies.

Despite the AUAs and SARs supporting statement, ultimately, a multi-pronged approach will be required to optimize the use of prebiopsy prostate MRI as well as minimize racial and geographic disparities. Its success and incorporation of the technology into small and community practices is dependent on many factors including but not limited to educational efforts, radiologist training, software accuracy, and urologist ability, skill and cooperation.

In conclusion, in this age of increasingly personalized healthcare delivery, there remains little reason to follow the standard random TRUS-guided biopsy pathway only approach. Ultimately, it is anticipated that MRI-targeted prostate biopsy, with its many proven advantages, will become established as the preferred approach of many, if not all, men suspected of having prostate cancer.

REFERENCES

Over the last few years, there has been tremendous activity in the area of molecular imaging for prostate cancer. Just about every day we have colleagues asking about the various PET/CT imaging tests - what is available? How do they compare? What are the parameters for successful imaging?

CONVENTIONAL TYPES OF IMAGING

Ultrasound has a role in doing prostate biopsies and the placement of radioactive seeds in primary prostate cancer. It is also useful for evaluating local recurrence after surgery in patients with an increasing PSA. CT Scans are commonly used for staging men with newly-diagnosed disease, and looking for enlarged lymph nodes in the pelvis. However, it is inaccurate for detecting cancer in the lymph nodes. If cancer is present in the nodes, a CT scan only finds it 35% of the time. Prostate MRI is used for staging, biopsy guidance, surgical planning, radiation planning, and restaging after PSA relapse. Multi-parametric MRI is being found to be very helpful for detection and local staging of untreated prostate cancer, to reveal features such as extra-capsular extension or seminal vesicle invasion, thus helping to confirm local (organ confined) disease. Additionally, multi-parametric MRI is emerging as a useful imaging tool for following changes in the prostate gland for men on active surveillance.

TECHNETIUM-MDP

Prostate cancer frequently metastasizes to the bone, therefore the mainstay of imaging for advanced prostate cancer has been technetium-labeled (Tc99) biphosphonate bone scintigraphy. Tc99 bone scans are used for initial staging of intermediate-to-high-risk disease and for restaging after PSA relapse. Unfortunately, it is not sensitive enough to detect small skeletal metastases. False positives are common due to interference from non-cancerous arthritic changes and/or prior trauma.
SODIUM FLUORIDE (NAF) PET/CT SCANS

NaF PET/CT is similar to standard bone scans, but uses PET imaging which is significantly more sensitive and specific than standard Tc99 (Technetium) bone scans. In the PCa recurrent setting, bone lesions as small as 2-3 mm with PSA values < 1.0 can be detected. Unlike Tc99m bone scan, arthritic changes and prior trauma are much less problematic with NaF PET/CT. Another advantage of NaF PET is the shorter scan time, typically less than one hour, compared to 4 hours for Tc99.

11C CHOLINE AND ACETATE PET/CT SCANS

Prostate cancer cells rely on fatty acid metabolism as their energy source. 11C-choline and 11C-acetate are lipid metabolism PET agents and appear useful for detecting recurrent disease after a PSA relapse. 11C-choline has been approved for use at Mayo Clinic while 11C-acetate remains under investigation for this purpose as is not yet FDA approved. Small direct published comparison studies of 11C-acetate and 11C-choline have revealed no clear clinical differences between these agents (Nuklearmedizin. 2003 Feb;42(1):25-30 , Eur J Nucl Med Mol Imaging. 2013 Jul;40 Suppl 1:S18-27).

In a large-scale study of 11C-acetate PET/CT imaging in 887 patients with relapsing PSA (at Phoenix Molecular Imaging), the overall detection rate of recurrent prostate cancer was 88% with a PPV of 91%. A PSA threshold of 1.09 ng/mL was established for optimal imaging. However, if the PSA was less than 1.0 ng/mL and the PSA doubling rate was brisk (less than 3 months), the detection rate was better than 90%. (Am J Nucl Med Mol Imaging 2017;7(1):1-11) The reported detection rate for 11C-choline generally ranges from 42-82% with a PSA threshold of 2.0 recommended for optimal imaging. At least one study in 102 patients has also demonstrated a significant influence of the PSA doubling time on 11C-choline with a 93% detection rate noted in a PSA range of 0.67-1.1 ng/mL if the PSA doubling rate was under seven months.

11C has a short half-life of 20 minutes, so 11C-Acetate and Choline are available only at sites with cyclotrons capable of producing this agent alongside of the imaging facility. This therefore limits its availability to specialized centers.

AXUMIN PET/CT SCANNING (18F-FACBC)

Amino acids, such as leucine, methionine, and glutamine, are absorbed into the cancer cells because of the increased metabolic demands of the growing cancer cells. The FDA recently approved Axumin (Fluciclovine or 18F-FACBC), which is a fluorine-18 radiolabeled synthetic leucine amino acid.

CLINICAL TRIALS OF AXUMIN

Scans were performed in 105 patients. The results were checked for accuracy with biopsy or surgery after the scan. Three independent reviewers analyzed the scan results. For men who had biopsy confirmation of cancer in the prostate bed, the true-positive rate ranged from 49-58%. The false positive rates ranged from 16-30%. For patients who had positive biopsies outside of the prostate bed, the results were much better, with a true-positive rate of 88-93% and a false-positive rate of only 7-8%. Optimal detection rates were seen when the PSA was above 1.78 ng/mL.
In another clinical trial of 96 patients, a comparison was made between Axumin and 11C-choline PET. The scans showed equivalent findings 61-77% of the time. However, this study did not include biopsy confirmation. In a third study performed in Italy, 89 patients with a rising PSA were studied. The overall cancer detection rate was 37%. In those patients with a PSA of less than 1.0 ng/mL, the detection rate was 21%, with a PSA of 1.0-2.0 ng/mL detection was 29%, and when the PSA was higher than 3.0 the detection rate was 59%. In a more recent multi-center study of Axumin in 596 patients, the overall detection rate was 67.7% with a true positive rate of 62% and false positive rate of 38%. The mean PSA level was 5.43 ng/mL. For those with a PSA levels <0.79 ng/mL the detection rate was only 41.4%. (http://www.jurology.com/article/S0022-5347(16)31518-X/pdf).

We and others have observed that with Axumin, there is typically much higher muscle and bone marrow background activity than that seen with 11C-Acetate or Choline. This makes small lesions in the prostate bed and bone difficult to detect (see examples below). In some patients, the muscle uptake of Axumin may be sufficiently high as to render the study non-diagnostic, despite having properly abstained from physical activity prior to the scan. These factors may explain the apparent significantly lower performance of this agent compared to other agents, such as PSMA which are more specific for prostate cancer.

**PSMA PET/CT SCANS**

The prostate-specific membrane antigen (PSMA) is a transmembrane glycoprotein that occurs much more commonly in prostate cancer cells compared to benign prostate tissue. The clinically approved imaging method using PSMA was ProstScint. ProstScint, however, has several limitations. The technique uses an intact antibody which targets the internal portion of the cell membrane glycoprotein (PSMA) which requires long circulating times. There is prolonged blood-pool retention leading to high background signals, low detection rates, and much lower spatial resolution compared to PET.

Better agents for detecting PSMA have been developed, such as 68gallium-PSMA-11. Several retrospective studies have indicated a higher diagnostic efficiency of 68Ga-PSMA PET/CT compared to 11C-choline PET. In one study, for example, with 319 patients with PSA relapse, an overall 82.8% detection rate was seen. As might be expected, the probability of detecting lesions was correlated with PSA level. A 50% detection was seen when the PSA was 0.2-0.5, 58.3% detection with a PSA of 0.5-1.0, 71.8% detection with a PSA of 1.0-2.0, and 93% detection when the PSA was over 2.0.

**AXUMIN VS. 68GALLIUM-PSMA-11**

A recently published small pilot retrospective study compared Axumin with 68Gallium-PSMA -11 in a case series of 10 patients with recurrent prostate cancer imaged in short sequence (medium time of 2.2 months between scans). Five of 10 patients...
Below is a list of some of the agents currently under investigation:

Competition for the “best” PSMA agent is likely to be fierce. How well they work and how they are different from each other.

Different molecular configuration, requiring study to understand. Not all prostate cancers exhibit PSMA overexpression. In one study, about 8% of patients with prostate cancer did not show PSMA over-expression. Additionally, PSMA ligands are not completely specific for prostate cancer and several benign lesions such as thyroid adenoma, Paget’s disease, schwannoma, adrenal adenomas, and several types of vascular tumors (colon, breast, renal, liver, thyroid) may also exhibit increased PSMA expression. False positive celiac ganglia activity frequently has been noted in the upper abdomen.

A few limitations of PSMA-targeting agents are important to understand. Not all prostate cancers exhibit PSMA overexpression. In one study, about 8% of patients with prostate cancer did not show PSMA over-expression. Additionally, PSMA ligands are not completely specific for prostate cancer and several benign lesions such as thyroid adenoma, Paget’s disease, schwannoma, adrenal adenomas, and several types of vascular tumors (colon, breast, renal, liver, thyroid) may also exhibit increased PSMA expression. False positive celiac ganglia activity frequently has been noted in the upper abdomen.

Finally, most PSMA-targeting agents to date are significantly excreted in the urinary tract and urinary bladder, which obscures the prostate bed, making detection of small locally recurrent lesions and lymph nodes in the lower pelvis challenging – see the example below. 18F-PSMA-1007 is one of the more recent additions to the long list of PSMA agents and is in the early pre-clinical study phase. This agent shows less prominent urinary excretion and may have an advantage compared to other PSMA agents.

**IN SUMMARY**

Accurate re-staging is essential for optimal management decisions in recurrent prostate cancer. Current imaging with computerized tomography, magnetic resonance imaging, and 99Tc bone scanning lack the sensitivity to provide the needed information for accurate re-staging.

The excitement surrounding the current and emerging PET agents is appropriately exuberant. Radical breakthroughs are occurring in this area of imaging; however, a fair amount of confusion exists, and further research is needed. There is still no “perfect” imaging methodology with 100% accuracy, with each of the current PET agents demonstrating some pros and cons.

Our experience at Phoenix Molecular Imaging has shown 11C-Acetate PET may be a valuable and accurate tool, providing a better understanding of the location and extent of local recurrences and distant disease - often leading to changes in treatment plans. This agent however remains under clinical investigation, is logistically challenging and is not yet FDA approved.

The recent FDA approval of Auxmin is exciting as its 18F tag makes it more readily available than 11C tagged agents. Its overall performance however appears markedly suboptimal compared to other agents, particularly PSMA. The very high false-negative rate of Auxmin scans in recurrent prostate cancer patients with relatively high serum PSA levels is concerning. Bone marrow and mostly muscle background activity appears to interfere with detection of lesions. The use of this agent perhaps should be avoided until further research is completed.

Despite some limitations, PSMA-targeted imaging appears to provide high sensitivity and specificity, and is clearly the future direction of most ongoing research. For patients with recurrent prostate cancer signaled by a rising PSA, performance of a sodium fluoride PET bone scan and seeking out one of the clinical trial studies for PSMA may be the best options at this time.

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The essential first step toward deciding the best treatment for your type of prostate cancer is to know your stage. In my new book, *The Key to Prostate Cancer: 30 Experts Explain 15 Stages of Prostate Cancer*, a self-administered quiz guides you to one of the 15 different stages of prostate cancer. Identifying your stage narrows the number of treatment options you need to consider. Your possible stage-specific treatment options are listed at the end of this article. Accurate staging is the only way to determine the cancer’s severity, and therefore which therapy is optimal.

There are five stages of prostate cancer: SKY (Low-Risk), TEAL (Intermediate-Risk), AZURE (High-Risk), INDIGO (Relapsed), and ROYAL (Advanced or Lupron-resistant). There are three subtypes for each of the five stages: Low, Basic, and High. To begin the process of determining your stage and subtype, answer the questions below. Once you have determined your stage (Part I), continue to Part II. Find the section labeled with your stage and answer the questions. This will tell you your subtype. Once you know your subtype continue to Part III where your subtype is matched with possible treatment options.

To answer the questions in the quiz, you will need information from your medical record such as your PSA and testosterone levels. Obtain your pathology report as well, which shows your biopsy results. In the path report, you will need to find the Gleason Score, which is reported as 3+3=6, 5+4=9, etc. Use the highest score for the purposes of the quiz. You will also need your radiology imaging scan reports such as bone scans, CT scans, MRI scans and PET scans. Lastly, you need to look in the progress notes section of your chart to find the report of your digital rectal examination (DRE), i.e., the results of the finger exam of the prostate. The results are reported as the “T-Stage.”

The table below explains the T-Stages.

<table>
<thead>
<tr>
<th>T1</th>
<th>Tumor that can’t be felt by DRE</th>
</tr>
</thead>
</table>
| T2       | T2A: Involves 50% or less of one lobe  
|          | T2B: Involves > 50% of one lobe   
|          | T2C: Tumor felt in both lobes     |
| T3       | T3A: Extracapsular extension      
|          | T3B: Tumor that invades the seminal vesicle(s) |
| T4       | Tumor that invades the rectum or the bladder |

**PART I: THE STAGING QUIZZES**

**QUIZ A**

**QUESTION 1:** Have you had surgery or radiation and now have persistent cancer or a rising PSA? If no, continue to question 2; if yes, skip down to Quiz B.

**QUESTION 2:** Do you have a scan or pathology report showing any metastases (mets) other than pelvic lymph node mets? If yes, skip down to Quiz B, if no, or if the mets are located exclusively in the pelvic lymph nodes, continue to question 3.

**QUESTION 3:** Your PSA at diagnosis was:

a. Less than 10 ng/ml (write #1)

b. Between 10 and 20 ng/ml (write #2)

c. More than 20 ng/ml (write #5)

**QUESTION 4:** The highest Gleason Score on your biopsy was:

a. 6 or less (write #1)

b. 7 (write #2)

c. 8 or more (write #5)

**QUESTION 5:** The “T-Stage” on your digital rectal exam (DRE) was:

a. Small or no nodule (T1c, T2a) (write #1)

b. Larger, unilateral nodule (T2b) (write #2)

c. Bilateral disease or extracapsular extension (T2C, T3, T4) (write #5)

**QUESTION 6:** Do you have any scan showing cancer outside the prostate?

a. No extracapsular extension (write #0)

b. Overt extracapsular extension (write #3)

c. Seminal vesicle invasion (write #4)

d. Abnormal pelvic nodes (write #4)

**TOTAL UP QUESTIONS 3-6:**

If your score is 3 your stage is SKY; If your score is from 4-6 your stage is TEAL; If your score is 7+ then your stage is AZURE. Now that you know your stage, continue to Part II and find the section that corresponds to your stage so you can determine your subtype.
QUIZ B: (ONLY TAKE QUIZ B IF DIRECTED TO DO SO BY QUIZ A)

QUESTION 1:
Is your current PSA:
  a. Less than 100 (write #0)
  b. More than 100 (write #1)

QUESTION 2:
Do you have a rising PSA and a low testosterone under 50?
  a. No (write #0)
  b. Yes (write #1)

QUESTION 3:
Does an MRI, PET/CT, bone scan show metastases detected outside or beyond lymph nodes?
  a. No (write #0)
  b. Yes (write #1)

TOTAL UP THE SCORE OF THE PRECEDING THREE QUESTIONS:

If your total score is 0 your stage is INDIGO; if your total score is 1 or more your stage is ROYAL. Now that you know your stage, continue to Part II, find the section that corresponds with your stage, and answer the question so you can determine your subtype.

PART II: THE SUBTYPING QUIZZES

Go to the section about your stage and answer the questions to determine your subtype. Once you know your subtype you can drop down to the end of the article to see proposed therapies appropriate for your particular stage and subtype.

SKY:
Question 1: When your prostate gland volume is divided by your PSA level, is the result greater than 0.15? If the answer is “Yes,” your sub-type is High. If “No,” proceed to Question 2.
 Question 2: Do more than half of the core biopsies (from a random biopsy) contain cancer? If the answer is “Yes,” your subtype is High. If “No,” proceed to Question 3.
 Question 3: Is more than 50% of any full-length biopsy core cancerous? If the answer is “Yes,” your subtype is High. If “No,” proceed to Question 4.
 Question 4: Does a well-performed 3-Tesla multiparametric MRI from a center of excellence show unequivocal extracapsular extension? If the answer is “Yes,” your subtype is High. If “No,” proceed to Question 5.
 Question 5: Do more than two biopsy cores (from a random biopsy) contain cancer? If the answer is “Yes,” your subtype is Low. If “No,” proceed to Question 6.

INDIGO
Question 1: Have unequivocal pelvic lymph node metastases been detected? If the answer is “Yes,” your subtype is High. If the answer is “No,” proceed to Question 2.
 Question 2: Is your PSA over 0.5 (after surgery) or over 5.0 (after radiation)? If the answer is “Yes,” your subtype is Basic. If the answer is “No,” proceed to Question 3.
 Question 3: Is your PSA doubling time less than 8 months? If the answer is “Yes,” your subtype is Basic. If “No,” proceed to Question 4.
 Question 4: Was your original Stage (prior to surgery or radiation) Basic TEAL or higher? If the answer is “Yes,” your subtype is Basic. If “No,” your subtype is Low.

ROYAL
Question 1: Do your scans show more than five metastases? If yes, you are High-ROYAL if “No” next question.
 Question 2: Do your scans show one to five metastases? If yes, you are Basic-ROYAL if “No” next question.
 Question 3: Do your body scans show metastases limited to the pelvic nodes or no metastases whatsoever? If yes, your stage is Low-ROYAL.

1 Biopsy cores can be fractured into smaller parts when they are removed from the needle gun. More than 50% involvement of a biopsy fragment is not the same as >50% involvement of a full core. Full cores are at least 12 to 18 mm or more in length.
2 If multiparametric MRI shows unequivocal seminal vesicle invasion the Stage is AZURE and if a biopsy is performed it will probably show a higher Gleason score than 6.
3 See footnote #1
4 See footnote #1
PART III: POSSIBLE TREATMENT OPTIONS LISTED BY STAGE AND SUBTYPE

SKY
Low .................................................. Active Surveillance
Basic .................................................. Active Surveillance
High .................................................. Active Surveillance

TEAL
Low .................................................. Active Surveillance
Basic ................................................. Monotherapy (Seeds or IMRT or SBRT or Surgery)
High ................................................. Seeds plus IMRT plus Short TIP* (4 months)

AZURE
Low .................................................. Seeds plus IMRT plus Short TIP*
Basic ................................................. Seeds plus IMRT plus Long TIP (18 months)
High ................................................. Seeds plus IMRT plus Long TIP plus Zytiga or Xtandi

INDIGO
Low .................................................. Salvage IMRT to fossa (after surgery)
  or focal cryotherapy to prostate (after radiation)
Basic ................................................. Salvage IMRT to pelvic nodes plus short TIP*
High ................................................. Salvage IMRT to nodes plus Long TIP*

ROYAL
Low .................................................. Erleada or Xtandi
Basic ................................................. Provenge plus Spot SBRT to Mets plus Zytiga or Xtandi
High .................................................. Provenge plus Zytiga or Xtandi Back up plan if PSA nadir is high = Xofigo or Taxotere

*TIP = Testosterone inactivating pharmaceuticals such as Casodex, Lupron, or both

Below are a few activities or means available to expand your knowledge of self-empowerment and self-advocacy:

1. To learn more, read The Key to Prostate Cancer: 30 Experts Explain 15 Stages of Prostate Cancer, available digitally or in print at Amazon, Apple Books and Barnes & Noble.

2. Stay up-to-date on the latest prostate cancer news at prostateoncology.com/blog

3. Share the quiz and learn about the keep your prostate movement at keytopc.com. Follow us on Instagram @keepyourprostate and Twitter @keepprostate.

Disclaimer: The information in this article is for informational purposes only. It is not to be used as a substitute for diagnosis, treatment, or medical advice. Please seek the advice of a medical professional and do not delay treatment or disregard professional medical advice based on the content of this article.

When a man presents with a prostate cancer diagnosis, I often feel like I am starting an intricate jigsaw puzzle with only one piece to build upon. The diagnosis can be a “corner” puzzle piece, but that is not enough to even guess what the finished puzzle picture will reveal.

We start with the diagnosis. How accurate is it? How complete is it? How old is it? In my estimation, one elevated PSA alone is not enough to go on. A one-time elevation can be a fluke, caused by outside forces and not prostate cancer (ejaculation within 48 hours prior to testing; bicycling and other trauma to the perineal area; acute or chronic prostatitis; etc.). What we would like to see is a PSA history to indicate the trajectory of the score. Also important is a review of the family history of prostate and other related cancers (breast, ovarian, pancreatic cancers), and information on the patient’s profession and lifestyle.

In addition to the PSA, I have always ordered a PAP (Prostatic Acid Phosphatase) lab test, especially since some prostate cancers produce little if any PSA. Meanwhile, even with higher PSA readings, an elevated PAP enzyme can alert the physician to early spread of cancer beyond the gland. In the past and even prior to PSA testing, urologists came to realize that an elevated PAP indicated a rate of nearly 100% cancer relapse following prostatectomy, such that patients with elevated PAP results were deemed non-candidates for radical prostatectomy. One can easily understand why most urologists quickly abandoned the PAP once PSA became available. Nevertheless, I strongly recommend PAP testing...
in my patients and treat these patients appropriately based on their test results with both PAP and PSA.

To me, the PAP is as important as the PSA (even more important if elevated), and provides another piece of the puzzle. I have published five studies on the continued importance of PAP in the PSA era. Johns Hopkins, Walter Reed and RTOG (Radiation Therapy Oncology Group) have corroborated my findings. Despite this published data, the PAP test is rarely ordered by urologists and other physicians in the staging of prostate cancer. A confounding fact is that not all prostate cancers produce PSA. Some of the most aggressive cannot be identified by PSA at all, especially Gleason 9-10 and proliferating intraductal cancers.

Serum markers other than PSA and PAP, such as CGA, NSE on CGA, are also important since their elevation typically suggests a more aggressive cancer and will require a significantly different treatment design.

The PSA elevation red flag usually triggers the need for a biopsy. Again, this is an area of controversy. The typical prostate biopsy consists of 8 to 12 tiny core samples from the gland, and this random sample biopsy of the gland can miss areas of aggressive, neuroendocrine variant growth (prostate carcinoma), giving the patient a dangerous false negative finding. This random sample approach may find some cancer but it is not able to reveal the extent of disease in the areas not sampled. The larger the gland, the higher the probability that cancer can be missed. We don't know how many men today are living pseudo-happy lives falsely believing that they do not have prostate cancer, based on a single random sample biopsy, when in fact their cancer is growing every day (in some cases, very rapidly!).

My preferred method for biopsy is using 3D Color-Flow Power Doppler Ultrasound (3D CFPD TRUS) to guide the biopsy needles. I have published a 98% predictive accuracy using this method. This advanced technology allows the physician to see, in real-time, areas of abnormal blood flow, indicating tumor growth within the prostate gland. Hypoechoic, dark areas in the gland and hypervascular areas indicate cancers are associated with increased neovascularity (many blood vessels). These areas become targets for a guided biopsy, allowing for a far more accurate analysis.

I also use the transperineal approach, which has many advantages over rectal biopsies, including the ability to reach every part of the gland including the largest prostate glands. I use a sterile technique and have had a 0% risk of infection, which is in stark contrast to obtaining prostate tissue using the transrectal route. When 3D CRPD TRUS is not available, I strongly recommend performing ultrasound biopsy fused with multiparametric MRI (mpMRI) using a 3 Tesla magnet.

In the puzzle analogy, we now add a few of the edge pieces to the diagnosis corner piece. What to do now?

The decision of how to treat the prostate cancer should never be made in haste. The choice will impact a man's life from that day forward. There are many, many solutions – some good,
somes not appropriate due to the man’s situation. I always recommend that the patient seriously look at all his options and take the time to get second (and third) opinion, if necessary.

I must insert a caveat here – buyer beware. Because prostate cancer is so common, the diagnosis is ripe for exploitation. There has been a 20-year tug-of-war between the surgeons and the radiation oncologists, to capture market share. In some ways, this has been good. It has inspired innovation in both arenas. Marketing of these treatment options is nearly as deceptive as the used car industry! The downside is that the unsuspecting and frightened patient is faced with making a critical decision to select from novel treatments lacking long-term data as it relates to cure rates and side effects.

Outside of the legitimate, mainstream treatment protocols, there are charlatans on the internet and elsewhere offering all kinds of herbal and magical “cures.” Even some certified physicians are sending their prostate cancer patients out of the country for non-FDA approved treatments that are essentially snake-oil quackery, such as NanoKnife, PhotoDynamic Therapy (PDT), MRI LITT, Radio Frequency Ablation (RFA), and Focal Laser Ablation, etc.

Meanwhile, others are using approaches which are investigational that offer only the advantage of convenience (shorter amount of time for treatment) with no compelling long term data (e.g. Cyberknife, SRS, Hypofractionated Proton and Photon regimens, Cryosurgery, and HIFU).

Innovation be praised! Because of this competitive environment, we now have tools to diagnose the patient to the nth degree, learning more about his particular cancer than ever before. Exquisite imaging innovations, such as 3D Color-Flow power Doppler TRUS, multi-parametric MRIs using PI-RADS analysis, have given the physician new ways of “seeing” the gland and the tumors within it. Information is key; the more the better.

With this barrage of testing and imaging, we are able to start building a profile of the patient and his cancer. The next step is to determine the most appropriate treatment, taking into consideration the patient's geographical location, other health issues, insurance, etc. Regardless of the patient’s ultimate choice, we encourage considerable research on his part, as his first choice of treatment will be his best chance for eradicating prostate cancer forevermore. Never go into a treatment choice, with the mindset of “well, if this fails I can always do x, y or z.” Find the best practitioner you can, even if you need to travel. Ask questions. If you don’t understand the answer, ask again. Request the names of several patients that you can speak with about their experience with a particular doctor. Research the doctor on the internet. Visit a support group. In most cases (with the exception of very aggressive malignancies), it is not imperative to make a decision right away. Take your time to find the doctor and office that you feel confident in and comfortable with.

A very important part of the patient’s research will involve evaluating the technology available at each doctor's office. Nearly every community and hospital across the U.S. now has access to robotic surgical options (especially the DaVinci robot). These sound high-tech, and they are, but they are no more effective than a regular scalpel performing a standard “open retropubic” prostatectomy in the hands of an experienced surgeon. Behind the advertising hype is a huge monetary investment in the robot that must be returned. We advise patients to investigate track records and ask for published success rates. Beware that quoted success statistics are worthless unless they have been reviewed by a third party or published in a respected medical journal.

The same considerations apply to the growing number of Proton Beam Therapy (PBT) treatment centers. Lots of money invested in Protons has inspired big marketing budgets, yet equivalent survival outcomes when compared to earlier forms of radiation, e.g. 3D CRT, while even more reported GI problems have been documented with Protons when compared to even conventional IMRT (Intensity Modulated Radiotherapy).

Insurance companies are now wising up and denying payment for Protons in patients having prostate cancer. I expect many Proton centers to close over the next 5-10 years.

My career has been based upon offering men a proven, published, curative option to the surgical one. It was my belief in medical school that technology would one day make radiation therapy a viable option for defeating prostate cancer with the best cure data and the least amount of side effects. Today there are thousands of men (my patients and those of other leading radiation oncologists) that have proven me correct.

My years of experience, my choice of the most talented staff, and my efforts at pushing the technology envelope have allowed me to assemble a technology armamentarium unmatched anywhere. In addition to highly advanced external radiation, my partner and I developed a “multi-modal” two-step protocol including brachytherapy (radioactive seed implantation) as the most effective method of irradiating the bulk of the cancer within the gland. Long ago, I identified the superiority of brachytherapy alone compared to Radical Prostatectomy with better local control rates while never having to say the word “incontinence” and maximally preserving sexual function. The problem is that the prostate gland has no real capsule (try Googling this) and most cancers are already microscopically outside of the gland before most treatments begin, e.g. Radical Prostatectomy (especially when using the DaVinci Robot, Brachytherapy alone, Cryosurgery, HIFU, Cyberknife, SRS, Protons, PDT, NanoKnife, etc.).

Today, many proponents of treating only the prostate from edge to edge either don't know the prostate has no capsule, or they do know but wish to use that word “capsule” to lure patients into their own particular type of treatment. I would point out that many urologists get away with using the term “capsule” to inform and convince a patient that his cancer is “contained,” so that he will mistakenly believe he is a candidate for Radical Prostatectomy.
We continue to refine both the application of external radiation and the design of implanted radioactive sources (brachytherapy). Our center remains the only “brachytherapy research institute” in the country. Patients routinely travel to Sarasota from all over the world to receive our tested and proven multimodal therapy.

Returning to the jigsaw analogy, after gathering information from the lab tests, imaging studies, patient interviews, medical records and other sources, we can complete the outer edges of the puzzle. An individualized treatment plan tailored to the patient's specific finding, rounds out the puzzle.

We began our medical center in the fall of 2000 by installing the first Varian Linear Accelerator in the world, using IMRT. This was in the days of major advances in External Beam Radiation Therapy (EBRT). As our patient flow accelerated, we purchased more sophisticated accelerators and high-end software programs in order to treat more men with greater precision. Concurrent to the widespread introduction of the DaVinci Robotic radical prostatectomy, our Center created an even more sophisticated radiation delivery system that we named DART – Dynamic Adaptive Radiation Therapy. This delivery system uses multiple 4-dimensional technologies which are all coordinated to achieve the most pinpoint, precise radiation delivery in the world. Today this unique coordination of DART along with the most advanced diagnostics provides our patients with unrivaled therapeutic results. Even the most advanced cases are offered significant relief and quality of life following our treatment.

Today, we often see men who have received treatment elsewhere, only to see their PSA continue to rise, meaning their treatment did not eradicate the disease. Perhaps he did not have a fully adequate diagnostic evaluation; maybe he bought the sales pitch for a therapy that was not appropriate for him, or was directed by an inexperienced provider, or perhaps he simply had bad luck.

Many of these previously treated patients can still be helped when they experience recurrence, and we are equipped to take on these challenges. Most often, we find that these cases of relapse involve prostate cancer that has spread into the lymph nodes and bone, with the majority being to lymph nodes. Sometimes this could have been discovered before the man's initial treatment, thus eliminating surgery and other treatments as an option. Once cancer has spread beyond the prostate's edge, Radical Prostatectomy, Cryoablation, Cyberknife, SRS, HIFU, NanoKnife, PDT, etc. are useless as potentially curative options.

Our Center has devoted great effort into finding a way to effectively irradiate lymph nodes outside of the prostate proper, which contain active prostate cancer cells, as well as sites of bone spread – and we have achieved great success! By building a suite of sophisticated diagnostic tools, such as USPIO (Ultra-small Super Paramagnetic Iron Oxide), ¹⁸F-Sodium Fluoride PET/CT bone scan, ¹¹C-Choline PET/CT, Carbon 11 acetate PET CT, ¹⁸F-Fluciclovine PET/CT, Gallium-68 based PSMA PET CT and mpMRI, we can image the exact nodes or bones containing cancer.

These lymph nodes can now be successfully irradiated by dynamically adjusting the DART “microbeams” to organ motion in “real time” (specialized radiotherapy created by and available only at the Dattoli Cancer Center). This radiation can halt the advance of prostate cancer through the lymph system, without exposing the critical organs in the path to any damaging radiation. Other methods can also be utilized to attack metastatic bone spread using denosumab and infusional “systemic” bone-seeking radiation. Even treatment of lymph nodes above the diaphragm may be extremely effective in eliminating symptoms associated with castrate-resistant prostate cancer, offering patients extended biochemical and disease-free survival, and even cure (defined as undetectable PSA, no evidence of cancer, five years or greater following treatment)!

We have been increasingly utilizing genetic/genomic testing to create a “designer cocktail,” often immunotherapy, which is given in conjunction with high tech and infusional irradiation, with or without DART. We are currently excited about the use of “systemic” infusional Lutetium-177 (Lu-177), which targets PSMA (prostate specific membrane antigen) in soft tissue, bone and even blood borne prostate cancer. We will soon be adding this to our armamentarium.

In addition to this panoply of diagnostic and treatment refinements, we are going beyond the disease itself to “treat” our patients holistically with helpful supplements and vitamins. I have long been passionate about the use of quality supplements to potentially thwart malignancies from the beginning, as well as slowing cancer growth, improving bone strength and up-regulating the immune system. Following many years of R & D, we recently introduced a proprietary line of these supplements to the public, under the name “D & K Brands.” These “prescription grade” and third party validated products are a boon to an industry that is woefully bereft of important regulation. Far too many over-the-counter supplements have been found to contain little of the actual ingredients they claim. Some are actually unsafe concoctions and can result in adverse interactions with prescribed medications. Many also contain impurities, especially prescription drugs, since they are packaged at pharmaceutical plants. Many products which claim to be “pharmaceutical grade” have failed third-party validation. Information about our uniquely created products is available at www.dandksupplements.com. You can rest assured that they are of the highest quality, safe, pure and manufactured at FDA approved facilities under the strictest GMP standards. All D & K products are rigorously tested and validated by appropriate third party authorities.

Discovering and assembling all the various “puzzle pieces” of an individual's cancer creates a fairly accurate picture of what is going on, and then allows us to design a treatment plan to defeat each specific manifestation of disease and return the man to wholeness. Over the years, solving each unique puzzle has also increased our knowledge of how to treat the next guy.
I’m not sure of the exact wording, but it was something along these lines: “Your scans look good, and you are five years out. Congratulations! The chances of this cancer recurring are now less than 10 percent.” When my oncologist said that, it put a smile on my face.

First off – less than 10 percent? Everyone who quotes that statistic says it like staying cancer-free is a sure thing. It’s not. That’s what they said my first go-round with melanoma, before it became metastatic. But, he did say, “good scans” and “five years out,” and the truth is my chances are good enough that if I were playing Texas Hold’em, I’d go all in. A smile indeed.

So, now seems like as good a time as any to look back over what I’ve learned these past five years.

WE SHOULD TRY TO STAY A LITTLE MORE IN THE PRESENT.

It’s cliché, but all any of us truly has is today. So, don’t let it slip away by worrying about the past or the future. This came home to me one morning as I rode in my car wondering what my chances of survival were. It dawned on me that perhaps the one certainty of my day was that I wasn’t going to die from cancer that day. There was nothing to say I was going to make it to supper, but it wasn’t going to be cancer that got me. So, I decided to just be where I was, in the here and now. On that day, I loved some people, tried to do good work, and said thank you a lot. Then, I got up the next day and did it again.

I’M ACTUALLY NOT AFRAID TO DIE.

(Except when I think about it too much.) Mostly, when I think about death, I’m just sad because what I’ve realized is that I love being alive. I love my family. I love laughing. I love loving. I’d like to see my youngest grandson graduate from high school. I want to meet his children. I’d love to go on vacation with a whole gang of grands and great grands (on them, of course). I love this life and the people in it. But I’m not afraid of the next chapter.

BEING BRAVE ISN’T BRAVADO.

It’s being able to keep moving. It’s caring about other folks, smiling, and doing your job. Mostly, it’s keeping an outward focus. Cancer wants to suck you inside yourself. It wants to scare you and make you focus on the lousy cards in your hand. The best way to fight cancer is to fight that. Whenever I’ve taken the time to focus on other people – loving them, encouraging them – I found that, as I did, I grew stronger, I grew braver.

WE DO GET STRENGTH FROM OTHERS.

Prayer shawls, meals, hugs, pats on the back, and listening ears impart super powers. Even more special sources of hope and comfort are the bonds you develop with fellow survivors and their families. Over the course of treatment and survival, the cancer family grows. Not everyone makes it, but all become precious to you and transform your life.

EACH DAY IS A GIFT.

Thanks to cancer, I’ve become more grateful, more appreciative, and more aware of the gift of a new day. That’s not to say I don’t still piss some time away (I guess that’s just part of the human condition), but it’s less, way less, than it used to be.

FINALLY, I’VE LEARNED A LITTLE BIT ABOUT MIRACLES.

I don’t mean the miracles of medicine. Yes, those are wonderful; they saved my life. But I’m talking about deeper and more profound stuff. I’ve learned that God (or a higher power, or the universe, or just our inner strength) can take something as awful as cancer and make it a teacher, a blessing even. You see, it’s when we’re at the end of our resources, when health, willpower, and even our human faith are depleted that the whole thing gets turned around and a transformation takes place.

Now, all of this is not to say that cancer is particularly fun, or that it’s a path I’d choose if given the choice. But if you have to go there, you may as well learn something. You may as well come through it seeing a little more clearly, loving a little more dearly, and following a little more nearly.

Jim Hunter is a metastatic melanoma survivor living in Old Fort, NC.
WHAT THE HECK HAS BEEN GOING ON IN MY WORLD
PART 78!!

Mark A Moyad, MD, MPH

(Mark A. Moyad, MD, MPH, University of Michigan Medical Center-Dept of Urology and one of the most special, sensitive, loving, caring, and under-appreciated individuals at the PAACT corporate headquarters facility in the Grand Rapids, MI area. Regardless, I still have profound admiration and love for the folks at PAACT because they are like family and you have to love family even if they hurt your feelings occasionally. Right? Right? Actually, I’m not sure about that…)

Note: A total of 78 times and for 20+ years I have written for this newsletter and have never been personally compensated with water, alkaline water, sushi, gluten, French fries, money, puppies, Michigan basketball tickets or even allowed a bathroom break (for number 1 or number 2)! Give me a break! And, yet I decided to continue to volunteer for this organization and newsletter because I am a very sweet, wonderful, incredibly good looking, and of course, a very modest person. In reality, I really decided to continue to volunteer out of deference to this organization and because I am in constant need of some kind of attention. Anyhow, it is time to review the latest, greatest, not so great and everything else in my twisted, silly, but lovable and huggable world.

374) VITAMIN D SUPPLEMENTS TAKE A HIT? YES, BUT AT LEAST THEY ARE SAFE RIGHT? MAYBE!

BOTTOM LINE
Vitamin D supplements at 2000 IU per day did not prevent or cause cancer in a massive phase 3 clinical trial known as “VITAL.” However, there were other things found in this clinical trial that could be positive for vitamin D or negative, depending of course on what side of the vitamin D fence you like to sit on (please never sit on a fence because it can be painful - like a bad biopsy of the prostate). In other words, I am not going to reveal the unsung or under-appreciated results from this trial in the bottom line section, simply because I want you to read the rest of the story! Oh, and by the way for the small group of people that read the newsletter and only see the glass half empty after a clinical trial shows nothing dramatic, I have one thing to say. It’s hard or actually impossible to appreciate how difficult it is to run a clinical trial of this magnitude. For example, this research group had to screen 401,605 people in order to ultimately get the 25,871 individuals utilized for this trial! Running clinical trials are a PAIN IN THE GLUTEUS MAXIMUS! So, please always appreciate the volunteers (patients) and researchers that are a part of a clinical trial. If you think you can run a clinical study better than these folks, be my guest and be prepared to work 7 days a week for countless years knowing that many critics will mock the results regardless of what they end up being…hey just like politics where democrats and republicans have trouble giving each other credit.

TELL ME MORE YOU BEAUTIFUL PERSON
The largest study of vitamin D supplements to prevent cancer and cardiovascular disease (CVD) in otherwise healthy people has now been completed! And, the results are…BORING CITY overall but there are moments of interest for sure! First, this was an amazing clinical trial with a total of 25,871 participants and the dosage of vitamin D3 was 2000 IU per day or placebo (RDA is 600-800 IU per day). Yes, they used vitamin D3, which is arguably the safer and more potent form of this vitamin. Vitamin D did not reduce the risk of cancer or Cardiovascular Disease (CVD) after a median follow-up of 5.3 years. Vitamin D had no impact on death from all-causes but with further analysis there appeared to be a lower risk of dying of cancer in the vitamin D group, but this could have been due to chance since this was not the primary design of the study (to look at cancer deaths in general). The authors also stated that there was no excess number of side effects of vitamin D compared to placebo, so it appears to have been safe. Still, there was a 12% non-significantly (p=0.08) higher risk of kidney stones in the vitamin D group. Is this real? This seems like such a small dosage. Why am I asking so many questions? 477 stones occurred in the vitamin D group and 426 occurred in the placebo group, but perhaps this was due to chance? Regardless, we are experiencing an epidemic of kidney stones in the U.S. for many reasons (obesity epidemic…), so whether or not vitamin D, even at small dosages, increases the risk of kidney stones should receive more attention and being heart healthy in general reduces the risk of kidney stones. We already have known for the longest time that mega-dosing on calcium or probably even vitamin C supplements can increase the risk of kidney stones so I would not be surprised if mega-dosing on vitamin D does the same thing folks.

Anyway, let’s dig a little deeper! Firstly, the average age of the participants was 67 years of age, which is a little too old in my opinion for a major cancer prevention trial that is only going to last a little more than 5 years. The average person in the trial was overweight (BMI of 28) because the average person in the U.S. is overweight and only 7% of the participants were smokers and most people in the U.S. are no longer smoking. This is precisely why these large phase 3 prevention trials are so powerful because they are often done so well and with such precision, that by the time they are done recruiting for the clinical trial they are a mirror reflection of the U.S. population in general. In other words, they are awesome!

What most people will report from this trial is vitamin D supplements did not do anything and that’s mostly true when looking at the primary results of this massive study. Yet, for the “glass is half full of vitamin D” folks out there, they will point to the ancillary finding of a 25% lower chance of dying from cancer when looking at data from later in the trial (after it was well underway). In other words, maybe over longer periods of time vitamin D could prevent people from dying of cancer. There have been some hints of this in other studies. Furthermore, it appeared that people closer to normal weight appeared to get more benefit than those overweight, which has led many of the pro-vitamin D folks to suggest that this dosage works better in skinnier folks. Pro-
vitamin D folks will also argue that 2000 IU is such a low dosage that it should not have been studied and rather mega-dosages should have been investigated. The RDA of vitamin D is 600-800 IU, so 2000 IU is barely more than twice as much as the RDA! Although, personally I think 2000 IU is a large dosage.

Those that believe the glass is half empty will point toward the fact that when looking at deaths from all-causes (collectively) vitamin D had no impact, even later in the trial. And, they might point to a slightly higher rate of death from heart attacks with vitamin D…blah, blah, blah! The point here is that when you chuck all of your data against a wall, something good or bad is bound to stick to it.

Here is my final take on the matter, because since this is my column, I am naturally bound to throw my opinion in the ring. Vitamin D did NOT prevent cancer or CVD when taking 2000 IU a day versus placebo and I wonder if the slightly higher rate of kidney stones is from vitamin D or just chance. There is little doubt that Americans are being exposed to more and more vitamin D from fortified foods and beverages (heck the organic milk in my house now claims more vitamin D added than ever before) and even multivitamins have primarily doubled or tripled their amount of vitamin D in them. In fact, recent research demonstrates that in the U.S. population alone the use of high dose vitamin D supplements has gone from virtually nothing to fairly, common, regardless if you are 20 or 70 years of age (Rooney MR, et al. JAMA 2017;317:2448-2450).

I am not for or against vitamin D but instead for history! What that means is that until someone actually DEFINITELY proves that more vitamin D is better versus less vitamin D then why would I recommend more vitamin D?! You see part of my problem is that I am getting older which means now my career has spanned more than 30 years working in diet and supplements (33 years to be exact since I published my first paper on the impact of cottonseed oil on fertility in 1987), so I have been around the supplement research block too many times! I was there when countless people tried to convince me that selenium or vitamin E was going to prevent cancer or fight cancer. I was there when people tried to convince me that certain other pills or beverages were magical blah, blah, blah. Wrong! So, suddenly I am supposed to jump on the vitamin D bandwagon, which is now a gigantic bandwagon, just because there is some promising preliminary data? No thanks! "First do no harm," right! There are already a plethora of people that want to deem vitamin D the greatest vitamin ever, but I say prove it before everyone is supposed to use it (hey, that rhymes - I am a poet and I didn't even know it). Stay tuned!

**375) VITAL TRIAL PART 2: FISH OIL SUPPLEMENTS DO NOT HELP OR HARM, BUT WHAT ABOUT EATING FISH OR TAKING FISH OIL FOR MEDICAL REASONS (OH BOY THIS IS GETTING GOOD)?**


**BOTTOM LINE**
What did the fish say when it ran into a wall? “Dam!!!” Sorry I know I have used that joke before, but it’s funny, so I wanted to repeat it! Fish oil supplements at 1000 mg per day for 5.3 years did not do much good or harm. However, before you give up on fish oil please read the next article on the good news about a certain type of fish oil! Of course, everything comes with a catch, including fish oil. Get it? “CATCH” and fish oil! Man, I am funny! Why are fish so smart? It’s because they travel in SCHOOLS!!! Yes, I know I have used this joke before also, but I am desperate for new material, and I am getting older and lazier (aka “slothful” or “indolent”) with my writing.

**TELL ME MORE YOU BEAUTIFUL, WONDERFUL PERSON (I LIKE FISHING FOR COMPLIMENTS)!!**
So, we talked about the VITAL trial above, but I didn’t mention that vitamin D was not the only supplement tested in this massive trial. Fish oil supplements (actually “Omacor” - a prescription fish oil) was also tested with and without vitamin D, and up against placebo and overall, nothing particularly exciting happened. There were no differences in risk of cardiovascular disease (CVD) or cancer and no impact on death from all-causes. The pro-fish oil folks will point to the lower rate of heart attacks in the fish oil group and the con-fish oil folks will point toward a slightly higher rate of invasive cancer or even colorectal and prostate cancer with fish oil, but again the difference was small and non-significant and could have been due to chance.

My bottom line is that the one piece of news from this trial that really grabbed my attention was that people who consumed lower amounts of dietary fish per week (less than 1.5 servings) had a greater chance of benefitting from fish oil pills compared to the group that ate more fish! In other words, people that already ate plenty of fish did not seem to benefit. Again, this could have been due to chance, but it’s interesting. Overall, this study showed that a low or moderate dose of fish oil appeared safe but did not result in anything dramatic within 5-years of taking it. What if the study were allowed to go longer? I have no idea what the heck would have happened!

Actually, one other thing needs to be mentioned and it’s kind of fishy! The other interesting point from this VITAL study is that the placebo contained “olive oil,” which one could argue could have theoretically provided some minimal heart healthy benefits to the group taking placebo thus mitigating the effects of fish oil. Is this possible? Sure! However, again if fish oil was effective at this dosage then it should still have done more than it did in this study. I bring up the placebo because I often find it interesting what researchers choose as a placebo for a clinical trial and in this case, I wonder if olive oil was a good idea? Sounds kind of unctuous. Again, I do not know, but I love to occasionally throw in a little controversy, because life and clinical studies are like reality TV shows, since both contain some level of drama! And, I like to watch both of them! Anyhow, just when I thought fish oil supplements or drugs could be in some trouble along comes the REDUCE-IT trial (cue the next part of the column and the dramatic music from the movie “JAWS”).

**376) PRESCRIPTION FISH OIL GETS SOME GOOD NEWS? YES! IN PEOPLE WITH HIGHER TRIGLYCERIDES VERSUS THOSE TAKING MINERAL OIL? SAY WHAT!**

The REDUCE-IT trial involved over 8500 patients on statins with excellent control of their LDL cholesterol (LDL of 41-100 mg/dL—now that is low) and some cardiovascular risk factors including higher triglyceride levels in general (from 135-499 mg/dL). The dosage was 4000 mg or 4 grams per day, which is not a small amount versus “placebo.” There was no dramatic difference in side effects between fish oil and placebo. Although there were slightly more bleeding events with fish oil (2.7% versus 2.1% for placebo), there were no fatal bleeding events. There were slightly and significantly (p=0.004) higher rates of hospitalization for atrial fibrillation or flutter with fish oil but rates were low (3.1% vs 2.1%). There were many pieces of good news for the fish oil group including:

- **20% reduction in cardiovascular death,**
- **31% reduction in fatal or non-fatal heart attacks,**
- **28% reduction in fatal or non-fatal stroke,**
- **35% reduction in the need for an urgent or emergency cardiovascular procedure**
- **Reduced risk of dying of any cause**

So, what would have happened in the study if weight loss from diet and/or exercise went up against fish oil, instead of a placebo? Oh man that would have made me happier than a Michigan fan watching Coach Urban Meyer retire and live out the rest of his days on the planet Mars (I love Coach Meyer about as much as the girl that dumped me at my senior prom)! Just 5-10 pounds of weight loss and a few inches of waist loss can drop triglycerides dramatically (as can low-carb and other diets). Yet, no one ever wants to do these studies! And, there was a second controversy! The placebo essentially contained MINERAL OIL! SAY WHAT!!!! Mineral oil is not the best placebo because it can reduce the absorption of many important drugs and create things like diarrhea, which is exactly what it did in this study in the placebo group! There were significantly more cases of diarrhea in the placebo group and significantly more cases of constipation in the fish oil group (probably because they were not getting mineral oil). In other words, it is possible that the use of mineral oil for a placebo tipped the balance in favor of the fish oil group. Still, the results were dramatic, so I believe the fish oil was still effective. Regardless, again the choice of using mineral oil was probably not the greatest idea.

What I also found interesting was the rate of pain or discomfort from back problems/issues to joint pain was similar between the fish oil and placebo groups. I found this interesting because many people use fish oil for joint discomfort and pain, but it didn’t seem to do much in this study. And, the most common side effect from two past 12-week studies (called MARINE and ANCHOR…no I can’t make up names like that - this is true) of Vascepa was actually
If you are taking individual folic acid supplements and have been diagnosed and treated for bladder or prostate cancer, then you may want to give them up (unless of course you are one of the rare people that need them for a medical reason). What about multivitamins that contain more than the recommended daily allowance (RDA) of folic acid? Well, time will tell but you may want to make sure your multivitamin contains the RDA or less just to be safe.

**TELL ME MORE YOU BEAUTIFUL, SAGE, HAPPY, AND HANDSOME PERSON!**

Why is Moyad talking about an important bladder cancer study when this is essentially a well-known prostate cancer publication? Well, PAACT stands for “Please Accept our Apology for Clipping your ‘Trees on accident’...oops wait that was what the power company did to my yard last summer (they left an apology message after they made a mistake). In reality, PAACT stands for educating on cancer and not just prostate cancer. One of the biggest mistakes I believe we make in research is that we do not look at the rest of the cancer world in terms of what is happening in diet, supplements or drugs. For example, breast cancer has published countless studies on diet and supplements that have related to prostate cancer. And, bladder cancer provides very interesting research that could apply to many other cancers, so we should be following it. My simple and simultaneously complicated point is that this story also applies to prostate cancer since this question of folic acid has not been answered in prostate cancer.

Bladder cancer is the 5th most common cancer in the U.S. and it has one of the highest rates of recurrence (coming back after treatment) compared to almost any other cancer. Thus, in the perfect world if researchers could identify anything that could reduce the risk of bladder cancer coming back then its potential application in other cancers with higher rates of recurrence could theoretically be awesome! For example, smoking is the biggest modifiable risk factor for bladder cancer and stopping smoking not only reduces the risk of getting bladder cancer, but it reduces the risk of bladder cancer returning after treatment. And, guess what?! It appears that smoking increases the risk of getting aggressive prostate cancer and increasing the risk of prostate cancer recurrence after treatment. So, you see what I am getting at here folks. If we can find other lifestyle factors that increase or decrease the risk of bladder cancer, then I believe there is a good chance we can provide this information to prostate cancer patients! YEA!!

So, now let’s turn our attention to folate and cancer. Keep in mind that when the word folate is used it could be synthetic folic acid used in many pills and in the fortification of some foods or it could be the natural stuff found in healthy foods (fruits/veggies...). So, it’s a general term for vitamin B9. The mandatory fortification of food with folate was given a green light in 1996 and a few years later, it was everywhere (kind of like cell phones). This is good news because it can have a profound effect in preventing neural tube defects (NTDs). Still, how many men, say above the age of 50, 60, or 70 are looking to become pregnant? Not many that I can think of except Rick Profit of PAACT (interesting dude). And, one possible dark side of getting too much folic acid is the belief, by some, that it can increase the risk of certain cancers, or allow cancer to grow faster or simply return. Why folate or more specifically folic acid? Folate plays a primary role in DNA production and
repair, and since some cancers have folate receptors, then it’s theoretically possible it can be a bad thing after being treated for cancer. In other words, it is possible that too much folic acid could further stimulate the growth of cells that like to grow fast in general (like adding fuel to a fire, so to speak). Still, the great news is that in general food sources of folate appear to be associated with a reduced risk of some cancers while folic acid from pills appear to have no effect or again some people believe preliminary data suggests it can encourage the growth of some cancers.

Well, along come these totally awesome researchers from MD Anderson Cancer Center and Baylor. They decided to look at 619 non-muscle invasive bladder cancer (NMIBC. . .aka localized cancer) patients, and there were 303 cancer recurrences after a follow-up period of 5.2 years. You see what I mean? Bladder cancer even when treated, loves to come back and show its ugly face. Anyhow, what these researchers found raised some flags (not good flags but primarily bad flags). Synthetic folic acid in pills for example appeared to be associated with a higher rate of recurrence (cancer returning after treatment) and folate from food appeared to be associated with a lower rate of recurrence. There was even a higher rate of multifocal tumors (more than 1 tumor site) in people getting the most folic acid. How much synthetic folic acid? Much more than the RDA of folic acid, it seems, and the RDA is 400 micrograms per day. This is part of the reason why taking extra individual folic acid pills does not make sense until this issue gets resolved. Again, this is not definitive proof but rather preliminary data that has me worried enough about these things because I have been following and writing about this story for over a decade now.

The controversy also exists in prostate cancer. So, again let me repeat that this is not definitive proof, but I suggest less is more and do not take extra folic acid, but dietary sources of folate (fruits, veggies, other healthy foods. . .) are not only safer but appear to provide protection or benefit. Look at your multivitamin because if it contains more than 400 micrograms then I would not take it. And, if it contains less than 400 micrograms then even better. I realize many foods are fortified with folic acid including countless breakfast cereals and some of you eat so healthy that you have no need for a multivitamin or any pills for that matter and I love you for that! “I do not love you in the romantic sense but rather in the friend sense” (that sentence basically captures my entire high school and college dating experience). Regardless, this is a story without a clear ending so I will keep you up to date as times goes on but in the meantime,. . .LESS IS MORE! LESS IS MORE!!! Personally, I am not even a fan of those fortified folic acid cereals for people with a high risk of bladder cancer recurrence, but the real point of this study is that the data of folic acid continues to be not good or neutral but it is not helping most of us old folks. Please continue to follow this story.

378) ALCOHOL - THE OTHER BIGGER ELEPHANT IN THE ROOM?

BOTTOM LINE

The U.S. Preventive Services Task Force (USPSTF) recently updated their clinical guidelines for unhealthy alcohol use. They gave a “B” grade for adults aged 18 and older which means that clinicians should screen patients for unhealthy alcohol use. According to the National Institute on Alcohol Abuse and Alcoholism (NIAAA):

- Healthy adult men, aged 21-64 years, should not drink more than 4 drinks per day or more than 14 drinks per week.
- Healthy men aged 65 years or older should not drink more than 3 drinks per day or more than 7 drinks per week.
- Healthy adult women of all ages should not drink more than 3 drinks a day or more than 7 drinks per week.

So, a drink is considered 12 ounces of beer, 5 ounces of wine, or 1.5 ounces of liquor. WHAT A JOKE!!!! It is impossible to find drinks that are that small anymore, unless of course you get in a time machine and go back a few decades! Every time I walk into a bar, (sounds like a joke is coming) I am offered a 16-ounce or 22-ounce beer and there always seems to be a discount on the 22-ounce beer! How special is that! And, 5-ounces of wine? Come on man! Come on woman! That is ridiculous! The last time I was in a restaurant or bar and my wine glass was 5 ounces (more like 8-10 ounces) was only because the waiter or waitress did not like me for some reason (who would not like me…I am the Switzerland of the cancer world). Oh, and don't get me started on 1.5 ounces of hard liquor. My favorite bartenders tend to throw in 2-3 ounces of hard liquor in my drinks (ergo the word “favorite” bartenders).

Here is my point. Research is beginning to demonstrate that there is NO SAFE LEVEL OF ALCOHOL. I am sorry to say this because man I love my beer as much as my dog Chauncey (don’t tell him I said that please) but I realize that alcohol in 2019 is not the same as alcohol in 1959. In other words, we are living in a time of a historical obesity epidemic and alcohol is 7 calories per gram (MORE THAN SUGAR) and in some people, it helps to pump out extra insulin! IN OTHER WORDS, IT IS GREAT AT ADDING POUNDS ON YOUR BODY! Patients or people in the audience, will tell me all the time, that when they quit alcohol they lost a ton (no pun intended) of weight! The other reason alcohol helps to increase weight is due to the forever increasing portion sizes and alcohol content in today’s world. Beer use to be 3.2-5% and now many beers are 7-10%, which means more alcohol content and more and more calories per ounce!!! More than ever before in human history! Yikes!

We are also beginning to learn that alcohol is also a true or real carcinogen, and when consumed in excess it can reduce the efficacy of many prostate enlargement drugs (dutasteride, finasteride, etc.). What? Yes, this is true, and this was learned from two large trials of these drugs. Furthermore, it is now accepted that excess alcohol increases the risk of aggressive prostate cancer.

Additionally, there are places that make you more sensitive to the effects of alcohol, for example airplanes. Yikes! People love to drink on airplanes! Airplanes keep cabin pressure several percentage points lower than normal pressure (sea level), which reduces oxygen intake/exposure so the brain is more susceptible to things such as alcohol. There is an old saying when you go to a higher altitude for vacation that you get “2 for 1” when you buy alcohol. One beer feels like two and so on and so forth. Yet, this is also true for airplanes! Dang, that stinks! So, what is your final point Moyad? Here it comes…wait for it!
Everyone picks on the lack of exercise or sugar or processed foods or sodium or fast food or whatever you want as the reason we are becoming unhealthier, but in reality, ALCOHOL has become the elephant in the room based on the latest research. Apart from causing weight gain, reducing the effect of pills, being a carcinogen, making you act like an idiot when you consume too much etc. and now being one of the leading causes of preventable death it is time to call alcohol out. Look, I am never going to quit my regular beer, but I am watching the amount they are selling me and the alcohol content more than ever before in my lifetime. ARE YOU DOING THE SAME THING RIGHT NOW?

379) NOCTURIA = NOT FUN! AND, NOT TELLING YOUR DOCTOR THE TRUTH ABOUT HOW OFTEN YOU GET UP AT NIGHT IS BAD FOR YOU!


BOTTOM LINE
Getting up at night (called “nocturia”) to go number 1 actually stinks! I am not talking about asparagus making your urine stink, but rather it’s not fun to wake up in the middle of the night to go pee, pee, and it’s even becoming dangerous. Nocturia is associated with many health issues including BPH, diabetes, sleep problems, some medications, blah, blah, and blah. Yet, is it the chicken or the egg? In other words, does a medical condition cause you to get up at night or does getting up at night increase the risk of a medical condition? It doesn’t matter, but rather what matters is that you tell your doctor how many times you are getting up at night to go number 1! This is as important as almost any other question your health care professional asks you. Please be honest and do not BS about your PP and tell your doctor ASAP (see what I did there).

TELL ME MORE MY FAVORITE DOCTOR IN THE WORLD/UNIVERSE

In reality, for many clinical studies it’s common for someone to underestimate their weight and overestimate their height. I understand this because I am about 6 feet tall and when my wife (girlfriend at the time) asked me how tall I was I told her “6 foot 3 inches” and she smiled brilliantly as if to confirm that she likes tall men like me. However, in reality I am only 6 foot 2 inches whenever I put on women’s high heeled shoes (I do not do this often). And, I like to tell people I weigh a little less than I do, especially when someone offers me cookies or homemade French fries. So, as humans we like to BS often to make it seem as if we are doing better or seem taller than we actually are and yet there is one place you never ever want to BS your doctor and that is with NOCTURIA (how often do you get up at night to go to the bathroom). It’s so rare for someone to accurately tell me how often they get up, and that includes health care professionals and even when they are honest it seems few folks understand the risk associated with getting up each time at night. So, every month or so we learn more and more how bad it is to get up at night especially if it’s a lot (2-3 times or more) and it’s medically untreated, so I decided to bring up the latest study about nocturia that scares me!

This research actually came from a famous prevention trial called “REDUCE.” Data included 7343 men, aged 50-75 years from North America and Europe. Nocturia in this study was defined as 3 or more times per night and death from all-causes was looked at here. Cutting to the chase (I just made up that saying) here folks, nocturia was associated with an increased risk of death. There was no significant risk of death for men reporting a lower nocturia threshold (2 episodes). Men with nocturia were more likely to be older, have bigger prostates and one of four diseases (coronary artery disease, diabetes, hypertension, or peripheral vascular disease). So, it’s possible that getting up at least 3 times per night is still just the result or simply a reflection of an unhealthy situation that can increase the risk of other problems and even death such as sleep apnea, or a neurological or even a cardiovascular problem. Nocturia has already been associated with an increased risk of falls and hip-fractures in men, which could also increase the risk of death. There are few lifestyle questions in medicine that appear to be so often falsely answered or underestimated than “how many times do you get up at night”? In my experience, the spouse often gives an answer that is far different than the answer given by the XY chromosome (aka “man”).

If you go on the wonderful wacky internet there are 2 common FABULOUS questionnaires that doctors like to give to patients, and you are always welcome to download them on your own and bring them to your doctor. One is known as the AUA Symptom Score and the higher the score the worse the symptoms. Interestingly, one of the questions is over the past month how many times per night did you “most typically get up to urinate?” There is another questionnaire known as the IPSS (should have been called the IPPSS…anyhow I lost my train of thought….). The IPSS (question 7) simply asks “How many times do you typically get up at night to urinate?” There is that word “typically” again! Somehow, that word is throwing off a lot of men and not allowing them to be honest. So, I propose that instead of the word “typically” it should say “Just be honest here man! How many times do you get up at night to urinate?” And, then next to that it should say “now ask your spouse the same question and record their answer next to your answer.”

380) OLEIC ACID GETS A QUALIFIED HEALTH CLAIM? IS THIS JUST ANOTHER WAY OF MAKING OLIVE OIL AND OTHER COOKING OILS LOOK GOOD?

(Reference: FDA November 19, 2018)

BOTTOM LINE
Cooking oils with large amounts of the mono-unsaturated fat known as “Oleic Acid” can now make a health claim (aka health advertisement thanks to the FDA).

TELL ME MORE, OH YOU GIFTED WITH AMPLE DIETARY KNOWLEDGE DOCTOR

Man, every day I love and simultaneously hate diet research. I love it because there is nothing better in medicine (I am a tad bias like a politician). Despite a lack of hardcore evidence, it is now possible for a variety of cooking oils high in the monounsaturated fat known as “oleic acid” to claim that they may reduce the risk of heart disease. In some studies when oleic acid is replaced by saturated fat, there have been the potential for additional cardiovascular benefits. So, what is the FDA allowing
here? They are allowing what is known as a QHC in the dietary world or QUALIFIED HEALTH CLAIM. Man, I do not like these things because it commercializes diet too much.

What exactly is a QHC? It suggests the evidence is limited and not as good as an “authorized health claim” (AHC), so QHC must also contain a disclaimer to explain to the consumer the amount of evidence that is there. So, now on some labels it can say “supportive but not conclusive scientific evidence suggests that daily consumption of about 1.5 tablespoons (20 g) of oils containing high levels of oleic acid may reduce the risk of coronary heart disease.” Cooking oils must contain at least 70% oleic acid to make the claim. Also, product labels need to also state that the oil “should replace fats and oils higher in saturated fat and not increase the total number of calories you eat in a day.” Say What! Oh boy! This is a lot to put on the label. Let me get this straight…cooking oils that contain almost as many calories in 1 tablespoon as a 12-ounce cola can tell you that they might be healthy. Oh man, oh man!

So, what oils are we talking about Doc Moyad? Here we go!

- High oleic sunflower oil
- High oleic safflower oil
- High oleic canola oil
- Olive oil
- High oleic algal oil (ever heard of this? Algal oil! Wow! I have it and it is actually kind of interesting I have to admit… you should buy it and try it just to impress your friends that you have tried algal oil…by the way you have noticed at this point that there seems to be a marine or water theme to my column).

Look, these oils could be healthy when used modestly or once in a cooking blue moon, but the idea that these oils, which are all high in calories is the way to become healthier while we are in the middle of obesity epidemic is comical! Well who really cares! I mean foods in the American diet that also contribute to our oleic acid intake include meats like burgers, cheese, chips, salad dressings, blah, blah, blah. My favorite is the AVOCADO! Why can’t the avocado get this type of health claim? Anyway, doctor Moyad what is your point, besides the fact that you are ranting and angry about diet right now? Here is my point, besides the fact that I need to cut down on caffeine! The next time you go into the grocery store and you want to find the healthiest foods!!! Well, just look for the ones that don’t have any health claims or stickers on them that claim to be healthy for countless reasons! These are some of the healthiest foods in the grocery store, but they are not allowed to say S __ _ T (rhymes with zit) about how healthy they are for you. Heck, I love to eat at least 1 tomato daily or love my celery or artichokes, but I do not see any sticker on the package that says they are healthier for you to eat than high caloric oils or other foods! Arggggghhhhhhh! I need to calm down! Someone needs to show me the score from the Michigan versus Ohio State football game in 2011…that will make me happy and calm me down. Oh, and do not show me the scores from 2012 to present day because that will freak me out!

381) CARDIORESPIRATORY FITNESS (CRF) RESEARCH NEEDS OR REALLY DESERVES A NOBEL PRIZE! JUST ASK THE CLEVELAND CLINIC!

BOTTOM LINE
Imagine a drug that reduced the risk of dying young by 80% in the U.S. population! Holy Ship! (Notice how I used the word “ship” there…again sticking with the water theme of my column in this issue). I can and it is known as “CARDIORESPIRATORY FITNESS” (aka “CRF”!!! JUST ASK THE CLEVELAND CLINIC (you know the number 1 cardiovascular center in the U.S. according to many surveys). Every week at the Cleveland Clinic, they perform countless cardiovascular procedures and this is what they are known for….but what if they become known for the secret to living longer and preventing the need for a cardiovascular procedure? In my opinion, they are known for that!

TELL ME MORE, YOU WONDERFULLY HANDSOME, FIT, AND GORGEOUS DOCTOR
Intensive regular exercise (aka crazy amounts of exercise) has been theorized to be potentially associated with harm to the body compared to moderate exercise, but more research was desperately needed on this subject. There is a growing number of “experts” on the internet that appear to claim that you should not exercise a lot because it can damage your arteries and increase the risk of early death. So, the idea of simple and regular exercise, that is not intense at all, is promoted by these folks. Additionally, individual stories of intense exercisers having heart attacks or dying young are used as evidence to promote less exercise with age. For example, one of the most famous running books ever written (The Complete Book of Running) is used as an example because the author died young of some kind of heart issue, despite the fact that he had such an incredible family history of heart problems, that I could argue that he would have died much younger had he not been an avid runner for much of his life. This has been my argument my whole career and it was also a theory. I believe most of us are rewarded for taking care of ourselves and for the smaller number of people that are fit and die younger it is bad luck, or really bad genetics and I believe they would have run into harm at a much younger age had they not been so fit. Fitness does not guarantee anyone a longer life, but rather it increases the chances that it will improve your mental health and potentially extend your life longer than if you had not taken care of yourself. Anyway, that is just Moyad being Moyad (not sure what the heck that means but it sounded good when I was writing this at 2 AM on a weekend when I should have been asleep next to my wife, but our silly dog will not go to bed unless he can sleep between the two of us, which basically and regularly kills any chance of romance that I envision on a regular basis…and the dog snores like a chainsaw in need of some WD40 but that is another story). Regardless, I now believe there is additional proof that staying as fit as possible makes you very smart, so we will now talk about this study that I personally believe was the most interesting study of 2018.
Data from the Cleveland Clinic of patients from 1991 to 2014 that received an Exercise Treadmill Test (ETT) was utilized. CRF groups were classified into the following: low (<25th percentile), below average (25th-49th percentile), above average (50th-74th percentile), high (75th-97.6th percentile), and elite (>97.7th percentile). CRF was quantified by peak estimated metabolic equivalents (METs) on ETT (a measure of how well or if fit you are when on a treadmill or another exercise machine). 122,017 patients (average age, 53.4 years; 59.2% male) were evaluated representing 1.1 million person-years of observation. Let me repeat this incredible fact! They had data on over 122,000 young, middle-age, and old folks that completed an ETT! THAT IS AMAZING!!! Death occurred in 13,637 patients over the course of the study period. Death from any cause was inversely correlated to CRF and the best results were in the elite groups with an 80% reduction (HR=0.20; p<0.01) in the risk of dying from all-causes (yes even in the older men and women). There was even a 23% reduction in elite versus high CRF (HR=0.77; p=0.02) groups. Reduced or poor CRF was similar or greater than conventional risk factors including heart disease, smoking, and diabetes in predicting who might live longer or not. Again, the highest levels of fitness were associated with the highest survival or longevity and this included older patients (70 and 80+). Now, get ready for the part that blew my mind more than anything else in this study! THERE WAS NO OBSERVED THRESHOLD IN BENEFIT!!! HOLY MACKEREL (notice how I refer to fish again in this newsletter as I did earlier? Brilliant! Look out JD Salinger, Steinbeck, or Hemingway your competition has arrived)! What does that mean?

The results from this study, at least preliminarily screams out loud, that fitness could be the greatest secret to longevity. What people do not realize is that in many fitness studies, people fill out a questionnaire. So, as mentioned earlier in this newsletter people do not like to tell the truth when it comes to how much they weigh, or how tall they are, and I also believe this is the case when it comes to exercise. ETT is a wonderful objective (not subjective) measure of CRF. You cannot lie on this test! It seems preliminarily at least that when it comes to exercise then more is better with no known upper limit of benefit or threshold for now! In other words, the more fit you can become the better. I believe this research will hold up over time for many reasons. Someone that takes the time to become more fit is also simply moving in a healthier mental and physical direction. One could argue that fitter people are able to stay fit because they are not dealing with a serious disease. So, is it that fitness lowers the risk of disease or is fitness a wonderful consequence of not having to deal with a disease? Again, this is the chicken and the egg argument, but in my opinion, I don’t care much if it is the chicken or the egg, but rather a fitter chicken appears to make better tasting eggs, and better tasting eggs come from a healthier chicken so I do not get caught up in this argument and can just tell you why people use the cliché or jaded term that “you never regret a workout.” It’s because when you complete a workout you feel darn good mentally and physically, and that is reason enough to get off your gluteus and try and exercise to the maximus in the future my friends! LOVE, LOVE THIS STUDY!!!

382) MORE LATE BREAKING NEWS ON VITAMIN D! DID YOU NOTICE HOW I USED THE WORDS “LATE BREAKING” TO GET YOUR ATTENTION SIMILAR TO WHAT THE TV NEWS DOES EVERY DAY NOW TO GET YOUR ATTENTION AND NOW IT IS GETTING BORING OR NO LONGER INTERESTING BECAUSE THEY USE THE WORDS “BREAKING NEWS” OR “LATE BREAKING NEWS” TOO OFTEN SO WE HAVE BECOME DESENSITIZED (“LATE BREAKING NEWS-SQUIRREL GETS CAUGHT IN TREE”).


JUST THE BOTTOM LINE PLEASE

There is a lot of preliminary data to suggest if you take vitamin D especially as you get older then it can help with muscle function. Hey, that is exciting! However, some awesome researchers at Tufts University in Boston (CLOSE TO WHERE TOM BRADY PLAYS!!! YEAH!!!) completed a fabulous 1-year randomized trial of 100 men and women 60 or older taking vitamin D (starting with 800 IU to a maximum of 1600 IU) or placebo. After 1-year, the blood level in the vitamin D group was 32.5 ng/ml and with placebo, it was lower at 19.8 mg/ml but there was no difference in “lower-extremity power, strength, or lean mass in older community-dwelling adults.” Now, the question becomes will increasing blood levels in patients truly deficient in vitamin D improve muscle function? In the meantime, taking more vitamin D when your blood level is near or at normal range (20+ or 30+ on the silly vitamin D blood test) did not seem to help muscle function and this is consistent with many of the past studies. So, Dr. Moyad what am I supposed to do in order to increase my muscle function? Here is a little secret that I rarely reveal for free when giving advice on how to increase muscle size and strength. Here it comes…LIFT WEIGHTS OR DO RESISTANCE EXERCISES AT LEAST 1 TIME A WEEK AND IDEALLY 2-3 TIMES PER WEEK THAT INCLUDES LOWER AND UPPER BODY. THE MUSCLES ARE A “USE IT OR LOSE IT” SYSTEM (just like the brain, heart, lungs, etc.). SCIENTISTS HAVE TRIED FOR DECADES TO DISCOVER A MAGIC ELIXIR FOR BUILDING MUSCLE THAT IS LEGAL (not steroids) AND THE ONLY THING THAT HAS BEEN PROVEN TO BEAT WEIGHT LIFTING IS…NOTHING!!!

MAN I LOVE THIS STUFF!!!

See you all in the next issue where I will discuss why it is never a good idea to tell your in-laws that they are welcome to stay in a cheap hotel when they visit you from out of town, or why taking too many magnesium supplements is never a good idea when driving through an area of the U.S. that does NOT have many toilets, or why trying to prove to your friends that you can juggle chain saws after drinking a 6-pack of beer is probably not a good idea either, OR WHY BETTING AGAINST TOM BRADY IN THE SUPER BOWL IS SIMPLY INSANE (GO BLUE)!!! PS. I AM THE TOM BRADY OF MEDICINE! TOM BRADY RULES AND HE IS MY BFF!!! Oh yeah, I forgot! Where did Tom Brady go to college? Sarcasm alert!!!!
Is Testosterone the New Therapy for Prostate Cancer?

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A board-certified internist and medical oncologist, Jeffrey Turner, MD, may have the most extensive experience administering testosterone to men with prostate cancer. Testosterone deprivation has been a mainstay in prostate cancer therapy for decades. In men whose cancer is under control, testosterone deficiency may need to be addressed with replacement. This article will also explore the far more controversial topic of using testosterone to treat prostate cancer, an area where Dr. Turner’s experience is unmatched.

Low testosterone (“Low T”) or hypogonadism is typically encountered by men when they arrive at middle or late stages of life. The symptoms are increased body fat, weight gain, low sex drive, fatigue, anemia, depression, poor memory, osteoporosis, and a higher risk of diabetes. The first step when considering whether testosterone replacement is appropriate is to determine if the cause is primary or secondary. “Primary hypogonadism” is when the testicles themselves fail to produce adequate amounts of testosterone. “Secondary hypogonadism” occurs when the pituitary gland stops producing sufficient amounts of LH (luteinizing hormone), the hormonal factor that stimulates the testicles to produce testosterone.

When a diagnosis of primary hypogonadism is made, direct replacement with testosterone is a reasonable course of action. In secondary hypogonadism, men can take medications, such as Clomid, which work by stimulating the pituitary gland to produce more LH, which in turn stimulates increased production of testosterone from the testicles.

Why do we care about the specific methodology of increasing testosterone? Because long-term testosterone replacement can further suppress any residual testosterone production from the testicles causing testicular atrophy. By stimulating natural production with Clomid, the functionality of the testicles is maintained in a natural state.

Even though testosterone is a natural hormone, supplementation or replacement is not completely free of potential side effects. Higher testosterone levels can enlarge the prostate, cause balding, acne, fluid retention, breast enlargement, testicular atrophy, emotional lability, decreased sperm count, and an excess of red blood cells. Due to this latter factor of increased red cell production, there is even a potential risk of heart attack and stroke if men who are treated with testosterone fail to be monitored.

For those who have prostate cancer or a history of prostate cancer, the use of testosterone is even more controversial. Historically, more than 99% of physicians would never consider supplementing a patient who has ever been diagnosed with prostate cancer in the past. This is because most doctors believe that testosterone will fuel prostate cancer growth. This association between testosterone and prostate cancer growth was documented back in 1941 by urologist Dr. Charles Huggins.

There is, however, no concrete evidence whatsoever that testosterone causes prostate cancer though it is clear that testosterone can stimulate existing prostate cancer cells to grow. The take home message, therefore, is that men who appear to have been cured of prostate cancer can indeed consider taking testosterone without concern that it will induce new tumors. There is currently a wealth of studies (including randomized controlled trials) in patients who have been treated with surgery or radiation who went on to use testosterone replacement without any evidence of higher relapse rates. This is, of course, a very different scenario from patients who have existing cancers, especially those who have aggressive, widespread, and castrate-resistant disease. Potentially such individuals could be harmed by taking testosterone.

Despite historical evidence indicating that testosterone is universally bad for men with active cancers, some avant-garde researchers have been hypothesizing that testosterone administration to castrate-resistant patients may help in restoring hormone-sensitivity and thus aid in transforming bad cancers into a less aggressive phenotype. The emergence of something termed “Bipolar Androgen Therapy” has now surfaced. Bipolar therapy is the concept of rapid cycling between high blood levels of testosterone and low blood levels of testosterone using hormone blockade and testosterone supplementation in a cyclical fashion. Preliminary studies done on tissue cultures in the lab have demonstrated that in certain cases high doses of testosterone do cause suppression of prostate cancer cell growth, whereas normal doses of testosterone stimulate cell growth. This concept that high dose testosterone may suppress cancer growth has been tested in men with prostate cancer in very small, retrospective studies. In one study, for example, that evaluated giving large doses of testosterone on a cyclical basis to 10 men with metastatic
castrate-resistant prostate cancer resulted in lower PSA levels and radiologic evidence of tumor shrinkage.

These findings mirror my own experience using high-dose testosterone to treat men with prostate cancer. On a number of occasions, I have certainly used both standard doses of testosterone and high doses of testosterone to treat prostate cancer patients. What I have found is that it is much safer to use testosterone in patients who are in remission after treatment with previous surgery or radiation. Supplementing castrate-resistant men with high doses of testosterone is a much riskier proposition. Even so, I have indeed seen rare cases where men with castrate resistant prostate cancer have been able to cycle between hormone blockade and testosterone replacement and keep their disease in check for over 10 years without developing radiologic progression of their disease. Unfortunately, for every one of these success stories, I have encountered far more cases where the disease not only failed to respond but the cancer appeared to progress more rapidly due to the high doses of testosterone.

So in my judgement, using high-dose testosterone in men who are hormone resistant is a RISKY proposition. What I believe is particularly inappropriate is administering testosterone to men with large tumors in the prostate or who have metastases in the spine. Such men risk catastrophic events such as urinary obstruction, spinal cord compression and paraplegia/quadriplegia due to progression of disease. Most of the men who I have treated with metastatic castrate resistant disease first underwent aggressive cancer debulking with hormone blockade and chemotherapy. But even with this aggressive preparatory protocol, the results were discouraging in the vast majority. Men would typically develop a relatively rapid rise in PSA and manifest radiologic progression quickly, prompting a return to aggressive therapy with chemo and hormone blockade. It is true that a small minority of men with high-risk prostate cancer seemed to have their disease suppressed for a longer duration of time with high doses of testosterone. However, I found it to be impossible to determine in advance, who might benefit and who would end up with rapid disease progression.

In conclusion, testosterone replacement is a viable option for prostate cancer patients who are suffering from the symptoms of low testosterone, as long as they are monitored closely. Monitoring should include regular PSA testing, digital rectal examination, and ideally prostate imaging such as color Doppler ultrasound or multiparametric MRI. Patients need to be fully informed regarding all the potential risks. In my experience, testosterone replacement is quite safe in low-risk patients who have undergone adequate local therapy and are considered to be in remission. Testosterone replacement in men with more advanced cases with metastatic castrate-resistance disease is far more risky. Further studies to evaluate testosterone in this role are ongoing. For the present, I recommend patient's exhibit cautious skepticism before embarking on such a treatment outside of a clinical trial as the risks may certainly outweigh the benefits.

According to the American Cancer Society, in 2018 over 164,000 men will be diagnosed with prostate cancer. For those men, treatment options range from surgery to remove the entire prostate, radiation to target the cancer in the prostate, or ‘active surveillance,’ monitoring carefully over time for signs of disease progression. The quality of life issues that arise from surgery and radiation range from diarrhea, rectal pain and bleeding, urinary leakage and loss of sexual function that can last for years.

For men that choose radiation therapy to treat their prostate cancer, there is an innovative product that can minimize side effects caused by the treatment. Because the prostate is located near the rectum, unintended radiation damage to the rectum and surrounding tissues can occur leading to lifelong complications. In April 2015, a product called SpaceOAR® hydrogel became available for use during radiation treatment for prostate cancer. The gel, which is mostly made of water, acts as a protective spacer between the prostate and the rectum and has been clinically proven to reduce the risk of side effects from radiation treatment. In a prospective, randomized, multi-center clinical trial in the U.S., patients treated with SpaceOAR hydrogel prior to prostate cancer radiation treatment demonstrated bowel, urinary and sexual benefit through three years of follow-up. The study found that the patients that did not receive SpaceOAR hydrogel experienced a clinically significant decline in bowel, urinary, and sexual quality of life 8 times more often than patients that received SpaceOAR hydrogel.

SpaceOAR hydrogel is placed in a minimally invasive outpatient procedure with local or general anesthesia. Patients can immediately resume their normal activities. The gel stays in the body for approximately three months and is then naturally absorbed and cleared in the urine in about 6 months.

As of 2018, SpaceOAR hydrogel is used in 19 of the Top 20 Cancer Hospitals in the United States and has been used in over 20,000 patients worldwide. To learn more about SpaceOAR hydrogel or to find a radiation oncologist or urologist in your area, please visit spaceOAR.com/prostate.

Our focus since the last update has been on coverage for focal laser ablation of prostate tumors (“FLA”). We frequently remind you that LAC-PAACT is here to help with any insurance or Medicare coverage issues that may arise as you seek to take advantage of the latest advanced cancer treatments. Frequently, in the early years of the use of new treatment options, coverage can be denied because the treatment is deemed experimental, or coverage amounts can be set unreasonably low.

Since the last update, we have continued to help a number of FLA patients who were denied coverage, evaluated the likelihood of success on appeal, and strategized about how to build a case for coverage for laser ablation. For individual coverage disputes, we can help gather support for coverage and point you to resources, building on our past successes in fighting for coverage for advanced cancer treatments.

We have been getting some great help in gathering information in support of coverage for FLA. We also have some more favorable and unfavorable results to report:

1. The one FULLY FAVORABLE decision from a Medicare Administrative Law Judge (ALJ) awarding coverage for FLA that we told you about in the 2016 update unfortunately was overturned by the Medicare Appeals Council, seeking to overturn the ALJ’s decision. I have not heard for sure yet whether the claimant decided to appeal to federal court, which would be the next step for him, but I think he decided not to appeal further, unfortunately.

2. One man obtained a favorable coverage letter for FLA from Blue Cross Blue Shield of Texas.

3. A patient of Eric Walser, MD received a letter approving coverage for FLA from Anthem UM Services, Inc. in New York City.

4. John Fortin, who I mentioned in the 2016 update has been helping gather information supportive of coverage for FLA received a FULLY FAVORABLE decision from a Medicare ALJ, and this one was not appealed or overturned, so things are improving!

As we continue to gather information and documents to assist with coverage for laser ablation, please contact Greg Teufel if you have had laser ablation, to let us know your experience with insurance coverage, whether it was with Medicare or private insurance, if you were successful in obtaining coverage. If you were unsuccessful in obtaining coverage for the procedure, and want to discuss the likelihood of successful appeal and/or suggested resources for building a case for coverage, please feel free to contact Greg Teufel.

We can also give useful suggestions to your local lawyer and provide support and resources that may help convince your local lawyer to take your case and ultimately help your chances of winning. So please, do not hesitate to take advantage of these free services.

Feel free to contact us regarding any coverage or other legal issues related to advanced cancer treatments. We want to help and need your help in identifying the areas of greatest need.

We are also always seeking volunteers to help with LAC-PAACT activities. Even if you are not a lawyer, you can volunteer if you are inclined to help with law related issues. Also, if you know any lawyers that would be sympathetic to our cause, please make us aware of them and them aware of LAC-PAACT. Just contact Greg Teufel regarding volunteer opportunities with LAC-PAACT.

If you have been denied coverage for an advanced cancer treatment, be sure to let us know and we will see if there is anything we can do to help.

**CONTACT LAC-PAACT**

If you have any questions or comments, or any suggestions about how LAC-PAACT can best serve your needs, please do not hesitate to contact me. The preferred method to contact me is via email at gteufel@OGCLaw.net. You can also call me at work at (412) 253-4622, home (412) 421-7123, or on my cell phone (412) 596-6316, or send me a letter at OGC Law, LLC, 615 Washington Rd., Suite 405, Pittsburgh, PA 15228 or a fax at (412) 253-4623.

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1. LAC-PAACT is PAACT’s legal advocacy committee. Despite the name of the committee, for various reasons, we generally cannot give you legal advice or act as your personal attorney. Please do not consider anything in this article as legal advice. If you want legal advice, we encourage you to consult a lawyer in your state, so that your specific situation and local laws can be considered. We cannot give you medical advice either and please do not consider anything in this article as medical advice.

2. Gregory H. Teufel, Esq. is the Managing Member and Founder of OGC Law, LLC, a law firm in Pittsburgh.
Dr. Deepak Kapoor, president of Advanced Urology Centers, Bethpage, is pleased with a new law that requires health insurers to cover the cost of routine screening for prostate cancer.

A new law quietly went into effect in January that requires health insurers to cover the cost of routine screening for prostate cancer, a measure aimed at encouraging more men to consider the benefits of being tested.

New York is the only state in the country to pass a law that supports full insurance coverage of the PSA (prostate-specific antigen) blood test, which helps determine prostate cancer risk.

The new law is the brainchild of a coalition of New York urologists and patient advocacy organizations that not only saw a need for the legislation, but over a two-year period made a case for the measure among legislators in Albany.

“As far as physician practices go, we were in the lead,” said Dr. Deepak Kapoor, president of Advanced Urology Centers, which has offices throughout Long Island and in New York City. “This is something that was done for the public good.

We had lawmakers on both sides of the aisle who really linked arms together to make this happen,” said Kapoor, a longtime advocate of PSA screening. “This is what happens with bipartisanship. It was also a great example of the private sector and nonprofit organizations working closely with legislators to make this happen.”

Hewlett-based 1 in 9 Long Island Breast Cancer Coalition was one of the leading advocacy groups to support the law, Kapoor said.

As far as insurance coverage, New York now puts men’s prostate screening on par with routine mammography, which under the Affordable Care Act became fully covered nationwide with the act’s passage in 2010. Framers of the ACA didn’t extend the same consideration to the PSA, despite the prevalence of prostate cancer in the United States and roughly similar costs for the two forms of cancer screening.

A PSA exam averages between $60 and $80, while a mammogram can cost anywhere from $75 to as much as $250, but generally runs about $100, according to several local and national patient advocacy organizations.

This is about removing barriers,” Kapoor said of the law.

Some men may have avoided screening because their insurance company required a copay. Others, Kapoor said, may have been wary of testing because of misinformation about the PSAs reliability.

Despite criticism of the test, the PSA in the last few decades has dramatically changed the trajectory of care by offering screening, early detection and prostate cancer management, Kapoor said.

The PSA is part of our armamentarium,” he said of tools to help lower the risk of prostate cancer. “It’s a gateway test. It isn’t perfect and no one would say the PSA alone is a perfect instrument. But it is a tool of a skilled provider to determine if further testing is warranted.”

Prostate cancer is the second-leading cause of cancer in men, with more than 240,000 new diagnoses and 28,000 deaths in the United States annually.

While no cancer screening is 100 percent accurate, Kapoor said the PSA has been fraught with controversy for years.

The U.S. Preventive Services Task Force discouraged screening in 2012 only to somewhat reverse itself last year. Seven years ago, the panel — an independent committee of health experts empaneled by the U.S. Department of Health and Human Services — gave the PSA a grade of D. The committee makes recommendations on clinical preventive services, particularly screenings.

In 2018, panelists issued their final recommendation, giving the PSA a grade of C for men between the ages of 55 and 69, noting those men should have a discussion with their doctors about the pros and cons of the test before undergoing screening. Committee members recommended against screening for men 70 and older, giving it a letter grade of D.

For older men, they concluded that benefits of the test do not outweigh the “harms,” which were defined as the anxiety produced by additional testing required in the event of a positive result. Older men are more likely to have slow-growing tumors that will not lead to their deaths.

Men at average risk should consider screening, starting at age 50, Kapoor said, while African-American men and anyone with a family history of the disease should consider screening starting at age 40. Men of all ages should discuss the test with their doctors.

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Before discussing recovery of erectile function in men following radical prostatectomy, it is important to understand the current causes and treatments for ED. There are many causes of ED. ED is a progressive disease in which 40% of men at 40 years old, 60% of men at 60 years old, and 80% of men at 80 years old will develop ED. [1] The most common causes are associated with diabetes and prostate cancer. Diabetics are four times more likely to have ED because they tend to have poor blood flow and nerve function in their penis. Radical prostatectomy can result in nerve injury to the penis. Unfortunately, some men never recover their erections after surgery. Other causes of ED include smoking, high blood pressure, high cholesterol, and certain medications. Many patients do not realize that beta-blockers, one of the most commonly used blood pressure medications, can be a potential cause of ED. Other causes include psychological issues, such as seen with marital guilt, new relationships, and divorce. In these cases, sex therapy is extremely effective. Peyronie’s disease, which is an abnormal curvature of the penis when it is erect, and penile trauma, can also lead to ED.

ED is a window to a man’s cardiac and overall health. In fact, the causes of ED and cardiovascular disease are very similar. The common causes include smoking, poor diet and lack of exercise, diabetes, obesity, advanced age, and elevated cholesterol levels. ED is one of the first signs of cardiovascular disease. Studies have shown that from the day a man develops ED, he has a 15% chance of developing a heart attack or stroke within seven years. [3] Many men believe that sildenafil (Viagra) is a good treatment for ED. However, you have to ask yourself if sildenafil, or sildenafil-like drugs, such as tadalafil (Cialis), are really addressing the cause of ED. I believe these medications generally do not cure ED, but instead allow the disease to become worse over time. There are two ways to give these medications. One way is to take these medications before sex and the other way is to take a daily dose whether you are having sex or not. These are referred to as “on-demand dosing” and “daily dosing,” respectively. In my opinion, Cialis, when used as on-demand dosing, does not cure the ED problem and actually causes it to worsen. ED is a progressive
disease process that can be reversed. Dr. Esposito and colleagues have shown that diet and exercise reverse ED.[4] Other studies have shown that the use of statins improves ED, and makes medications such as Viagra much more effective. Improving diabetic control and stopping smoking are also ways to reverse ED. Finally, daily dosing of Cialis and the use of testosterone have been shown to reverse ED and improve the muscles within the penile tissue. Prior to treating men with ED, I strongly encourage lifestyle modifications in order to reverse the disease process and to prevent further worsening of the disease.

There are many treatment options for men with ED. The most commonly used medications are oral medications, such as sildenafil (Viagra), vardenafil (Levitra), tadalfil (Cialis), and recently introduced avanafil (Stendra). Stendra is the only FDA approved drug in this class that has an onset as early as 15 minutes. Other treatments include testosterone therapy. Testosterone alone has been shown to improve overall erections in men. Other medications include small suppositories (MUSE) that are placed in the tip of the penis and dissolve, causing blood to enter the penis and permitting an erection. Vacuum erection devices (VEDs) have been available for many years. A VED is simply a cylinder that is placed on the penis, functioning like a vacuum and causing an erection. The man then places a band at the base of the penis so he can maintain his erection. Another effective treatment for ED is penile injections. These injections administer a small amount of medication that is injected at the base of the penis at the 10 and 2 o'clock position. Usually within 5-10 minutes the man is able to achieve a rigid erection sufficient for sex. This is an effective form of therapy and is one of the cheapest types of ED medication, if obtained from a compounding pharmacy. However, many American men are reluctant to insert a needle into their penis. Finally, there is the penile prosthesis, which was invented in the early 1970s by Dr. Brantley Scott. The penile prosthesis has revolutionized how we treat men for ED. The penile prosthesis involves a surgical procedure where an inflatable device is placed in the penis. There is a pump in the scrotum which allows the man to inflate and deflate the prosthesis. The entire prosthesis is placed inside the body and is not noticeable if a man takes off his clothes. The benefit of the penile prosthesis is that almost every man can be treated for ED if he is willing to have the procedure. Also, a man is able to get an erection whenever he wants for as long as he wants. Many of my patients are also offered a sex therapy referral. Sex therapy is especially helpful in men who suffer from psychogenic ED. Psychogenic ED can occur frequently in men following prostate cancer surgery. One cannot underestimate the large psychological impact radical prostatectomy can have on patients. This can have a devastating psychological impact on the patient and his wife. Many men start to experience ED once they are given the diagnosis of prostate cancer. This is why sex therapy plays such an important role in the recovery of sexual function following prostate cancer treatment.

One of the best ways to improve a man’s erections is to treat his wife. There have been many studies showing that if you increase a woman’s sexual desire, her male partner’s erections also significantly improve. There are also studies showing that if you improve a man’s libido and erections, his wife’s libido and sexual function also improve. The reason for this is that sexual dysfunction is a couple’s disease. You cannot treat one person without at least addressing the other partner. I published a study several years ago demonstrating that one of the best predictors of whether a man would be compliant to a penile rehabilitation program after surgery was based on how good his partners sexual function and desire was.[5] It makes sense that men who have a willing sexual partner are more likely to be motivated to recover their erectile function. The best way to treat sexual dysfunction is to treat both partners together. By treating one partner, you are also treating the other.

As discussed earlier, following a radical prostatectomy, approximately 77% of patients have ED due to blood flow or nerve injury causes. Although the penile nerves may be preserved during a radical prostatectomy, a majority of men suffer from temporary nerve paralysis, which may last from months to years. Nerve injury can also lead to penile scarring. In the past, we gave men Viagra and had them follow-up in 1 year to assess how their erections were progressing. I disagree with this approach, as the penis is mostly composed of muscle, and should be exercised just like any other muscle in the body. For example, if I put your arm in a cast for one year and then took off the cast, you would have muscle wasting (atrophy) and the arm would be weak. The same is true for the penis. The concept of “use it or lose it” is very relevant here. Thus, we now ask patients to start exercising the penis immediately after surgery. This is called penile rehabilitation. The goal of penile rehabilitation is to increase blood flow and oxygen to the penile tissue and thus prevent scarring and permanent damage to the penis. It is important to take this proactive approach because many times the scarring that occurs in the penis after a radical prostatectomy is irreversible.

There are many exciting potential future treatments for ED following radical prostatectomy. Currently, we are working with stem cells to reverse the ED process.[6] The stem cells are harvested from the patient’s fat and then processed and injected back into the patient’s penile tissue. Our initial human studies were promising, as stem cells allow more blood to flow into the penile tissue as well as increase the muscle within the penile tissue. We are also beginning our study to deliver low intensity shockwave therapy to the penis. In this procedure, a patient undergoes 1500 penile shocks three times per week for six weeks, inducing growth factors and new blood vessels to come into the penile tissue. This technology has been used for several years in Europe, and initial results appear promising in improving overall erectile function.

References
The clinical effectiveness of stereotactic body radiation therapy (SBRT) for prostate carcinoma in some studies are showing a superior cure rate when compared to conventional radiation. Stereotactic body radiation therapy is a non-invasive form of radiation treatment that involves high dose radiation beams entering the body through various angles while intersecting at the desired target. It is a state-of-the-art technology that allows for a concentrated dose to reach the tumor while limiting the radiation dose to surrounding healthy tissues. Most of this type of treatment has been performed with CyberKnife® stereotactic radiosurgery which is available in Saginaw at Ascension / St. Mary’s. Other centers have used a LINAC-based approach (a linear accelerator machine that uses x-rays (photons)). The CyberKnife® is considered a very popular treatment option for stereotactic body radiosurgery (SBRT) for prostate cancer because a tumor in or near the prostate can move as you breathe, making it difficult to accurately target with standard radiation. As a result, the tumor may not receive enough radiation and healthy tissue may be damaged. The CyberKnife® software and respiratory/bio tracking system is unique. It allows us to confirm the location of the prostate tumor and continually track its movement in real-time, so we can more precisely deliver the radiation without damaging healthy surrounding tissue. Unlike standard radiation, CyberKnife® allows the destruction of tumors with high radiation doses in four to five sessions, depending on the location of the tumor and other factors. Conventional radiation treatment to the prostate is performed over 5-9 weeks. The biologic advantages of high dosage per fraction is that hypo fractionated regimens (higher dose per day) may be more advantageous compared with conventional regimens because of a low alpha / beta ratio of prostate cancer, which means it has a high sensitivity to dose per fraction.

A five-year study from UT Southwestern Medical Center published in 2016 showed a 98.6% cure rate with SBRT treatment. This is striking compared to the five-year cure rates from other approaches such as surgery or conventional radiation, which range between 80%-90%, and the side effects seem comparable.

This study at UT Southwestern was a multi-institutional trial which involved newly diagnosed prostate cancer patients diagnosed with stage I or II (low and intermediate) prostate cancer. The study totaled 91 patients that were treated prospectively and followed for five years with only one patient experiencing recurrence. This was published in the European Journal of Cancer.

Treatment related side effects, were not necessarily different when compared to other forms of prostate cancer treatment. SBRT side effects can include urinary issues, urgency, frequency, burning, and rectal irritation which are often temporary and occur within the first four weeks of treatment. Researchers found a small risk of longer term urinary rectal complications which is also comparable to conventional treatment. Decrease in erectile dysfunction was seen in 25% of patients.

Current other approaches with this type of treatment are designed to try and reduce the side effects to the rectum. More recently, medical professionals are using unique and biodegradable rectal spacer gels to protect the rectum. SpaceOAR® is a hydrogel that’s injected between the rectum and the prostate to create additional space to help increase the sparing of rectal tissues during radiation treatment, while reducing the risk of rectal injury during treatment. This has become increasingly popular, not just for stereotactic radiosurgery, but for conventional radiation therapy as well.

When we looked at the cost of care for treatment, the average cost of SBRT was $13,645 compared with $21,023 for typical IMRT (intensity modulated radiation treatment) treatment. There are some studies that suggest that the increased acute side effects are higher with SBRT, but this has been the subject of much debate and felt to be related possibly to physician and/or center experience. A recent study that came out in January of 2019 reviewed stereotactic body radiosurgery therapy with patients with low and intermediate risk prostate carcinoma. Doses of 35, 37.5 and 40 Gy over five SBRT treatments were used in low risk patients. The medium follow up was 5.9 years and it showed that doses from 35 to 40 Gy with SBRT were safely tolerated without severe urinary rectal toxicities. Patients had biopsies at two years suggesting improved rates of tumor clearance particularly with higher doses. Particularly, the 37.5 and 40 dose gray showed higher rates of tumor eradication.

SBRT for prostate is a promising and value-based approach for the treatment of prostate cancer. Patients no longer must endure 8-9 weeks of treatment to achieve an excellent clinical outcome. Now they can be treated effectively with respect to their time and quality of life.

Dr. Bertrand Tombal, Chairman of the Division of Urology at the Cliniques universitaires Saint Luc and Professor of Urology at the Université catholique de Louvain (UCL) in Brussels, Belgium, is the current President of the European Organization for Research and Treatment of Cancer (EORTC), the leading European academic research organization in the field of cancer.

Dr. Tombal is keenly interested in treating advanced prostate cancer and in the development of hormonal treatment and new biological agents.

Prostatepedia spoke with him about how newer agents like Zytiga (abiraterone), Xtandi (enzalutamide), and Erleada (apalutamide) have changed the prostate cancer arena.

WHY DID YOU BECOME A DOCTOR?

Dr. Bertrand Tombal: My mother was a nurse who went to patients’ homes. When I was young, I went with her on weekends and became interested in healthcare. I was very scientific. I have always been driven by science, so it was natural for me to become a doctor.

When I was around 17, I got interested in archaeology. Maybe because of Harrison Ford’s movie, I wanted to be an archaeologist. But I wasn’t sure what major to declare for college, so I decided to become a doctor while still enjoying archeology.

For a long time, I wanted to be a pediatrician, and I was quite good at that, so I was preselected to do pediatrics. In Belgium, we had a certain number of obligatory rotations. You have to do four months in internal medicine and four months in surgery. Because I so wanted to be a pediatrician, I skipped one month of surgery, but they wouldn’t let me graduate without that month.

I ended up working in a peripheral hospital for a month with a private urologist. I became crazy about urology, went back to my professor in pediatrics, and told them I didn’t want to be a pediatrician anymore. I wanted to be an urologist. And that’s how I started as an urologist.

FUNNY. LIFE TAKES YOU ON DIFFERENT PATHS.

Dr. Tombal: I like that urology is a broad specialty. You treat cancer patients and incontinence patients. You engage in a lot of private emotional things, so I liked it from day one. After two years, I did my PhD thesis on prostate cancer, which took about four years in the end, and that’s when I got interested in prostate cancer.

HAVE YOU HAD ANY PARTICULAR PATIENTS WHOSE CASES HAVE CHANGED HOW YOU EITHER SEE YOUR OWN SPECIFIC ROLE AS A DOCTOR OR HOW YOU VIEW THE ART OF MEDICINE?

Dr. Tombal: After completing my PhD thesis in 1998 in Brussels, I got an appointment at Johns Hopkins, where I finished my PhD. My former boss recognized that I liked to treat prostate cancer, but he preferred surgery, so he had me take care of the advanced cancer. I took care of advanced prostate and bladder cancers, which was not really a multidisciplinary approach at that time because there was no Taxotere (docetaxel) yet. Medical oncologists were not involved at all. We had a handful of old, hormonal treatments like estramustine phosphate (estrogen) or dexamethasone. That’s how I got interested in this. The bottom line is that I would follow many of my patients until death.

In 2000, supportive and palliative care were not yet developed. As an urologist, you would take care of guys usually in their 70s, and that’s where I started to speak with them and learn about interesting things, such as the relative importance of overall survival as compared to quality of life. That was meaningful. I learned from a few patients that, at some point, the only advantage you have as a doctor is that your patient has started the last round or two. You know he will die from the disease. You don’t know when, but you know it’s not that good.
I learned that it’s important to have discussions and ask lots of questions. Where do you want to go? What is important for you? Do you have a point you want to reach? What are you ready to accept?

It’s always been extremely important that we don’t impose the treatment sequence at the very end. There is always a point beyond which we should discuss with the patient the philosophy of the treatment and what we expect. In the end, we have to make the choice together. To me, it’s always been extremely important having that kind of conversation, so many of these patients gave me this philosophical approach.

I still believe that managing castrate-resistant prostate cancer is more about philosophical choices than scientific evidence. That’s why my background, having seen many patients before these drugs existed, is so important to me.

**BECAUSE WE HAVE ALL THESE NEW AGENTS, THE CONCERN IS WHEN, WHY, AND HOW TO USE THEM?**

**Dr. Tombal:** Yes. And that’s why I’m kind of disconnected from the rest of the world. I don’t think we should be so invested in these precise questions. We should rather generate data so that, at some point, we can talk with the patient and determine the benefit of starting now vs. delaying the treatment.

**MANY OF YOUR COLLEAGUES BRING UP QUALITY OF LIFE, FINANCIAL TOXICITY, AND ALL THESE SORTS OF ISSUES IN OUR CONVERSATIONS, AS WELL.**

**Dr. Tombal:** Sure. We physicians should find the words to explain different options to a patient rather than make a choice for them.

**HOW HAVE THE NEWER AGENTS, LIKE ZYTIGA (ABIRATERONE) AND XTANDI (ENZALUTAMIDE) CHANGED THE TREATMENT LANDSCAPE FOR MEN WITH CAstrate-RESISTANT PROSTATE CANCER?**

**Dr. Tombal:** These drugs changed treatment in three ways. First, urologists know that hormone therapy may have a profound effect on some patients. Having said that, in the late 90s, we had hormone therapies of limited efficacy. For better or worse, there was no regulatory platform development for historical hormone therapy, so we are missing good evidence that they increased overall survival or even significantly delayed progression.

These two new hormones build upon things we already knew for years, but they are far more effective, and more importantly, they have been developed following a strong regulatory context so that we know exactly their benefit.

But before that, the Taxotere (docetaxel) story was interesting for me because that’s one of the first studies I participated in. Seeing all these guys dying from prostate cancer, I thought it was unbelievable that we could increase overall survival.

I was thus extremely surprised that urologists in charge of managing advanced prostate cancer at that time would negatively react to chemotherapy and claim that the benefit was limited and toxic. Hence, patients would be referred by the physicians. I thought that was strange. From day one, I thought that we should ask what the patients think.

But the landscape changed again when we saw the results of the post-chemotherapy trials with Zytiga (abiraterone) and Xtandi (enzalutamide), how much they increased overall survival, and their major effect on PSA. We realized that we had game-changers.
But to me, changing the game was not necessarily about having patients live a little bit longer. I always go back to the many discussions I have had with patients who ask not whether they will live longer but if they will live better.

That’s why I was so excited about being one of the Principal Investigators on the Prevail trial. The Prevail trial was not about Xtandi (enzalutamide); we already knew the drug worked. Prevail was about having a discussion early on in the course of the disease, when the patient was becoming metastatic and castrate-resistant. We would ask: what do you want to do? Do you want to wait a bit and only start chemotherapy after you’ve got symptoms? Or do you want to start the drug immediately?

The patient would then ask about the side effects. I would say that there are side effects, but to give it a try, and if they didn’t want to live with them, we could simply stop the drug and the side effects would go away. These are oral drugs, so if you have side effects that are severe, you can just stop the drug.

That’s what was new, that not only could we help the patient live longer, but we could delay complications of the disease and buy him quality time.

It has really changed the way we treat patients.

If you look at newer trials, like Prosper and Spartan, they are having the same discussion but going one step further.

You have no metastases, but your PSA is progressing rapidly. What do you want to do for the rest of your life? Do you want to do nothing, enjoy a few additional months until you develop metastases and then start the treatment? Or do you worry enough that you would like to try one of these drugs to see if you tolerate it? To me, it’s no more complicated than that.

These drugs, Zytiga (abiraterone), Xtandi (enzalutamide), and now Erleada (apalutamide), have brought the possibility of discussing early on in the course of the disease what is important for that particular patient. Do you want to delay progression? Because in the end, these drugs are not very toxic.

That’s why these drugs are so important. And this is just the beginning. We’re not going to speak four years from now about giving Xtandi (enzalutamide) or Zytiga (abiraterone) in the metastatic castrate-resistant prostate cancer space because we’re going to give these drugs earlier and earlier to patients with high-risk disease together with radiotherapy and surgery.

We have a chance. What we want is to have prostate cancer patients die from something else.

A few years ago, Andrew C. von Eschenbach, an urologist that became the twelfth Director of NCI, said that his grail was to make cancer a chronic disease. That’s what we’re doing with these newer drugs: we’re making prostate cancer a chronic disease. We have never said we were going to make someone immortal, but hopefully we still delay the appearance of metastases and symptoms, so that they will die from something else.

That’s the beauty of trials like Spartan, Prosper, and (hopefully) Aramis in which Xtandi (enzalutamide), Erleada (apalutamide), or darolutamide are given at early signs of rapid PSA progression to delay the metastases. We used to say that at that stage of the disease, everybody will die from prostate cancer, but now we’re delaying progression so much that patients are going to start dying from something else and not have to go through all of the suffering associated with prostate cancer. That’s a major change.

That’s the change these drugs are bringing. They bring the possibility of intervening early and making prostate cancer a chronic disease. And yes, there is a slight increase in toxicity. And yes, at a huge increase in cost. But that’s how the world is.

DO YOU THINK IT’S OF ANY CONCERN THAT WE DON’T REALLY UNDERSTAND THE LONGTERM IMPACT OF THESE DRUGS?

Dr. Tombal: When people discuss this aspect, they assume that we have effective treatments to treat the progression. That’s not true.

It’s the same with bone-targeted therapy. I remember when bone-targeted therapy came on the scene, a famous medical oncologist said that what we are delaying is simply giving a little bit of cheap radiotherapy to the spinal column (on the lumbar spine). I said that was true, but you assume that cheap radiotherapy to the spinal column is effective. And it is not.

WHEN ARE BONE-TARGETED THERAPIES LIKE BISPHOSPHONATES AND XGEVA (DENOSUMAB) TRADITIONALLY USED, AND HOW HAS THEIR USE CHANGED NOW THAT THESE NEWER DRUGS HAVE COME ONTO THE SCENE?

Dr. Tombal: Less frequently. And that’s a major drama. Once again, it comes from a wrong interpretation of the data, from that oncological view that overall survival drives all decisions.

When the major study on zoledronic acid and Denosumab was published, people said it doesn’t make patients live longer or increase overall survival. I said that I didn’t care: increased survival is not what we expect from this drug.

What we expect from this drug is that it delays skeletal complications. It reduces the total number of bone complications in a patient’s lifetime. This means that, if you’re a gentleman of 70 years, and God has written in your book that you’re going to live another two years, you’ll get your first skeletal event in 12 months.

Xgeva (denosumab) will not make you live longer, but it will delay your first skeletal complication to 16 months. Once again, you’re buying quality time. You define that quality time as time without bone complications.
Then came Taxotere (docetaxel), Xtandi (enzalutamide), and Zytiga (abiraterone). They all extend overall survival and skeletal events. Physicians are starting to not prescribe these drugs because they say we don’t need them now that we have Zytiga (abiraterone) and Xtandi (enzalutamide).

Recently, Bayer conducted a clinical trial comparing Xofigo (radium-223) plus Zytiga (abiraterone) versus Zytiga (abiraterone) alone. The trial ended after a little more than one year because there was a significant excess of fractures and death. One of the striking observations is that only one-third of the patients in the trial received bone-protecting agents even though they had high-volume bone metastases with no visceral disease. (That was the inclusion criteria: high-volume bone metastases.) We believe so much that Xtandi (enzalutamide) and Zytiga (abiraterone) have a good effect, that we think patients don’t need bone protecting agents.

The European Medicines Agency’s statement says that, most likely, this excess of fracture happens only in patients not receiving bone-targeted therapy. Clearly, avoiding bone-targeted therapy has been a big mistake.

We believe that if we have drugs that increase overall survival, we don’t need bone-targeted agents. But now we realize that if patients live longer with bone metastases, we increase the likelihood that they’re going to have complications. These drugs are even more important than they were before.

**WOULD YOU SAY THAT MOST MEN ON DRUGS LIKE ZYTIGA (ABIRATERONE), XTANDI (ENZALUTAMIDE), OR ERLEADA (APALUTAMIDE) SHOULD CONSIDER BONEPROTECTING THERAPY?**

Dr. Tombal: If they have bone metastases, I would say yes. The question then becomes what to do if you only have one bone met.

In Europe, we use a lot of modern imaging technologies, such as PSMA and whole-body MRI. Sometimes, you see a man with a rising PSA and one or two bone mets that you don’t see in a bone scan. If that man has two, three, or four bone metastases that show signs of progression, such as increased alkaline phosphate, he should be on bone-protecting agents.

**WHAT SORT OF COMBINATIONS DO YOU THINK SEEM THE MOST PROMISING OR HAVE THE MOST BENEFIT?**

Dr. Tombal: At this point in time, we have failed to show that any combination is better than a single agent for prostate cancer.

When I’m speaking about combinations, I’m speaking about combining drugs to increase overall survival.

When Taxotere (docetaxel) came out, there was an epidemic of shotgun experiments where everybody tried to combine Taxotere (docetaxel) with all sort of agents, all usually having shown a strong rationale in the lab. Not one of those trials was positive. Most of them showed a benefit in favor of Taxotere (docetaxel) alone.

When Bayer said we’re going to combine Zytiga (abiraterone) with Xofigo (radium-223), that seemed like low-hanging fruit. They were combining two drugs with different modes of action and different toxicities that both showed an increase in overall survival when used alone. Nobody could have imagined that it would end in catastrophe—that combining the two agents would shorten survival.

At this point in time, there is not a single indication that one combination is better than a single agent in prostate cancer.

**WHAT SHOULD PATIENTS TAKE AWAY FROM THAT?**

Dr. Tombal: These agents: Zytiga (abiraterone), Xtandi (enzalutamide), Erleada (apalutamide), Taxotere (docetaxel), Jevtana (cabazitaxel), and in the United States, Provenge (sipuleucel-T), have been used sequentially, but not in combination. Combinations don’t have any benefit.

**DO YOU THINK THAT IS BECAUSE THERE IS SOME SYNERGISTIC EFFECT IN TERMS OF SIDE EFFECTS?**

Dr. Tombal: I have absolutely no idea.

That’s where we stand today.

**DO YOU HAVE ANY THOUGHTS FOR MEN WHO’VE BEEN PRESCRIBED ZYTIGA (ABIRATERONE), XTANDI (ENZALUTAMIDE), OR ERLEADA (APALUTAMIDE)?**

Dr. Tombal: I would say that one of the great messages of the Prosper and Spartan trials is that we probably do too much imaging, that it’s probably better to follow a patient just with PSA. Then when his PSA starts to increase rapidly, that is probably the time to talk about earlier treatment with one of these agents. That is when to have the overall discussion about what you want to do and where you want to go.

**WHY SHOULDN’T WE USE IMAGING AS MUCH?**

Dr. Tombal: Because we are tempted to offer additional treatments, such as radiotherapy, which have limited value, when we have at least five or six large Phase III trials that establish the philosophy of starting Zytiga (abiraterone), Xtandi (enzalutamide), and Erleada (apalutamide) earlier.

In Europe, we do a lot of imaging and a lot of salvage treatment. But we have to be honest, it’s driven by belief more than data.

**EUROPE IS AHEAD OF THE UNITED STATES IN THAT REGARD.**

Dr. Tombal: Being ahead has started to make us realize that we probably overtreat more patients than we help.

**THAT’S A HUGE ISSUE BECAUSE MEN CAN LIVE FOR A LONG TIME WITH OFTEN DEBLITATING SIDE EFFECTS.**

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

All radiation kills cells by damaging DNA; this damage prevents cellular replication and results in cell death. In most cases, death is NOT immediate – it can take months to years! (That’s why PSA does not drop to zero immediately following radiotherapy). All cells can be killed by radiation, but the needed dose varies. In general, malignant cells are less able to repair radiation injury – which means they can be killed by radiation doses which will not kill their healthy, normal counterparts. All advances in radiation therapy technology since 1896 have been stimulated by the desire to LIMIT radiation dose to normal tissue while INCREASING dose to the target. This is true of:

- **IMRT and other forms of external beam therapy with photons (x-rays or gamma rays)**
- **Protons**
- **Brachytherapy (temporary use or permanent implants of radioactive “seeds”)**
- **Radioimmunotherapy (a radioactive element carried by a protein or other molecule)**

We understand the physics of radiation therapy far better than we understand the basic radiation biology; hence, Research & Development has been focused on methods which exploit physics as opposed to radiation biology. Millions of patients were treated with “2-D” radiation therapy, based on squares or rectangles drawn on the skin. Many were “cured,” but of necessity, large amounts of normal tissue received large doses of radiation.

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

The dose bath received by surrounding tissues is substantial: The intestines receive 2500-3000 rads (equivalent to a curative dose for lymphoma; or to several thousand CAT scans!). Nevertheless, IMRT has become the de facto standard of care for external beam treatment of prostate cancer – not based on Phase III data (there is none) but because of a) physics vs. non-modulated protocols and b) widespread availability.

Protons have superior physics (because they stop instead of passing all the way through), but far inferior availability, largely due to cost and complexity of facilities. Whether we like it or not, protons will
continue to fall under intense scrutiny and restricted applicability unless we can show that there is a demonstrable clinical benefit to justify the increased cost and/or the cost of proton therapy can approximate IMRT.

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

The California Protons Treatment Center (which cost something like $200-250 million) has five treatment rooms in 100,000 square feet. Now, hospitals can opt for a single-room center that fits the area of a tennis court, and costs only about $20-25 million. This is a huge cost reduction that will allow many more centers to be built around the country, and make proton therapy more affordable and available.

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

There are now 28 operational proton treatment centers in the USA, with more than 18 of various sizes under construction or in planning. Construction can be done within 24 months from groundbreaking to first patient treatment. A small center in England was completed in a single year.

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

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

See the video and slides for impressive pictures of how well the dose with proton treatment spares the surrounding tissues, compared to x-ray treatments, and how effective the SpaceOAR® gel helps to separate the prostate from the rectum, thus protecting the latter from damage. Details on the SpaceOAR gel are in the Q&A section of the video. Video/DVDs of our meetings are available in our library for $10 each. Refer to the index available in the library. They can also be purchased through our website: http://ipcsrg.org Click on the “Purchase DVDs” tab. The DVD of each meeting is available by the next meeting date. Also, see an example of retreating the prostate after recurrence, either in the prostate or in regional lymph nodes.

The first proton treatment of prostate cancer was done in 1977. Since then, over 100,000 men with prostate cancer have been treated with protons. Recent publications: A University of Florida study showed that patients with low or intermediate risk prostate cancer treated with protons had lower biochemical recurrence rates than others treated with IMRT, despite the fact that ADT was used more frequently and for longer duration in the IMRT patients. Also, toxicity (to the rectum or bladder) was significantly lower in the proton therapy patients, despite their being given a higher median dose. A study at Northwestern University showed that 5-year overall survival of intermediate-risk patients was 93.6% for proton treatment, and 87.9% for IMRT patients. The difference was explained by an increase in “secondary malignancies” beginning to appear after three years, with the 5-year rate being 6% vs. 10.6%, respectively, especially in pelvic malignancies and leukemias. This is likely due to the protons stopping at the target, vs. x-rays passing clear through the body.

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

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

**QUESTION & ANSWER SECTION:**

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

Proton treatment after surgery and prior radiation? Dr. Rossi does this regularly. Often the SpaceOAR is a big help, to protect the rectum.

Treating several spots within the prostate? Those spots are given a higher dose, but the whole prostate is treated, to try to eliminate other (microscopic) tumors that are likely present.

Side effects after proton therapy? Similar in kind to those for X-ray therapy. More frequent urination is very common, for a time. Bowel problems are much less of a problem compared to X-ray therapy. Other issues are quite rare.

Radiation-induced fatigue? The amount of fatigue depends on the amount of normal tissue irradiated in conjunction with the cancer treatment, because that tissue has to recover. So fatigue is a lot less with proton therapy than with X-rays, because there is much less damage to normal tissue from proton therapy.

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

What are the new algorithms that are coming out, and how do they help? “Monte Carlo” calculations help better predict the stopping power for protons in various tissues (so the dose will be more accurate), doing CT scans with two different X-ray energies gives better info, and faster software is beginning to allow “real-time” adjustments of the treatments (what used to take two weeks can now be done in 15 seconds!). This all gives more accuracy and tighter “margins.”

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

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

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

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

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

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

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

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

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

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

More details and images from various scans are shown in the video of this presentation, which, including the PowerPoint slides, are available for purchase via the website http://ipcsrg.org.
Proton beam therapy, a form of external beam radiation, has been around for a while but is less commonly utilized than other forms of radiation therapy, which is partly due to availability. Certain properties of protons show potential for a different approach to radiation therapy. This article also considers how implementation of imaging helps improve treatment outcomes.

BASICS OF PROTON THERAPY
Proton therapy for prostate cancer was first performed in 1977, long before the development of intensity modulated radiation (IMRT). Proton therapy first became clinically available in 1990. Proton therapy is a type of external beam radiation. However, unlike the commonly available type of x-ray therapy such as IMRT and SBRT (ex. Cyberknife), proton therapy utilizes subatomic particles (protons). Protons and x-rays have equal anticancer effects. The advantage of protons lies in their ability to reduce radiation exposure to the normal body tissues surrounding the prostate.

Protons interact with human tissue differently than x-rays. X-rays pass straight through the body with a substantial amount of radiation energy exiting out of the body. Everything within the path of the beam receives radiation. In contrast, protons deliver a low ‘entrance dose’ (radiation dose to tissues in front of the target), and place their highest dose within the target, and sharply limit exposure beyond the target. These unique physical properties are called the “Bragg Peak.” The Bragg Peak phenomenon is unique to proton therapy.

ENHANCED PROTON TECHNOLOGY
To date, the vast majority of prostate cancer patients who have been treated with proton therapy have been treated with passive-scatter proton therapy (PSPT). With PSPT, the proton beam is shaped by a solid lead block which is manufactured and customized for each individual patient. The type of beam it creates completely covers the target volume with a uniform dose of radiation. However, with PSPT it is impossible to vary the radiation dose within the target area. So PSPT, for example, is unable to boost the dose to the high-value target area or dose attenuate (minimize radiation) in adjacent normal structures. In addition, PSPT technology, due to limitations inherent to its lead-block methodology, is unable to treat larger target areas, such as the pelvic lymph nodes in the pelvis.

These limitations with PSPT have motivated the development of intensity-modulated proton therapy (IMPT). IMPT steers the proton beam to the target using electromagnetic forces. The proton dose is laid down throughout the target volume in a fashion analogous to a 3D printer manufacturing a complex solid object, with the protons typically being placed in layers that are approximately 1 millimeter thick. This ability to “paint” the proton dose makes it possible to create differential radiation doses throughout the target volume, so that areas containing the greatest amount of tumor can receive substantially higher doses. IMPT is not constrained by field size limits as was PSPT, making it feasible to treat targets within the pelvis. Commencing in February 2014, the Scripps Proton Therapy Center in San Diego was the first facility in the United States to implement intensity-modulated proton treatment.

OPTIMAL TREATMENT PLANNING AND TARGETING
Multi-modality imaging enables the creation of a three-dimensional map of the target area. At Scripps, all prostate cancer patients undergo a thin-slice pelvic CT and a multi-parametric prostate MRI. The image sets are combined to create a composite, three-dimensional reconstruction of the prostate and pelvis. The addition of multi-parametric MRI has been a significant advance which has enabled us to target intra-prostate disease with a higher radiation dose. The planning session is performed with a rectal balloon, which stabilizes
the prostate, and minimizes gland motion. All patients are treated on a six-degree-of-freedom robotic couch that can move in sub-millimeter increments. Patients are typically treated lying on their back.

Prior to entering the treatment room, each patient undergoes a daily bladder ultrasound to verify that a minimum amount of fluid is present within the bladder. The patient’s position is verified by performing a daily CT scan in the treatment room. A planning system then analyzes his position and commands the robotic treatment table to move in such a fashion as to match the original treatment plan developed at the patient’s first visit.

Typically, the “beam on” time is approximately 20–30 seconds per radiation field. The average time spent by the patient in the treatment room, including all of the above set-up and positioning, is less than 20 minutes. There are no restrictions placed on physical activity during treatment and most patients tolerate treatment with little, if any, difficulty.

**A SHORTER COURSE OF TREATMENT**

Historically, a course of proton therapy was administered over a 9-week period. At Scripps, our most common protocol requires 5 ½ weeks to complete. During that time, the entire prostate receives a radiation dose equivalent to 80 Gray. The cancer itself is boosted an additional 10 Gray to a radiation dose equivalent of approximately 90 Gray.

**CLINICAL RESULTS WITH IMPT**

Since the availability of IMPT in the United States is very new, the number of IMPT-specific prostate publications remains limited. The largest study comparing patients treated with IMPT and patients treated with PSPT concluded that the cure rates were identical (as might have been expected), however, there was a decrease in gastrointestinal toxicity (primarily rectal toxicity) favoring those patients treated with IMPT.

**FUTURE DIRECTIONS**

IMPT technology is rapidly evolving with the primary advances being in more sophisticated planning and delivery systems. For example, we expect that within five years that patients will be able to be planned in “real time.” This means that the treatment plan can be adjusted as necessary on a daily basis to reflect any changes in tumor size or patient anatomy. In addition, there are a number of trials taking place which examine the feasibility of shortening the duration of treatment further. Hopefully, these efforts will prove successful which would permit a greater number of prostate patients to take advantage of this technology.

Carl Rossi, MD is a radiation oncologist specializing in proton beam therapy, specifically for prostate cancer and lymphomas. He is also the current medical director for the Scripps Proton Therapy Center, which will provide treatment to target tumors with high control and precision. Dr. Rossi has a research focus on the quality of life and cure rate in prostate cancer and lymphoma treated with proton beam radiation.
followed for 2 years after nerve sparing radical prostatectomy, almost all men can experience the orgasm sensation. The majority of our men either describe it as different/diminished or similar to the pre-surgical orgasm/climax sensation. A small percentage of men have a more intense climax after prostatectomy. There is no problem with having an orgasm with no erection or a partial erection. It is difficult to not compare it to your memory of pre-surgery orgasm intensity, but to fully enjoy the sexual experience and orgasm you need to be fully present (and not comparing in your mind).

As you continue to recover after radical prostatectomy, you may find it helpful to be completely open and present during your sexual experiences to enjoy each sensation and pleasurable feeling. Anxiety can impact your erections and your ability to climax, so try and keep your mind directed to sex and pleasure. Being completely present experiencing every nuance of the sexual encounter may help you enjoy sex more fully.


You can access the new edition of my book or download a free copy of my original book at [www.drjeffalbaugh.com](http://www.drjeffalbaugh.com).

Do you have a question about sexual health or intimacy? If so, we invite you to submit it for possible inclusion in future Between the Sheets columns. Please email your question to: ustoobTS@ustoo.org or mail your letter to: Us TOO International Between the Sheets, 2720 S. River Road, Suite 112, Des Plaines, IL 60018
Your sex life can be affected when any change happens in your life, and cancer is certainly no exception. However, whether your diagnosis is recent or long in the rear-view mirror, being diagnosed with cancer doesn’t disqualify you from having a satisfying sex life. It may be different from what it was before, but that doesn’t mean your sexuality is gone. To make the most of your sex life after cancer, keep in mind these three P’s of sexual intimacy

**THE THREE PS OF SEXUAL INTIMACY**

1. **Pressure:** Talk to your partner about removing intimacy expectations. Create a pact against all-or-nothing thinking and movie-performance expectations.

2. **Pleasure:** Write down a list of intimate activities you want on your pleasure buffet. When it comes to your intentional intimacy time, pick what you can say yes to right now, in whatever form that takes. This may change from week to week, and you can add to or remove anything from the list at any time.

3. **Priority:** Experiment with what helps you feel good and sexy throughout the day and with what helps transition your brain into pleasure mode.

**1. AVOID THE PRESSURE MINDSET**

Physical intimacy isn’t about a perfect, movie-quality performance. Unfortunately, many people believe this to be true because that’s what Hollywood has conditioned us to expect. Cue steamy movie scene where eyes lock from across the room, a lip-bruising kiss occurs, clothes are ripped off, and 60 seconds later the actors are lying beside each other sweaty and sighing with gratification. Is this realistic? No. Are real-life struggles like cancer ever even considered in these love scenes? Not typically.

If you try to live up to this unrealistic model of sex, then you are guaranteed to feel like a satisfying sex life is unreachable. With this pressure around what sex is “supposed” to look like, you may find yourself thinking, “I just don’t have the energy to go through the whole charade, so why even bother?” This can especially be the case when you are grappling with the ups and downs and all arounds of cancer.

It is essential for couples dealing with cancer to dump this perfectionist, all-or-nothing mindset that says sex just happens spontaneously, that intimacy is always effortless, and that circumstances like cancer and all its side effects can be easily put on the backburner any time sex is on the table. Not only does this way of thinking add tons of pressure when it comes to sexual intimacy, but it also limits your opportunities for intimate connection. It leaves no space for the many diverse ways in which couples can connect emotionally, physically, and sexually.

**2. FOCUS ON THE PLEASURE**

When it comes to physical intimacy, you must throw the movie script out the window. It is not realistic. What is realistic – and wonderful – is the fact that the human body is a pleasure smorgasbord that offers abundant options for intimate connection. This is especially important to remember as you go through cancer, and beyond, because your sexual needs and how you experience pleasure will continually evolve. And when you shift your focus away from the pressure-fueled obligation to achieve orgasm every single time you become intimate and instead choose to focus on the pleasure of genuinely connecting with your partner, then intimacy can look however you want it to.

Simply ask yourself, *What intimate activity can I say yes to today?* Kissing on the couch? Exchanging sensual massages in bed? Offering your partner a genital caress? Enjoying a shower or bath together? Intimacy is a buffet of pleasure, and the possibilities are endless. Choose what works for you, where you are today. These activities certainly may include penetration or orgasm, but neither is required. And, no matter what pleasurable activity you choose, know that it doesn’t have to lead anywhere beyond simply enjoying the activity itself.

**3. MAKE YOUR SEXUAL SELF A PRIORITY**

You are a sexual being, and cancer will never take that away from you. Yes, your sexuality may look different than it did before cancer, and your desires will likely evolve and change as you journey through this chapter of your life and beyond. But your sexuality will always be an important part of you. Keeping this part of you alive is essential.

One of the most effective ways to prioritize your sexual self is to put sex on the calendar. I know, I know, it’s not what they do in the movies. But, remember, your life is not a movie. In the real world, where jobs, kids, and cancer cause mayhem, we must eschew our expectations that things will just happen spontaneously! It is imperative to set aside time for sexual intimacy, and to make it a priority. Even if you don’t have a partner, setting time aside to feel sexual in your body and to connect with yourself sensually helps you to fulfill this natural, normal, and essential part of your being.

Once you set the time aside, you then need to be intentional. You can’t just show up and expect something to magically happen. Prepare yourself for your intentional intimate time by taking a few moments earlier in the day to do things that help...
you feel good about yourself. For example, exercise, getting out of your pajamas and putting on a flattering outfit, and eating healthy rather than stuffing yourself at dinner-time (say hello to feeling bloated and so not sexy).

Preparing also means transitioning from the regular part of your day into the intimate space by stimulating your mind, as the mind holds the key to sexual desire. To get into the pleasure mindset, try listening to sensual music; smoothing lotion on your body, slowly and intentionally; or reading erotic literature, either alone or with your partner.

Remember, a cancer diagnosis does not mean you have to say goodbye to your sex life. But, to make the most of your sexuality, it is important to embrace the changes brought on by cancer and to be intentional about prioritizing this vital part of your life. This includes asking your doctor about how your cancer diagnosis and treatment may affect you sexually and what you can do to mitigate these effects. With some patience and a little effort, you can keep your sex life alive and fulfilling, even after cancer has entered the picture.

Dr. Chelsea Holland is a sex and relationship therapist in Colorado. She has helped many individuals and couples find fulfilling intimacy by encouraging them to explore, embrace, and enhance their relationships and sexuality, while mitigating problems that may be hindering their fullest potential. You can read her blog and find her free “Oh Yeah!” sex guide at DrChelseaHolland.com.
Immunotherapy is the most revolutionary advance in the treatment of cancer. This new therapy is based on recognition of the immune system's role in identifying and killing all "foreign" invaders, including bacteria, viruses, and cancer cells. Cancer cleverly escapes detection and destruction by chemically blocking the immune cells at their checkpoints. What if we could un-block this blockade, thereby unleashing the full targeted killing effect of the immune cells and perhaps destroy cancer? Well, we soon may succeed in doing so...and probably with fewer side effects.

Such checkpoint targeting is precisely the basis of the immunotherapy revolution--the Nobel Prize committee agreed in granting the 2018 Medicine awards to the investigators whose work resulted in two new classes of drugs: anti-CTLA-4 and anti-PD-1 checkpoint inhibitors. These drugs unblock the immune blockade and facilitate the immune system, and include medications with unpronounceable names such as ipilimumab (anti-CTLA-4), nivolumab (anti-PD-1), pembrolizumab (anti-PD-1), and many others. These drugs are now routinely used in certain forms of cancer of the lung, skin, bladder, kidney, and other sites, with more indications being added monthly. A small, but significant number of patients have dramatic and durable responses with otherwise-hopeless metastatic cancer, demonstrating proof of the success of targeted manipulation of the immune system.

Yet, despite widespread success in many cancers, many patients do not benefit from these new therapies, with only 15-20% responding (up to 40% in malignant melanoma), and the benefits are often not durable. Further, the side effects are limiting, with numerous unique and serious immune-related responses, including death. In addition, these new drugs have failed to provide significant benefit in treating prostate cancer, an unexpected outcome given the early success afforded by the first FDA-cleared immunotherapy for cancer: Sipuleucel-T (Provenge™), a leukapheresis cell-based treatment.

Can we salvage any benefit from checkpoint inhibitors for prostate cancer? Can immunotherapy be improved so that it is more successful in those cancers with only limited response? There is significant cause for optimism. The field of immunotherapy is moving faster than any other domain in medical treatment today. New treatments are constantly being proposed, with literally thousands of immunotherapy clinical trials currently underway for cancer and other diseases, including more than 100 that are specifically directed against prostate cancer (see Clinicaltrials.gov, Feb. 2019). The table below presents a select list of available therapies that directly or indirectly affect the immune system.

### SELECT THERAPIES FOR DIRECTLY OR INDIRECTLY HARNESSING THE IMMUNE SYSTEM TO TREAT PROSTATE CANCER

<table>
<thead>
<tr>
<th>Drug or Treatment Class</th>
<th>Examples</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Checkpoint Inhibitors: anti-PD-1</td>
<td>Pembrolizumab</td>
<td>Disrupts cancer evasion signals, exposing cancer to the immune system</td>
</tr>
<tr>
<td>Checkpoint Inhibitors: anti-CTLA-4</td>
<td>Ipilimumab</td>
<td>Suppresses specific immune cells (T-regs) to unleash cell-mediated cancer cell destruction</td>
</tr>
<tr>
<td>Leukines and cytokines</td>
<td>GM-CSF, IL-2</td>
<td>Stimulates the immune system to attack cancer cells</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>Cyclophosphamide</td>
<td>Direct cell toxicity; suppresses select immune cells (T-regs) at low dose to unleash cell-mediated cancer cell destruction</td>
</tr>
<tr>
<td>Therapeutic Cancer Vaccine</td>
<td>Prostvac-VF</td>
<td>Facilitates targeted immune response and cell-mediated cancer cell destruction</td>
</tr>
<tr>
<td>Radiation Therapy</td>
<td>External beam irradiation</td>
<td>Mixed effect: both stimulates and suppresses immune system</td>
</tr>
<tr>
<td>Ablation Therapy</td>
<td>Cryoablation</td>
<td>Induces cell necrosis that stimulates the immune system</td>
</tr>
</tbody>
</table>

Promising strategies and tactics with immunotherapy include the following:
- Optimize cancer-specific protein presentation.
- Combine multiple immunotherapy drugs.
- Combine immunotherapy with other therapies such as chemotherapy, radiation, or ablation.
- Decrease side effects with intra-tumoral injection of drugs.
- Harness the Abscopal Effect.

### OPTIMIZE CANCER-SPECIFIC PROTEIN PRESENTATION

Cancer cells have molecular signatures that are specific for each individual and each cancer, referred to as cancer-specific proteins (also called cancer-specific antigens). To create a personalized patient-specific immunotherapy vaccine, it is first necessary to expose the unique foreign proteins within the cancer cells to prime the immune system. The surface of the living cancer cell--the cell membrane--is fluid, allowing the cancer-specific
antigen proteins to extend above the surface and then quickly submerge, disappearing from view, reminiscent of the game “Whack-a-mole.” When cancer cells die, membrane fluidity stops and the membranes disintegrate, exposing antigens to immune cells in the surrounding tissue that act as sentinels for such “foreign” proteins.

Cell-destroying treatments such as; radiation therapy, cryosurgery, radiofrequency ablation, or high-intensity focused ultrasound are useful in killing cancer cells and exposing cancer-specific antigens as targets for the immune system (see below). To ensure specific activation of cells of the immune system, it is critical to avoid altering the 3-dimensional protein structure of antigens so that they remain in their recognizable native form. This approach is now under active investigation by multiple groups.

**COMBINE MULTIPLE IMMUNOTHERAPY DRUGS**

With cancer treatment, it is often accurate to state that “…more is better than less.” For example, cure of certain types of childhood leukemia emerged in the 1960s when chemotherapy drugs were used in combination rather than as single agents. Combination chemotherapy using more than one drug is now of proven value in controlling and often curing many cancers. This successful strategy targets multiple weaknesses in cancer cells at the same time, and may have additive or synergistic benefits.

For immunotherapy, investigators are now discovering the value of combining more than one drug to block multiple mechanisms of cancer cell growth. There are multiple combinations to consider, including immunotherapy drug combinations (such as anti-PD-1 and anti-CTLA-4) of immunotherapy and chemotherapy drug combinations (such as anti-PD-1 and low-dose cyclophosphamide).

**COMBINE IMMUNOTHERAPY WITH OTHER THERAPY SUCH AS CHEMOTHERAPY, RADIATION, OR ABLATION**

Cancer cells killed by chemotherapy, radiation therapy, and all forms of ablation have immunostimulatory activity. Ablation is a surgical technique used to destroy cells, organs, or abnormal growths (such as cancer). For example, cryosurgical freezing with massive destruction of cancer cells and tissue often elicits an immune response through the presentation of an unique array of cancer-specific antigens to the patient’s immune system. Unfortunately, this “cryoimmunologic effect” is variable and unpredictable. It is possible that a combination of immunotherapy and one or more of these other cancer treatments may provide substantial benefits beyond conventional therapy. How best to identify patients who would benefit from these combined modalities remains an important question.

**DECREASE THE SIDE EFFECTS WITH INTRA-TUMORAL INJECTION OF DRUGS**

The delivery of immunotherapy drugs is most commonly performed intravenously, which can have serious and sometimes fatal systemic toxicities as a result of nonspecific distribution of cytotoxic agents in the body, killing both cancer cells and normal cells and often negatively impacting the treatment regimen and patient outcome. Side effects of immunotherapy are often limiting, but shrewd tactics such as intra-tumoral injection of drugs or combination with low-dose chemotherapy will likely decrease adverse events. Intra-tumoral injection of immune-stimulating drugs significantly lowers the adverse event rate when compared with systemic immunotherapy by intravenous injection. Intra-tumoral injection avoids most (but not all) adverse events and allows combinations of drugs with different mechanisms of action to be employed.

**HARNESS THE ABSOCOPAL EFFECT**

The abscopal effect (‘ab’ - away from, ‘scopus’ - target) was first described in 1953 to describe the creation of systemic effects following local radiation treatment. For example, the abscopal effect is observed when brachytherapy induces regression of distant lymph node metastases; unfortunately, this is a rare and unpredictable occurrence, likely resulting from immune system stimulation. Today, the “abscopal effect” may result from localized ablation treatment other than radiation therapy, including cryosurgery and electroporation, although the effect is exceptional and erratic. Medications whose effects result from circulation through the blood stream are not considered an abscopal response. Current efforts are underway to understand mechanisms underlying the abscopal effect in order to harness this process predictably.

**CONCLUSION**

Recent advances in immunotherapy have uncovered a mother-lode of exciting new treatment strategies that promise to create personalized patient-specific and cancer-specific vaccine to harness the natural power of the immune system—including the abscopal effect—and eradicate cancer with decreased risk of adverse events when compared with conventional treatment.
Dr. Mario Eisenberger is a professor of urology and oncology at the Johns Hopkins School of Medicine who focuses on treating prostate, bladder, kidney, and testicular cancers.

He spoke with Prostatepedia about how drugs like Zytiga (abiraterone), Xtandi (enzalutamide), and Erleada (apalutamide) have changed the prostate cancer treatment landscape.

WHY DID YOU BECOME A DOCTOR?
Dr. Mario Eisenberger: I was born in Brazil. I always heard that, if you are Jewish (even in Brazil) you have to be a doctor or a lawyer. Then I was sick when I was growing up. I don’t remember what it was, but I stayed out of school for maybe six weeks. There was this doctor who came to visit me daily, and when I recovered and saw how happy he was for helping me, that is what I could see myself doing.

ARE THERE ANY PARTICULAR PATIENTS WHO STICK OUT IN YOUR MIND, WHOSE CASES MAY HAVE CHANGED HOW YOU SEE YOUR OWN ROLE AS A DOCTOR OR HOW YOU THINK OF THE ART OF MEDICINE?
Dr. Eisenberger: I changed completely from the way I started. When I finished medical school, I wanted to get in a field of internal medicine, either gastroenterology or cardiology. I became fascinated with oncology even before it was recognized by the American Board of Internal Medicine (ABIM) as a sub-specialty of internal medicine. As soon as I got in the cancer ward, I was impressed by how little one could do to help cancer patients. Many times, we couldn’t even take care of their pain adequately. I wanted to be part of a team to help these patients and perhaps contribute to improve the quality of life and survival for patients with cancer.

I finished medical school in Brazil in 1972 and my training in medical oncology in 1978. Then, I became an oncologist with an interest in prostate cancer. I subsequently went to the National Cancer Institute and the University of Maryland, and now I’ve been at Johns Hopkins for the past 25 years.

My views on oncology and medicine in general have changed over the years. Oncology has shaped me to become a better person – more understanding, more considerate.

YOU’RE CARING FOR PEOPLE. IT’S NOT JUST ABOUT THE SCIENCE?
Dr. Eisenberger: Absolutely.

HOW DO XTANDI (ENZALUTAMIDE), ZYTIGA (ABIRATERONE), AND ERLEADA (APALUTAMIDE) WORK? HOW ARE THEY DIFFERENT FROM EACH OTHER?
Dr. Eisenberger: Over the years, we thought that androgen deprivation would induce a remission in a majority of patients in about 18 months to two years later, and then the disease would become active again. The thinking was that prostate cancer cells were not responsive to hormonal manipulations. The next step was chemotherapy. Today, we know that’s not the case.

We now know that a cancer cell adapts to the environment of low levels of androgens and survives. Now, it is recognized that the androgen receptor, which is a potent driver of prostate cancer growth, amplifies and undergoes important molecular changes and continues to drive the growth of the disease. In addition, a process called intracrine production of androgens inside the cell enhances intracellular testosterone production. Drugs that bind to the androgen receptor, such as Xtandi (enzalutamide), and Erleada (apalutamide), inhibit nuclear translocation, binding to DNA, and inhibiting cancer growth. Clinical trials tested the hypothesis, and Xtandi (enzalutamide) was approved.

Earleada (apalutamide) is similar to Xtandi (enzalutamide) with a few minor differences. Erleada (apalutamide) was tested in patients with non-metastatic disease. They were never compared head-to-head, but they’re similar, with some differences in side effects or safety profiles.

Zytiga (abiraterone) is a drug that works a little differently. It targets the synthesis of androgens that activate the androgen receptor. By blocking androgens inside of the cancer cell, it can induce another response.

Zytiga (abiraterone) doesn’t bind to the androgen receptor but starves it further. After surgical castration, there is still some residual testosterone, which is further suppressed with Zytiga (abiraterone). These three compounds are a “proof of principle” that the role of the androgen receptor and residual testosterone remain important and that targeting this mechanism induces additional benefits, such as improvement in responses, salvage of responses, improvement in survival, or prolongation of progression.

A number of years ago, I was part of a panel examining ways to design trials for patients with non-metastatic castrate-resistant prostate cancer. The agency wanted to understand the approach for drug approval pathways in that space.

The FDA staff asked why they should approve drugs in a paradigm that evolved from a non-FDA-approved treatment that was also clinically unproven. In other words, even
though androgen deprivation treatments were not approved for men with rising PSA levels after local treatment (without metastasis), they were used that way. So, they were reluctant to enable use when patients present later with another rise of PSA and no metastasis. They thought we should educate physicians that, before they treat patients with non-metastatic disease, we should run support clinical trials to determine whether that’s in fact a benefit to the patient.

In the end, the consensus was that regardless of whether it was right or wrong, men with castrate-resistant disease eventually developed metastasis, and if a metastasis can be deferred in a major way, this constitutes a clinically meaningful benefit. That's why these drugs were approved.

**WHAT ARE THE SIDE EFFECTS LIKE? ARE THEY SIMILAR FOR EACH OF THE AGENTS, OR DO THEY VARY?**

*Dr. Eisenberger:* Erleada (apalutamide) and Xtandi (enzalutamide) have similar side effects. They cause fatigue, skin rashes, changes in liver function (blood tests), nausea, decreased appetite, and rarely, may induce seizures (enzalutamide) in patients with a history of seizure disorders.

These drugs bind to an enzyme in the central nervous system called GABA. The binding is not prominent, but that's what we think is the mechanistic cause of the increased incidence of seizure, particularly in patients who are taking certain medications or who have a prior history of seizure. The incidence is less than one percent.

Enzalutamide has a relatively long half-life of six days. After one month of Xtandi (enzalutamide) a “steady state” is reached. We think that there is a relationship between the pharmacology of enzalutamide and the side effects.

In my opinion, it is possible that a lower dose could be used after one month of full dose treatment. It would be interesting, and probably cost-effective, to give these drugs for about four weeks and then give a lower or half-dose – maybe one pill instead of four a day. This has not been tested clinically, it is only my opinion.

Zytiga (abiraterone) causes fatigue and some changes in the liver function test, but these are not common. Zytiga (abiraterone) is used together with steroids because there is a tendency of increased blood pressure, fluid retention, edema in lower extremities in particular, and potassium levels in the serum go low. A lot of this is counteracted by low doses of prednisone.

These drugs were approved in clinical trials with a relatively short follow-up time. Based on the data, we saw late side effects due to longer use of these compounds in patients with less advanced disease and hormone sensitive disease, and that's why we're considering the use of Zytiga (abiraterone) earlier in the course of the disease. In my view, more information is needed in this area. There's not a lot of information on what happens in patients who are taking Zytiga (abiraterone), Xtandi (enzalutamide), or Erleada (apalutamide) for periods longer than five years, which is what will happen if you use these early on.

Drug interactions are also important issues with all these drugs, especially because they are used in age groups where multiple other drugs are often used.

**IS THAT BECAUSE THESE DRUGS ARE RELATIVELY NEW, AND WE DON’T YET HAVE LONG TERM FOLLOW UP STUDIES?**

*Dr. Eisenberger:* Yes.

**ARE THESE DRUGS, INDIVIDUALLY AND AS A CLASS, COMBINED WITH OTHER KINDS OF AGENTS? IF SO, ARE THERE CERTAIN AGENTS THEY’RE ROUTINELY COMBINED WITH? ARE THEY USED IN SEQUENCE, AND ARE THEY SWITCHED FROM ONE TO ANOTHER?**

*Dr. Eisenberger:* Zytiga (abiraterone), Xtandi (enzalutamide), and Erleada (apalutamide) were approved for patients who have castrate-resistant disease. They were tested at almost the same time and were approved within two to three years of each other. The results were very similar and the best sequence for using these drugs has not been determined. It is clear that the efficacy of these drugs decreases when used sequentially.

One of the mechanisms of resistance discovered by my colleagues at Johns Hopkins was a mutation of the androgen receptor. This is an RNA mutation. The actual androgen receptor is still there, it truncates, so the site to which these compounds or testosterone bind is no longer present.

The first androgen receptor variant is called the AR-V7, which is a truncated androgen receptor that is still active but doesn't have the hormone-binding domain, and it doesn't respond to current therapy. The cancer still depends on it, and this is a good example of adaptation.

About 15-25 percent of patients with castrate-resistant disease will have AR-V7 in circulating tumor cells. I find the blood test helpful to determine subsequent treatment for my patients. If there is AR-V7 in circulating cancer cells, the response to Xtandi (enzalutamide), Erleada (apalutamide), or Zytiga (abiraterone) is virtually zero.

Here is where the sequence is important. I would anticipate that the same thing occurs if you use it earlier.

Zytiga (abiraterone) is approved for use combined with standard androgen deprivation treatment up front in patients with hormone-sensitive disease. While we don’t know for sure, it’s reasonable to assume that the earlier you introduce these compounds, the earlier the mechanisms of resistance will occur, and therefore drugs are likely to be less effective later, when the patient becomes castrate-resistant.

That’s especially important in castrate-resistant patients who have no metastases (non-metastatic castrate-resistant disease), and Xtandi (enzalutamide) and Erleada (apalutamide)
are approved by the FDA for these patients as well. You're going to start using Erleada (apalutamide) and then Xtandi (enzalutamide) later, when patients develop metastatic disease. It's unclear how sensitive they remain to androgen receptor-targeted compounds.

The sequence is important.

**WHAT ABOUT USING THE AGENTS IN COMBINATION WITH OTHER TYPES OF DRUGS, LIKE IMMUNE-THERAPEUTIC AGENTS OR CHEMOTHERAPY?**

**Dr. Eisenberger:** That is all still being investigated. There is some potential here. There is a major need for effective predictive biomarkers to help determine what treatment we should use, hormonal therapy, some types of chemotherapy, and perhaps even precision medicine.

**I SUPPOSE THE MORE AGENTS YOU ADD, THE MORE SIDE EFFECTS A PATIENT WILL EXPERIENCE?**

**Dr. Eisenberger:** Absolutely, and it becomes prohibitively expensive.

**YES, THE COST OF THESE AGENTS IS A CONCERN FOR MANY. DO YOU HAVE ANY THOUGHTS ABOUT THAT?**

**Dr. Eisenberger:** It's a major problem. A recent study published in the Journal of Clinical Oncology compared a single 250 mg tablet of Zytiga (abiraterone) to the standard 1,000 mg in a large, randomized Phase II trial. The study was conducted because it was suggested that when Zytiga (abiraterone) is administered with food, it would be better absorbed and have an effect that could be comparable to the full dose. The study met its endpoint, and I hope that this will lead to further testing of Zytiga (abiraterone) with food because this could cut drug costs substantially and possibly improve its safety profile.

Similar considerations could apply to Xtandi (enzalutamide), which has a half-life of six days. A steady state plasma concentrations occurs after about 28 days of daily 160 mg doses, and this could be maintained at lower doses, such as half or even one fourth the full dose, without affecting blood levels significantly. Again, this could mean it becomes safer and would cut the costs significantly. I also have patients who responded extremely well with drugs every other day, given that way because they could not tolerate full doses after one month of treatment.

**OBVIOUSLY, BY REDUCING THE DOSE, YOU WOULD REDUCE THE SIDE EFFECTS IN TERMS OF FATIGUE, AS WELL.**

**Dr. Eisenberger:** Absolutely. That’s an important piece here. It’s certainly safer to give somebody half doses of Xtandi (enzalutamide). The lower toxicity would also be much less for the pocketbook. Insurance companies would be more motivated to cover most of it. It certainly would be safer. If you’re going to use the drug longer – because we’re now using it for patients before they have metastasis – then the outcome figures are interesting. Then safety is important.

**DO WE JUST HAVE TO WAIT FOR THAT DATA?**

**Dr. Eisenberger:** It is preferable to await clinical trials; however, these studies are expensive and take a long time to conduct.

**IS THAT BECAUSE THE PHARMACEUTICAL COMPANIES AREN’T MOTIVATED TO SPONSOR THOSE TYPES OF TRIALS?**

**Dr. Eisenberger:** Right. Post-approval data is not as meticulous as in the approval phase.

Because PSA testing was introduced into clinical practice in the 1980s, many patients whose PSA rose after radical prostatectomy with no other evidence of disease were treated with hormonal therapy, despite the fact that little was known about their natural history. There is now a large body of data on the natural history of patients with biochemical relapse (PSA relapse) who, instead of receiving treatment immediately, were managed with the more expectant approach of deferred hormonal therapy.

Patients managed with deferred treatment often live longer than 10 years after biochemical relapse. Compare this to the recent data from clinical trials in men treated with immediate hormonal therapy before they developed metastases. They subsequently had a rise in their PSA levels with no evidence of disease on scans or physical exam. The SPARTAN trial with Erleada (apalutamide) and the PROSPER trial with Xtandi (enzalutamide) showed similar results in terms of prolonging the development of metastasis. The drugs were approved by the FDA for use in these patients, men who were initiated on hormone therapy before they developed metastasis. They then developed castrate resistance before they developed metastasis. While there is a delay in the development of metastasis, it remains unclear if this is also associated with improved quality and quantity of life. That's still an open question.

We looked into patients who had a radical prostatectomy followed by a biochemical relapse and were given no treatment until they developed metastasis. The survival of those patients treated with deferred hormonal therapy from the time they were diagnosed with prostate cancer was about 15 years.

I’m not sure that we are helping patients by treating them earlier. I get concerned that we’re going to add hormones, add a great deal of side effects, and add costs.

**DO YOU HAVE ANY ADVICE FOR MEN WHO’VE BEEN PRESCRIBED ONE OF THESE AGENTS?**

**Dr. Eisenberger:** These are great compounds for patients who have metastatic castrate-resistant disease. Each is probably equally effective.

Men who don’t have metastasis but develop castrate-resistant disease need to have a conversation with their physician in terms of pros and cons. They need to ask about the cost/benefit from these drugs. Ask if alternatives, such as older androgen receptor-targeted treatments help with fewer side effects and cost and whether you can still derive some benefit.
Most people with dementia or Alzheimer’s have a buildup of plaque in their brain – mostly beta amyloid plaque. This kind of plaque has been associated with Alzheimer’s disease. But does it cause Alzheimer’s and memory loss, or is it simply a result of the disease process?

Amyloid plaque is a natural protein that can be found in your brain. In fact, it often functions to aid your own immune system protect your brain. But once it builds up, it retards other important cells in your brain from clearing away toxins and debris. This allows for damage and death of your major brain cells called neurons. This process results in memory loss, dementia, neurodegeneration, and death. And it is intrinsically involved with Alzheimer’s but does not seem to be the underlying cause.

MAJOR CAUSES OF ALZHEIMER’S
We now believe there are a handful of major causes of brain damage, dementia, and Alzheimer’s. Any or all of these can lead to a buildup of amyloid plaque. These are…
1) Chronic inflammation in your brain.
2) Poor circulation, which can be caused by lack of exercise, hardening of your arteries, or heart disease.
3) Toxins in your brain, which can be the result of poisons, drugs, vaccines, fluoride, and more.
4) Physical damage to your brain, which can be caused by concussions or other head traumas, also known as TBIs – Traumatic Brain Injuries.
5) Diabetes.
6) Lack of sufficient brain nutrients, which can result from a poor diet and diabetes.

Any or all of these brain insults and more can result in what is now considered the main cause of Alzheimer’s – chronic brain inflammation.

CHRONIC BRAIN INFLAMMATION
It’s all so complicated, especially if you are beginning to lose your memory.

- Toxins: There are so many toxins in our world. Almost everyone gets a daily dose of fluoride from their drinking water. Yet fluoride is a powerful neurotoxin (brain toxin). There are thousands of other toxins in our environment as well, from chemicals in our food, beauty, cleaning, gardening, and home maintenance products, to the air we breathe, to the electronics in our homes and work places.
- Exercise is often difficult, especially if you are losing your memory. Yet exercising improves memory loss, perhaps by increasing blood supply to your brain and inducing certain healthy brain chemicals.

- Heart Disease for most people is routinely treated with drugs and surgery, rather than strengthening the heart by eliminating the underlying causes of heart disease, which are usually nutritional. But proper nutritional care of heart disease can increase brain circulation and potentially help you with memory loss. And the same type of care with a healthy Mediterranean diet and the right whole-food supplements can increase nutrients and better glucose flow to your brain, helping with memory loss.

THE MOST TESTED NUTRIENT
Considered the supreme healthy nutrient or food containing a myriad of phytonutrients, turmeric root, with its curcumin content, has withstood hundreds of years of use and testing – with thousands of peer-reviewed studies. When it comes to your brain and beta amyloid plaque, turmeric reigns supreme. The reason is simple. Turmeric actually lets you treat all six major causes of memory loss.

Turmeric provides specific nutrition in the form of a host of phytonutrients for your brain, with curcumin being the most tested. Turmeric provides specific nutrition that rehabilitates blood vessel linings, allowing for better circulation into your brain. Turmeric can mediate sugar metabolism, allowing for better glucose levels in your brain. And perhaps most important, turmeric is a powerful anti-inflammatory in your brain – actually reducing beta amyloid plaque buildup. About the only thing turmeric cannot do for your brain is prevent a concussion or blow to your head. But even in these cases, it can help relieve the inflammation in your brain caused by this kind of damage.

TURMERIC AND CURCUMIN HAD A PROBLEM
In the past, and with all past turmeric and curcumin supplements, there was a problem with bioavailability. Turmeric with curcumin is one of those plants which is very poorly digested and absorbed by the body. Even if you were to eat a whole cup of organically grown, raw, ground up turmeric root, very little of it ever did you any good. And to make matters worse, turmeric and curcumin did not pass through the blood/brain barrier to get into your brain where it is needed. For this reason, we could never really recommend curcumin supplements, until now.

A way has been developed to allow raw turmeric and its high curcumin content to be easily absorbed and bioavailable. By infusing turmeric root into the fiber from seeds of the highly absorbable Fenugreek plant, we have finally gotten around the poor bioavailability of turmeric and curcumin. In fact, the new, highly activated turmeric/curcumin supplement Turmeric Forte is absorbed into your blood and made ready for bioavailability and activity from 24 to 45 times greater than ever before.
And better still, it even passes through your blood/brain barrier to get into your brain's circulations, helping to quell brain inflammation – the major cause of Alzheimer's and memory loss. In fact, the amount of free curcumin and turmeric compounds found in the brain with Turmeric Forte are measured at pharmacological levels, or more than 240 times greater than ever seen before.

STOP AND EVEN REVERSE MEMORY LOSS AND ALZHEIMER’S?!

As I said, turmeric/curcumin has not only withstood the test of time, it is the most tested (with positive, published, peer-reviewed results) of all nutritional compounds or supplements. And now results are far, far greater. Turmeric Forte gives you the phytounutrient material to improve your glucose metabolism, with more steady brain glucose levels. It allows you to improve brain circulation with its blood vessel lining support. It provides a host of specific brain nutrients that will all cross the blood/brain barrier into your brain. And most important, it allows you to treat brain inflammation and plaque buildup, whether from toxins, poisons, concussion, or any other kind of inflammation.

Remember in the latest study, the phytonutrition in Turmeric Forte proved amazingly anti-inflammatory in the brain. Within 18 months, virtually every subject stopped their memory loss and had major memory improvements – a medical impossibility. And all subjects with beta amyloid plaque buildup had reduced plaque in the same time period – another medical impossibility.

Furthermore, of the study subjects who were prediabetic, none progressed to type 2 diabetes. And most had improved glucose control. Considering that almost all Americans over age 60 are prediabetic, this is powerful news indeed. So go ahead, treat your brain. It is so easy with Turmeric Forte. Thanks to its activation by infusing turmeric root into the fiber from plant seeds, one tablet contains the activated equivalent of 5 ounces (a whole cup) of powdered root with 6 grams of curcumin!

PREVENT AND/OR TREAT WITH TURMERIC FORTE

There is medically nothing for Alzheimer's. The drugs don't work and can make you psychotic. And you can go crazy trying to find the right treatment or protocol for memory loss – especially given treatment complexities and lack of any real success. But one medicinal food transformed into a supplement releases all the power of turmeric and curcumin. Turmeric Forte will help you stop memory loss, reverse memory loss and regain memory; stop progression from prediabetes to type 2 diabetes; help control chronic and severe pain and inflammation; and regain your life. Let's face it, 18 months is going to come and go anyway. So start treatment now. You will feel better far sooner than 18 months.

For prevention take 1 tablet daily (always consumed with food that contains some fat). With early Alzheimer's, chronic pain, or memory loss, take the same dose twice daily. And with type 2 diabetes, Alzheimer's, and/or severe chronic pain and inflammation, take 2 tablets twice daily (with food containing some fat).

A NEW MEDICAL FRONTIER

Please let me know how you are doing. This is new territory – a new medical frontier. Nothing like this has been available before for you to test and mount an all-out effort to beat Alzheimer's.

BRAIN INFLAMMATION PROTOCOL

For Prevention….

Turmeric Forte: 1 daily (with food containing fat)
With early Alzheimer's, chronic pain, memory loss…
Turmeric Forte: 1 tablet 2x daily (with food containing fat)
With type 2 diabetes, Alzheimer's, severe chronic pain, and inflammation…
Turmeric Forte: 2 tablets 2x daily (with food containing fat)

MEMORY LOSS – SUPERCHARGE YOUR TURMERIC PROTOCOL WITH COCONUT AND MCT OILS

Almost 10 years ago I told you that coconut oil could help you with your memory and with Alzheimer's. I told you about Mary Newport, MD, a pediatrician and neonatologist. Dr. Newport discovered the coconut oil – brain connection thanks to her husband who came down with Alzheimer's at the early age of 51. He became so bad so quickly that he could no longer function on his own.

Dr. Newport got to researching and learned that medium chain triglycerides, or saturated fat from coconut oil, could fuel a brain damaged with Alzheimer's. She started giving her husband two tablespoons of organic, virgin coconut oil daily, always trying to up the dose to 3-5 tablespoons daily. Amazingly, her husband responded, almost overnight! As we hear so many times, he actually "woke up," and began to get better.

Always being a researcher, Dr. Newport had her husband attempt to draw a clock before she started coconut oil treatment. She had him do the same after 14 days of coconut oil therapy, and again after 37 days of therapy. The results are clearly shown in her now-famous clock drawings by her husband. See for yourself the massive improvement that is absolutely impossible medically.

This initial research changed her life and career work. She fully launched into medium chain triglyceride research related not only to Alzheimer's, but to multiple sclerosis, Parkinson's, even the always fatal ALS (Lou Gehrig's Disease). She found the oil therapy potentially helpful to people with all these different brain problems. She then published her first book, Alzheimer's Disease: What If There Was A Cure.
From here, research led to MCT oil. This is a saturated medium and shorter chain triglyceride oil. It has become popularized by the ketogenic diet. The objective of both coconut and MCT oils is to raise the level of ketones in your blood. Ketones are a type of fat/acid produced in your liver that can be burned as fuel. Your liver will make more ketones if you have lost your sensitivity to insulin, retarding your ability to burn glucose as fuel. And ketones are always burned and never stored as fat.

**KETONES AND YOUR BRAIN**

With memory loss and Alzheimer’s, higher ketone levels in your blood can be highly beneficial because ketones can be burned as fuel by your brain cells, even when they can no longer burn glucose properly. Dr. Newport has learned that brain cells called neurons previously thought dead or completely inactive in Alzheimer’s patients are not dead. Instead, they are just “sleeping,” like parked cars with no fuel. But when the blood flow to your brain is rich with ketones, these neurons – formerly thought dead – take up the ketones as fuel and come back to life.

This is very exciting indeed. And it is especially exciting for seniors who have trouble with glucose metabolism, prediabetes, and type 2 diabetes. Fully 75% of all people in America over age 75 have pre- or type 2 diabetes! That is a gigantic number of people who are beginning to, or have already, lost their memory. The notion that “switching fuels” from carbohydrates and sugar (glucose) to fat (ketones) might help us recover lost memory and brain function is so encouraging.

Dr. Newport was the pioneer with this idea. Based on her early and newer work with ketones, she recently published a second book that I highly recommend – The Coconut Oil and Low Cost Solution to Alzheimer’s, Parkinson’s and Other Diseases. This is a highly practical book on the use of coconut and MCT oils in boosting ketone levels to improve memory, double your endurance, lower your inflammatory levels, help you maintain better glucose levels, sleep better, and much more.

**HOW DID WE GET INTO THIS MESS IN THE FIRST PLACE?**

Much of the problem with glucose metabolism, increased Alzheimer’s, diabetes, chronic pain, and universal high inflammatory levels began with the medical low fat diet. This ridiculous notion that fat causes heart disease was totally debunked years ago. Yet the low fat diet has lived a life of its own for more than three decades. It is still recommended routinely, especially by cardiologists.

But when it comes to your brain, your inflammation level, your insulin sensitivity, your energy, and your memory, healthy fats are critical. In fact, a high fat diet is far healthier than a high carbohydrate diet. Millions of Americans, struggling with their low fat diet prescription, started substituting carbohydrates (some good and lots bad) for fat.

The glut of bad carbohydrates got worse as more and more processed and industrialized carbohydrates and fast foods began to flood the market. Within a few decades, the result of the

Did the low fat recommendations improve America’s heart disease problems, as promised? It accomplished nothing beneficial. Heart disease is rampant, with a death from a heart attack occurring every single minute. But something did get accomplished with this diet – a financial windfall for the drug companies who produced and sell hundreds of billions of dollars of statin (cholesterol-lowering) and other heart drugs which, even when combined, have done nothing to slow the heart disease epidemic in this country.

**TURMERIC FORTE AND COCONUT OIL**

To date nothing outperforms curcumin as found in Turmeric Forte when it comes to memory loss, Alzheimer’s, chronic inflammation, and glucose metabolism. If you haven’t already, be sure to see my article on this medical miracle, “Alzheimer’s, Memory Loss, Dementia, Diabetes, Chronic Pain, Heart/Blood Vessel Disease, and the Amazing Curcumin Breakthrough.” It is on my site, www.healthalert.com. If you don’t use a computer, not to worry. Just call my office and one of my Subscriber Support Specialists will get you a copy – for free.

Even though nothing outperforms the results of Turmeric Forte, you can probably make these results even better if you combine Turmeric Forte with coconut and/or MCT oil. I suggest you get a copy of Mary Newport’s second book. It is practical and will take you step-by-step through the process – from someone who really cares, who has done the research, and who has personal first-hand experience.

If you start oil therapy, remember to start with 1 teaspoon daily. Slowly work your way up to 2-4 tablespoons daily. If you rush it, you may suffer from nausea and diarrhea. Mary’s book will help. Dr. Newport discovered that after a very short time on coconut oil, her husband with Alzheimer’s began to remember his dreams again – something he had not done in years. Indeed some people take a teaspoon or tablespoon of oil at bedtime to enhance deeper sleep with better dreams.

Getting back to healthy fats is definitely the way to go. It can do so much to help with your brain, your sugar handling, your chronic inflammation, your strength and endurance, and more. Actually, it does the same things that the curcumin found in Turmeric Forte does. But combined you truly have a superfood to use in your battle to retain and regain your memory and more.

Right now, nothing outperforms the activated curcumin in Turmeric Forte. But imagine if you can take these results with problems that have become epidemic in America and make the results even better!

Notes:
Orgasm is something that is often a very important part of the sexual experience. Well the “Big O” is made into a big deal given the role it has in many movies with the sigh of contentment being highlighted as the key sex scene in many movies. Although I advocate for the importance of not putting so much pressure on orgasm but rather sharing connected pleasure, which I talk a bit more in next week’s blog post, I do know it’s not necessarily something to ignore. So I want to give you a guide to what helps you have an orgasm in your relationship, and I also send your way some good ol’ analogies so get ready.
BRING ON THE MIND
The first thing about orgasm that is important to understand is that you need to set the stage first. Before you even get to the bedroom, you need to make sure that your mind is on board. Your mind is your biggest sex organ and because of this it needs to be open to intimacy and you need to help your mind get there. Especially for women, you can’t expect to go from a busy kick-butt day and then expect the mind to leap over to intimacy land in a single bound. Although you are awesome, you aren’t superwoman. If the mind doesn’t want to be there, it’s not going to be there just on its own AND even if it does want to be intimate, it’s not going to happen with the flip of a switch.

To be really engaged in your intimate experience and increase the likelihood of orgasm happening this means that you have to help stimulate and open your mind with the things that have you relax and feel open. And on the flip side need to make sure that you don’t have a lot of things that are clogging up your mind such as stress, thinking about the to-do list, worrying about what your body looks like, what your partner is thinking, or what the sexual experience needs to look like. *This creates pressure* and pressure is one of THE biggest killers of potential orgasm. When your brain is clogged up with these things, it can’t be open to the sexual experience and you need your mind to be relaxed and open in order to have any chance at orgasm.

ATTEND TO THE BODY
The next key piece of orgasm is making sure that you attend to the arousal of your body. This means making sure that you’re getting the right kisses; the right touch and sensations like hard, soft, or playful; and you’re getting those touches in the right areas. AND importantly you need to have those touches for the right amount of time. This is especially essential for women because women take a bit more time for their arousal to build before the action really starts taking off. Women are like dial-up internet whereas many men, with the help of their testosterone, are more like the high-speed internet.

So this could mean you might need 20 minutes or more to build your arousal before any type of genitals are actually included in the experience, and especially before penetration happens. In that way women are kind of like ovens, you need to warm things up before you put anything inside. And on that note, only about 30% of women have an orgasm through penetration even with time for arousal to build. So if it doesn’t happen with penetration, don’t worry about it.

ORDER DOES NOT MATTER
An important note about arousal and desire is that they don’t necessarily have to happen in a particular order. You might expect that you need to feel desire and a “heck yea” thought before you say yes to intimacy. For some this spontaneous desire to take action does occur but for many (well most), it doesn’t in long-term relationships. Think about it in terms of working out. Have you ever experienced those times when you see “Gym Workout” in your calendar and you think “ugh, I don’t know if I really want to go. I’m not super jazzed about it,” but then once you go you are so glad you went and you feel super good after?

I don’t know about you but if I waited until I was super excited about going to the gym I would like never go. Instead, I know that once I get there and move my body my brain kicks in and is like “heck yea I’m so glad I’m here.”

The same thing goes for intimacy for many women. This is because they have what is called Responsive Desire. If this is you, this means that once you start actually having your body touched in the bedroom and your body gets in motion, then your brain has a chance to hop on board to join the fun. So it’s totally OK to start intimacy when your brain is in neutral or not exactly jumping up and down in anticipation because what your brain is actually needing is for you to get to the bedroom and start moving your body before it comes in and joins. And heck, just like the gym, if you start up and after 10 minutes your mind is just still not into it then *you can raincheck for a different time or activity*. You aren’t stuck with keeping going, you can change direction or end things at any time.

VULNERABILITY
Once you have the brain on board and the body is getting highly aroused, the other key piece of orgasm is vulnerability. This means surrendering into the experience with your partner and letting go of any worries. This is essential for orgasm because orgasm is a place where you are completely surrendering your body and you are in full exposure. When you are completely surrendering your body to the experience and to the person that you are with that is vulnerability to the max. Because of this, many control their vulnerability during intimacy. For many, the letting go means a loss of control and it’s scary to be vulnerable, so they don’t open and surrender. This is why having a good, safe, partner is so vital to your relationship. Taking steps to surrender into the intimate experience will help you move closer to orgasm.

LET’S WRAP UP
When you focus on the desire of your mind, the arousal of your body, and you’re also surrendering and embracing the vulnerability of the experience, that’s when the possibility of orgasm can happen. I say a possibility because 1) it’s not a given that it will happen, because you are not a robot and life can impact the three areas discussed, and 2) it’s not necessary for orgasm to happen with every intimate encounter. Orgasm is a wonderful piece of the sexual experience and now you know what it takes to help it be a part of your experience but it doesn’t define the sexual experience. It’s more about the sharing of pleasure and connection, which is something I could write a whole other blog post on and that’s exactly what I did! But patience you eager learner, I’ll get that to you next week, promise!

THINGS TO REMEMBER
- Your Mind is your biggest sex organ
- The arousal of your body needs time and the right touches
- Arousal can come before Desire
- Vulnerability is about surrendering and letting go
- Don’t pressure yourself to orgasm every time
Recent advances in the field of ablative procedures are changing the paradigm of surgery as the main approach to treating localized cancers. Ablative procedures on the local tumor create a systemic immunologic response in remote tumor locations, known as the Abscopal Effect. This shows a systemic effect on metastatic disease. To pave the way for new therapy, we need to research Abscopal Effect.

In 1953, R.H. Mole M.D. coined the term abscopal effect. The term is derived from the Latin words: “Ab,” meaning away from, and “Scopos,” meaning target. The term relates to “an action at a distance from the irradiated volume within the same organism.” In the oncology literature, the abscopal effect describes the ability of localized radiation to initiate an anti-tumor response that kills cancer cells in areas that are remote from the primary tumor which was targeted.

Ablation can be achieved by many different procedures. Cryoablation seems to be the most promising ablation procedure. A paper published by Yan Wang from the Department of Interventional Therapy from Tianjin Medical University Cancer Institute demonstrated that cryoablation of a local site not only retarded the rate of untreated tumor growth, but also reduced the incidence of lung metastasis in mice and significantly prolonged survival time (1).

The Abscopal Effect was described in patients who underwent prostate cryoablation in the 1960s (2). Early observers noted that cryoablation of the prostate released antigens. Dr. Richard Ablin coined the term Cryo-Immunology. He published clinical observations of three patients with regression of their cancer in the cervical spine, lungs and left supraclavicular lymph nodes following cryoablation, published in the 1970s.

The same group of researchers from Tianjin, mentioned above, also published work on patients with metastatic hormone refractory prostate cancer, except that this time they added GM-CSF (Granulocytes Macrophages – Colony Stimulating Factors (3). The researchers demonstrated a 69.7% decline in Median PSA. Lung metastases were reduced by a significant number as well.

An unintended abscopal effect by cryoablation was also demonstrated by Japanese researchers who removed spinal metastatic disease by removing the cancerous vertebra and dipping the specimen in a cup with liquid nitrogen. The procedure was done for relief of pain. After 20 minutes in the freezing solution, the tumor fragments and bone were gathered into a mesh that was reinserted in the spine in the location of the missing vertebra. Patients did indeed achieve relief from pain. But in an unexpected consequence, there was a patient whose metastatic lung disease disappeared, which excited the researchers. The Japanese group of researchers are continuing their work now to further take advantage of this abscopal effect when treating bone (4).

There are also reports of significant advances in the field of tumor immunology with checkpoint inhibitors leading the new developments. Checkpoint inhibitors enable the immune cells to overcome inhibitory forces in the tumor microenvironment. The problem is that only about 20% of the patients who benefited in clinical results, actually reported using checkpoint inhibitors alone. Also, the annual cost of $120,000 will be prohibitive to many patients. While immunotherapy has a reputation for being safe and having a low side effects profile, there are significant side effects that can be severe enough in some patients to cause death or severe incapacitating long term side effects. Therefore, we need to find new immune-modulators that can still enhance the abscopal effect to replace checkpoint inhibitors.

Ablative procedures are considered in-situ vaccinations. The destruction of the tumor spills tumor antigens into the micro tumor environment (MTE). With the right immune-modulators added to the MTE locally or systemically, we can enhance the abscopal effect. We can get the desired effect on the local tumor and stimulate the immune system to eradicate all metastatic disease remotely. Dr. B. Golden MD from Radiation Oncology at the University of California, San Francisco wrote a paper demonstrating radiation as inducing the abscopal effect. His recent study used the immune agent GM-CSF, granulocyte macrophage stimulating factor, a cytokine that activates dendritic cells (5).
abscopal effect is not always robust enough because of immune suppressive mechanisms in the tumor microenvironment. These immune suppressive effects can be overcome by checkpoint inhibitors. But due to shortcomings in efficacy, side effects and cost, there is a movement to find new immune modulators. The Myeloid-Derived Suppressor Cells (MDSC), as the name denotes, are present in the microenvironment of the tumor and suppress the immune stimulators factor from acting against the cancer. Blocking these suppressors will free the immune cells in the tumor microenvironment to attack the cancer cells locally and systemically (6).

Israeli researchers from the Hebrew University in Jerusalem found a group of medications that can block the unwanted suppressors of the immune system. In this list of medications are some common drugs that can be repurposed to block MDSC, thus increasing the ability of the innate immune system to fight and destroy the cancer. The article, “Paving the road to tumor development and spreading: myeloid-derived suppressor cells are ruling the fate” (6) lists a few of the blocking suppressors of immune therapy drugs.

A new study, published in OncoImmunology (7), shows that a common treatment for erectile dysfunction using Cialis combined with the flu vaccine may be able to help the immune system to fight cancer cells that are left behind after surgery. The study shows that this unconventional strategy can reduce the spread of cancer by more than 90% in a mouse model. It is now being evaluated in a clinical trial for patients undergoing surgery.

Our interest at PCREF (Prostate Cancer Research and Education Foundation, San Diego, CA) is to study these immune modulator agents in conjunction with cryoablation of local tumors to achieve the Abscopal Effect. Using Immunotherapy to boost the Abscopal Effect opens new frontiers for treating cancer in a non-aggressive manner by recruiting the body’s own mechanism of defense - the immune system. Harnessing the Abscopal Effect is a breakthrough concept - treating cancer in one location (the auto vaccination/in situ vaccination) but causing a cancer regression or disappearance in a remote untreated area.

**The Abscopal Effect is Highly Desirable in Three Situations:**

1. Treating a primary tumor site and having metastatic locations disappear, whether seen by imaging or not, may avoid metastatic disease and the need for future treatments.
2. In cases of multiple cancer locations, the ability to treat only one accessible location and achieve regression in other remote areas makes it feasible to treat a location not accessible to treatment.
3. Physicians at the Mayo Clinic have demonstrated that palliative treatment of metastatic disease in the bone with cryoablation is feasible and beneficial for bone pain. If we add the new immune modulators, we can turn this palliative approach into treatment for metastatic disease. In other words, the bone palliative approach will open new therapeutic opportunities. Figure 1

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References


Promising ideas need funding to make them a reality, and patients themselves can have a role by supporting “seed money” research grants to get the ball rolling. Take a promising idea, add funding in the form of small seed money research grants, and you have the opportunity to turn ideas into reality. We have seen time and again that patients themselves can be the driving force in stimulating and supporting research for new treatments. To learn more about supporting research on the Abscopal Effect, contact Dr. Barken at 619-906-4700 or write to info@pcref.org.
LETTERS TO THE EDITOR

DEAR PAACT EDITOR,

Just a note to say that I’m finally contributing after being on your mailing list for over 20 years. PAACT was one of a number of organizations I contacted when I was writing a book on locating reliable medical information. Although PAACT was mentioned only twice in the book, you’ve sent me the newsletter ever since.

I’ve been a faithful reader of Dr. Moyad’s column (and even bought his book) and am now old enough to have a prostate nodule of my own (which my urologist and I are monitoring). If at some point we decide that treatment is necessary, I expect to make a much more informed decision on my own.

No need to reply to this, but please do let Dr. Moyad know that (speaking as the author of a few books and a few hundred articles) I admire his style.

Best wishes.
- FB

DEAR MR. PROFIT,

In memory of my dear husband who passed away last year, I enclose this check for $80 to show appreciation for your support and excellent information from your team of doctors in your PAACT magazine, which “B” found very helpful since he met you at the 2010 prostate conference in L.A.

Many thanks.
- JM & Family

HELLO,

I am sending my email address for future issues of the PAACT magazine to help eliminate mailing costs. Thanks for all the under-appreciated hard work, kindness and intelligence. You truly are making a difference one person at a time. Well done and Thanks.

- FS

THANK YOU...

...for years of helpful information. My husband died and we no longer need your publication. Hugs to Dr. Moyad!

- LE

Thank You for what you do.

I am the President of ASPI and our goal is to target newly diagnosed and men on Active Surveillance. I hope we can be as professional with information as you are and once we get our new website up, I would like to come to you and offer working together for the good of the PCa patients.

Our vision is to develop pro-active patients by providing the latest data and fostering the understanding necessary to pursue the best outcomes with the least intervention.

Please say Hi to Dr. Moyad as I am a follower of his.

To show my respect for Mark and you for what you do I have enclosed a donation of appreciation. We will stay in touch and look forward to working with you.

Thank you.
- GS

DEAR RICK & DR. MOYAD,

I have just read your Volume 34, Spring 2018 booklet, and it is very good!!

I was diagnosed with PC about 18 years ago at age 74 (am now 92) with a Gleason 3+4=7. Mr. Profit got me on to Dr. Lam out in Marina del Rey about 8 years ago, and am still with him. He is a good man. The only treatment I have had is hormones, but I seem to be doing okay, but very tired, my “T” is down to 10 after a 3 month Eligard shot (my 4th one).

Anyway, I like your informative publications, they seem to be the straight dope, & not biased.

Keep up the good work.
- CF

Check for $500 enclosed

HEY GUYS!!

As always thank you very much for what you do. My email address is……

I enjoy seeing and reading the letters in the most current “PCC” magazine. I do like the paper feel, like newspapers, but fully understand the need to save $$ as I have no doubt you guys struggle for money. I’ll call right now and make a donation and update my “membership.”

Small world – one of the Letters to the Editor in the current issue is from a close friend with whom I worked way back in the late 70’s in the Pacific NW. I recognized his prostate cancer issues that he wrote about to you guys then me reading here in the Rockies and you publishing it back in Michigan (also near where I worked in the Upper Peninsula again back in the late 70’s). He is the one who actually contributed a “ghost” subscription for me nearly 10 years ago now – so we’re all connected.

Again thank you very much for being there for all of us “old guys.”
- B
MEMORIAL CONTRIBUTIONS

ACKNOWLEDGEMENTS OF CONTRIBUTIONS
June 1, 2017 through January 31, 2019
(YOUR NAME WILL APPEAR BELOW IF WE DEPOSITED YOUR DONATION BETWEEN THE ABOVE DATES)

In Loving Memory of **Lloyd J Ney, Sr., Founder of PAACT, INC., Grand Rapids, MI**

IN LOVING MEMORY OF LLOYD

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In Loving Memory of **Janet E Ney-PAACT Co-Founder**

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In Loving Memory of **Robert Bieker**

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In Loving Memory of **Dale Cryderman**

- James Brian

In Loving Memory of **Donald Nowak**

- Patricia Nowak

In Loving Memory of **Gene Saunders**

- James Kettler

In Loving Memory of **Dr Fred Lee, MD**

- James O’Hara

In Loving Memory of **Bernard McCauley**

- Andrew McCauley

In Loving Memory of **Milton R Wessel**

- Joan Wessel

In Loving Memory of **G Frederick Perkins, Jr.**

- John Perkins

In Loving Memory of **N David Neimark**

- Sheridan & Dana Neimark

In Loving Memory of **Dan Bush**

- Judith Bush

In Loving Memory of **Sid Berman & Mike Zimich**

- Carl Modig

In Loving Memory of **Robert E Swisher**

- Cynthia Aulbach

In Loving Memory of **Donald T Huang**

- Jin Nge Huang

In Honor of **Dr. Mark Moyad, Adriano Lott - Go Michigan!!**

- Robert Kanter
GDIT is contracted by the Department of Defense (DOD) Congressionally Directed Medical Research Programs (CDMRP) to recruit patients, and survivors to serve as “consumer reviewers” on panels reviewing prostate cancer research grant applications. Consumer reviewers act as subject matter experts on prostate cancer bringing their experience and perspectives to the evaluation of research grant proposals. Consumer reviewers provide crucial input to the panel, serving alongside scientific and medical experts to represent those most directly affected by prostate cancer. Visit https://cdmrp.army.mil/pcrp for more information. For details on the consumer nomination process, contact Amber Nalley, amber.nalley@gdit.com or 240-762-4106.
### PAACT MEMBERSHIP FORM

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- [ ] Patient ................................................ $55
- [ ] Advocate ............................................ $55
- [ ] Professional ..................................... $100
- [ ] Other ...................................... $________
- [ ] Include me as a PAACT member, although I currently cannot contribute $________
- [ ] Donor ............................................. $500
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- [ ] Anonymous ...................................... $________

**Tribute gifts support the daily operations of PAACT, Inc., by furnishing PC patients, doctors and advocates with the latest information available on the methods of detection, diagnostic procedures, evaluation and treatments for prostate cancer. We also participate in matching gift programs and United Way. For more information contact us at (844) PAACT4U • (616) 453-1477.**

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Enclosed is $ ________________________________, In memory of Lloyd J. Ney, Sr.
Enclosed is $ ________________________________, for PAACT’s general operation expenses.
Enclosed is $ ________________________________, I wish to remain anonymous.

In Memory of ___________________________________________________________________________________________

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| Address: |_____________________________________________________|
| City: | State | Zip |
| Account Number: | ________________________________ | Amount $ | 3 digit CVV/Security Code | 

Signature: __________________________________________________ Expiration Date: __________________________

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