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A STRATEGY OF SUCCESS IN THE TREATMENT OF PROSTATE CANCER

By Stephen B. Strum, M.D., F.A.C.P.

INTRODUCTION

“It is the Destination, but it’s the Journey that gets you there.”

After a diagnosis of prostate cancer (PC) has been made and the initial shock of a life-threatening diagnosis has begun to lessen, the thoughts of the patient almost invariably focus on “What should I do to get rid of this disease?” Family and friends reinforce this mental set, as well as add to the anxiety of the situation by asking, “What are you going to do?” **The main focus in the context of a new diagnosis of PC, however, should not be on what particular treatment should I select, but rather on understanding the specific expressions of your illness, and how they lead to a rational choice of therapy.** In such a setting or context, the patient and his team act as medical detectives—to gather information—analyze—re-evaluate, and then begin to consider what to do.

No patient or family is magically transformed into a PC expert upon being diagnosed with this disease. Life is not that simple. Amazingly, there are patients who rise to this threatening “occasion” and educate themselves to a degree that many physicians find astoundingly impressive. Many other men delegate this empowerment process to others -- especially their wives or their partners. ***These men do not enter the empowerment process and do not optimize their chance of a successful outcome. They also miss the opportunity to bond with other men and/or women and the ability to not only receive guidance but to give it to others in return.***

“Our humanity lies in our human unity.”

The heart of Empowerment involves taking responsibility for, and authority over one’s own outcomes based on education and knowledge of the consequences and contingencies involved in one’s own decisions. This focus provides the uplifting energy that can sustain in the face of crisis.

Let’s Conquer Cancer in OUR Lifetime

“Out of crisis, comes opportunity.”

Few men employ a team approach, working together with their wives or partners, their family and friends, and in co-partnership with their physician(s), devouring literature, searching the Internet, attending support group meetings and becoming involved with e-mail lists focused on PC. These empowered patients have created a Strategy of Success that serve them not only in their quest to understand and conquer prostate cancer, their immediate project, but they also now have a tactic that is instrumental in a comprehensive and pro-active approach to all health issues.

THE IMPORTANCE OF EXTENT OF DISEASE

After a diagnosis of PC, most physicians in the United States suggest an evaluation of the extent of disease (EOD). Surely, we cannot advise a man to have a local treatment with curative intent with therapies such as radical prostatectomy (RP), seed implantation (SI), external beam radiation therapy (EBRT) or cryosurgery if cancer has spread beyond the scope of the scalpel, beyond the boundaries of the radiation portal, or beyond the periphery of the cryosurgical ice ball.

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This is the concept of staging. Staging involves the determination of the extent of disease. It is applicable to any type of cancer, not just PC. Staging is a basic principle of cancer medicine. Until we have a universal “antidote” or cure for cancer, we need to individualize the treatment based on what works best for the particular stage of disease the patient is found to have. This is a sound concept. **Unfortunately however, the way the extent of disease is currently determined for prostate cancer patients is overly simplistic.**

Staging

Virtually every newly diagnosed patient with PC is referred for a nuclear medicine bone scan, along with computerized tomography (CT) scans of the pelvis and of the abdomen. This particular approach to staging PC had greater value 10 to 20 years ago at a time before PSA testing was routine. These tests were also still appropriate to use in the early years after PSA testing was approved as a critical tool in the diagnosis and evaluation of PC. During those times it was not uncommon to find—at diagnosis—an abnormal bone scan, CT scan of the pelvis and/or abdomen, and a digital rectal examination which re-

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vealed bulky PC. Indeed, all of these *staging tests* reflect a serious volume of cancer (called the tumor burden) as well as a significant extent of disease. Cancer volume and extent (stage) usually go hand-in-hand. The more cancer volume you have, the more likely it has been there for a long time and/or that it is more aggressive in its growth characteristics, and given those findings, the more likely that it is no longer confined to the prostate gland.

However, PSA testing in the U.S.A. has dramatically changed the profile of the newly diagnosed man with PC. Annual PSA testing has caused a “stage migration” with the result that advanced disease at diagnosis is, or should be, a rarity. Today, advanced PC at diagnosis is mostly seen in men who have not undergone periodic PSA testing due to their own neglect or due to neglect that reflects the medical and economic policies of certain so-called “Health Maintenance Organizations (HMOs).” Amazingly, we still face the controversy over whether PSA testing should be done routinely for all men because a randomized study has not been published that shows a survival benefit when PSA screening is employed. Critics of PSA screening point out the morbidity and mortality associated with treatments for PC. They assert that since many men will die with PC and not because of it, why bother to test men with annual PSA determinations. Such critics truly are guilty of “throwing the baby out with the bath water.” In this millennium, we as physicians and you as empowered patients should clearly realize that when we establish a diagnosis of PC at an early stage, we have the ability to make an informed decision about what to do next. The decision needs to be based on the inputs of the patient’s biology that informs us of the nature of the PC. Most importantly, the decision needs to be made in the context of the patient’s life. What are the other health conditions and additional factors relevant in this full equation of decision making? Clearly, not every early diagnosis of PC mandates that an operation, radiation, hormone blockade or chemotherapy be initiated. Certainly, in this new setting of an earlier diagnosis of PC we can invoke life style changes, while evaluating the nature and tempo of this disease on an individual basis, and make appropriate adjustments to our overall strategy. Isn’t that far more appropriate than being “caught with your pants down” and detecting extensive disease that cuts life short?

Fortunately, common sense is prevailing and the most common history now associated with the diagnosis of PC in the United States is that of a rising PSA or of an absolute PSA value that raises concern for PC being present. The migration from an advanced stage at diagnosis to an earlier stage manifests itself clearly in the fact that abnormal digital rectal examinations suspicious for PC are found in only 20% of men at diagnosis today, compared to 60-80% or higher percentages from twenty years ago. This reflects a smaller tumor volume within the prostate gland that the DRE no longer signals a concern that PC is present. In other words, the volume of the disease is below the threshold of the examining finger. This impact of PSA screening is akin to the change in cervical cancer diagnostics where the presence of this disease is essentially made via seeing changes involving the microscopic appearance of cells, rather than by a woman presenting to her doctor with pelvic pain, bleeding from the cervix or a detectable mass on pelvic examination. **We can thank the use of the PSA for the change in the nature of presentation of PC we see in the U.S.A. today.**

To all of this, most physician-scientists would say “Elementary, dear Watson.” This is simply a matter of earlier discovery using higher resolution tools. It is merely improving our ability as detectives by using a magnifying glass (es) of sorts. A good M.D. is therefore, in this setting, a great **Medical Detective**, a Sherlock Holmes, M.D., so to speak.

CALLOUT

DOING YOUR HOMEWORK

All of us have to put in the hours and try to understand the problem at hand. In today’s world of medicine, this also means the patient. The Internet and its powerful tools of learning are of monumental importance to the PC patient and his family. The full circle of patient-family-friends-physician should be involved in this learning process

There is a “catch 22” that comes with all of the above. The man diagnosed with PC today, James Potter for example, now presents with a PSA level of less than 10, no palpable abnormality on DRE (T1c clinical stage) and most commonly with an average degree of aggressiveness upon microscopic review,

i.e. a Gleason score of (3,3). He will have a normal bone scan and, 99% of the time, a normal CT of the abdomen and of the pelvis. When the hypothetical Mr. Potter is told of these results, he assumes the PC is confined to the prostate, and he, his family, and friends breathe more easily. They assume that the situation is controlled and most likely curable. This entire scenario usually transpires within a week or two after the diagnosis of PC has been established. Again, the patient focuses on “What treatment should I have to cure me of this disease?” Family and friends again ask, “What therapy have you decided to select?”

To summarize the foregoing, the man newly diagnosed with PC has had a PSA (or multiple PSA determinations) and a DRE. In addition, some physicians might have also obtained a free PSA percentage to heighten or lessen concerns that the nature of the PSA is, or is not, most likely related to PC. The PC patient has undergone a transrectal ultrasound of the prostate (TRUSP) which enables the urologist or radiologist to visualize the prostate gland, determine the gland volume, see abnormalities within the gland and/or at its borders, assess angiogenesis (if color Doppler TRUSP is used), and determine PSA density (PSAD) for the entire prostate gland or specifically for zones like the transition zone, which are meaningful inputs in an assessment for the presence of PC.

However, it should be emphasized, that the vast majority of urologists use the TRUSP primarily as an imaging tool to direct the needle biopsies of the prostate gland, which are used to unequivocally establish the diagnosis of PC. Once the diagnosis of PC has been confirmed upon microscopic review and a Gleason score has been assigned to the PC, the patient is most often advised to have a bone scan and CT scans to “resolve” the issue of whether or not the PC is confined to the prostate.

After the above procedures have been performed, the patient and his family are advised to make a choice of treatment, which hopefully will be definitive and result in cure of the patient. The patient and his family are left with the impression that he has had definitive staging of the PC. The physician will most commonly discuss the pros and cons of all major modalities with the patient and his significant other. This remains the state of PC medicine for the newly diagnosed patient in the United States, and for much of the world in 2004.

Although this represents a far more favorable approach than what was in use thirty or even twenty years ago, it still reflects a superficial approach to the evaluation of a man with PC. **We still are not listening to much of the biological expressions of the wide spectrum of illnesses called PC. In addition, because we fail to listen to the rest of the story, we fail to optimize our assessment of the individual man with this disease.** The staging of disease therefore remains limited in scope and is unsophisticated in its understanding of the biology of this heterogeneous group of diseases called prostate cancer. How can this be? It is because of a lack of a coherent process, a near-sighted view of a disease that has multiple manifestations that speaks to its nature, a failure to translate that which is currently available to the actual care of the patient, and perhaps because of a bias that is inherent to the specialists that see newly diagnosed men with PC. An entire strategy that optimizes success is lacking. All of this can and should be overcome.

THE IMPORTANCE OF STRATEGY

“The only place where “success” comes before “work” is in the dictionary.”

Successful strategies in virtually every aspect of medicine and life in general involve work. This is especially true in PC. The work being referred to is strategy – developing a plan of action intended to accomplish a specific goal. Strategy is derived from the Greek word “*stratēgiā*”, meaning *the office of a general*. The root word is “*stratēgos*”, or *general*. This is a military strategy as it applies to eradicating the enemy, or at the very least controlling the enemy. **Strategy implies a process of logical thought and rationale. This is the key to the successful outcome of virtually every problem faced by humankind.**

After counseling thousands of men and their families from all over the United States and abroad for over the last twenty years, a strategy associated with a successful campaign against cancer became apparent. What are the characteristics of such a strategy of success? These are the essential ingredients:

- 1. LISTENING TO THE BIOLOGY OF CANCER.**
- 2. VALIDATING CRITICAL DATA INPUTS.**
- 3. ESTABLISHING A BASELINE.**

4. **INTEGRATING INFORMATION WITH COMBINED VARIABLE ANALYSIS.**
5. **SYNTHESIZING ALL OF THE ABOVE DATA TO REPRESENT A “REFINED” ANALYSIS.**
6. **PRESENTING STRATEGIES TO THE PATIENT WITHIN THE CONTEXT OF HIS SITUATION.**

This is a roadmap that works in the world of the prostate cancer patient. It involves the six basic steps outlined above and detailed in the text that follows.

STRATEGY TO ENHANCE THE OUTCOME IN THE MAN WITH PROSTATE CANCER

Listening to the Biology of Cancer

The biology of cancer is the expression of life forces. It relates to everything we know about health and disease. It is the essence—the underlying dynamic that is behind the chronicle of the cancer patient. Biology, the science of life, is ubiquitous. For the man with cancer, some expressions of biology involve genetics, social and occupational exposures involved with cancer development, stress and dietary factors, and nutritional deficiencies. Scientists investigate these manifestations and relate their understanding of them in various forms such as:

- History and physical examination of the patient.
- Laboratory test results.
- Radiologic imaging that may involve routine x-rays, nuclear medicine scans, CT, MRI, spectroscopy and newer developments.

The patient and his family should understand that all the complex-sounding medical terms and issues that so often are confusing are simply reflections of biological interactions—the chemistry of life. How a car runs is reflected in how the engine sounds, the energy or performance of the car, the smoothness of the ride, the effectiveness of the brakes, etc. The public has grasped an understanding of car evaluation, preventative care, maintenance and early diagnosis of problems. It needs to understand that the same principles are involved with human health as well. When this philosophy is appreciated and utilized, the patient’s understanding of medical interventions becomes eas-

ier, and the anxiety of the patient when threatened with a serious illness lessens as well.

Family History of PC and Relation of Breast Cancer to PC and Vice-Versa

At the current level of what is commercially available to the patient-physician team dealing with PC prevention and epidemiology, we have some basic inputs of information that are pertinent. Is there a family history of prostate cancer -- especially in the first-degree relatives such as the father or brother(s) of the man suspected of having PC? **If two first-degree relatives have a history of PC, the risk of PC is 4.9 times greater, and if three then the risk of PC is 10.9 times greater.¹ Having a brother with PC imparted a 4.5 times greater risk for being diagnosed with PC compared to having a father with PC which resulted in a 2.3 fold greater risk.² In a different study, these increased risks were noted to be of similar magnitude in African-American men compared to Caucasian men with the overall risk associated with history of prostate cancer in brothers and fathers being 5.3 and 2.5, respectively.³ A family history of PC in first-degree relatives also increases the chance of developing PC earlier in life (less than 55 years of age).¹**

A history of PC increases the risk of breast cancer in the PC patient’s family.⁴⁻⁷ A family history of maternal breast cancer increases the risk of developing PC.⁸⁻¹¹

Mutations in a gene on chromosome 17q known as BRCA1 are responsible for a large proportion of inherited predispositions to breast and ovarian cancer, and possibly other cancers. Ford, et al. studied 33 families with evidence of linkage to BRCA1 and examined the risks of other cancers in BRCA1 carriers. Significant excesses were observed for colon cancer (estimated relative risk [RR] to gene carriers 4.11 [95% CI 2.36-7.15]) and prostate cancer (3.33 [1.78-6.20]).¹² In another study of BRCA1 gene carriers, prostatic cancer was the most frequent associated malignancy, after breast cancer. Of 16 paternal carriers, 7 (44%) had developed prostatic cancer.¹³

Nutritional Factors and the Risk of PC

Does the patient’s nutritional status relate to his risk of developing PC? This is apparently the case for selenium, boron, vitamin E and lycopene. **Low plasma**

selenium levels, for example, are associated with a 4 to 5-fold increased risk of PC development.¹⁴

Studies by Clark, et al. showed that selenium supplementation at 200 mcg per day reduced the incidence of PC in men by 63%.¹⁵ Boron is an element found in nuts and fruits such as plums, prunes and grapes. **Three and half servings of boron-rich fruit per day and one serving of nuts per day lower the risk of PC by 64%.**¹⁶ Basic research studies have shown that vitamin E reduces growth rates of PC tumors that were transplanted into mice and stimulated by a high fat diet.¹⁷ There is a 32% decreased incidence of PC and 41% lower mortality in men taking synthetic vitamin E.¹⁸ Another study published in the *Journal of the National Cancer Institute* determined that statistically significant protective associations for high levels of selenium and alpha-tocopherol (vitamin E), were observed only when gamma-tocopherol (the gamma isomer of vitamin E) levels were high.¹⁹ The mechanism of this beneficial effect of vitamin E was investigated in a study of the effects of vitamin E succinate (VES) on prostate cancer cells grown in culture. VES was found to inhibit the growth of LNCaP cells and suppress the expression of PSA. VES was shown to suppress the androgen receptor and was synergistic with the anti-androgen hydroxyflutamide, the active metabolite of Eulexin® (flutamide).²⁰

Although the genetics and prevention of PC and use of nutritional factors before and after the diagnosis of PC are of importance, this article's intent is to focus on the concept of strategy and the realization that it is a logical and rational step-wise process which leads to the successful treatment of men with an established diagnosis of PC.

Within this latter setting or context, we can learn to listen to the biology of PC at a more astute level than that which is generally being done. We can use basic inputs like PSA, clinical stage and Gleason score and increase the value of such inputs by a number of easy maneuvers.

The PSA and PSA Dynamics

The absolute values of PSA, the changes in PSA over time, factors associated with increasing PSA, and the volume of the prostate gland itself are some clues that enhance our understanding of what is happening with men at risk for PC or with men already diagnosed with PC.

Absolute Values of PSA

The so-called "normal" range of PSA from 0-4.0 ng/ml is no longer considered valid. First time PSA values of 2.0 or higher are associated with a diagnosis of PC in approximately 20-25% of men studied.²¹ Initial first-time PSA values of less than 2.0 ng/ml relate to a greater state of prostate health and such PSA values appear to change minimally over a sequential 3 year follow-up. In contrast, first-time PSA values of 2.0-2.99 are associated with progressive increases of PSA to ≥ 4.0 in 6.9% of men by year 1, 15.1% of men by year 2 and 23.6% of such men by year 3 of serial PSA testing. The proportion of increase is worse when the first-time PSA values are in the 3.0-3.99 ng/ml range. Increases in PSA values to ≥ 4.0 ng/ml in this setting are 35.7%, 57.1% and 66.0%, respectively with serial testing at years 1, 2 and 3.²²

PSA doubling time (PSADT)

The history of the patient's PSA values over years of observation, before the formal diagnosis of PC, provides important clues as to the rapidity of PC growth. This is true because for most prostate cancers, the PSA level correlates well with the cancer volume. If the PSA has been done using the same laboratory assay technique in ideally the same lab, the time it takes for the PSA to double provides valuable information about the nature of the PC. PSA doubling times of less than six months indicate a rapid cell proliferation and in such situations metastatic PC must be ruled out. Most commonly, PSA doubling times in newly diagnosed men with PC range from 24 to 48 months.

Factors other than PC that elevate the PSA

Within the context of this consideration, the medical detective must take into account factors that can elevate the PSA but are apparently unrelated to the existence of prostate cancer. For example, sexual activity with ejaculation in the 48 hours preceding a lab draw for PSA,²³ instrumentation of the prostate gland with TRUSP or biopsies within the preceding six weeks, or the insertion of a urethral catheter are all explanations for increasing levels of PSA. In the past, bicycle riding²⁴ and possibly horse-back riding were also considered potentially confounding factors regarding PSA testing. Studies by Crawford, et al. and other papers have shown no significant effect of bike riding on PSA values.²⁵⁻²⁷ In any event; these situations do not explain a persistent progressive rise in PSA over months to years. A history of prostatitis with ex-

pressed prostatic secretions showing white blood cells &/or bacteria, a drop in PSA in response to 4-8 week courses of antibiotics,²⁸ and a DRE detecting a soft or tender prostate are clues that prostatitis may be a cause for PSA elevations and fluctuations -- but these do not usually cause serially progressive rises in PSA.

PSA Trend

Therefore, the PSA trend, just like a stock market trend, is the important concept here. This is true at the time of diagnosis of PC and all throughout the course of the disease. The patient and his physicians should be observing trends reflecting values over time.²⁹ Too often we see patients jump from one treatment to the next without seeing a definite trend in the PSA, or applying other tests to judge success or failure of treatment. In a different context, a man diagnosed with PC with a stable or slowly creeping elevation of PSA over many years may be a good candidate for watchful waiting. **All of this relates to listening to the biology and working with your physician to observe what is happening in your case.**

Prostate Gland Volume

Other factors need to be brought into this analysis as well. A large prostate gland associated with benign conditions such as benign prostatic hyperplasia (BPH) contains more prostate cells.³⁰ This results in a greater amount of benign PSA being secreted into the blood. The basic formula we use to evaluate this is:

Gland volume (cubic centimeters or grams) x 0.066 = benign-related PSA

Subtracting this result—the benign-related PSA—from the total PSA results in unexplained PSA that might well reflect the PC component. For example, a hypothetical patient, Charlie Darwin, is diagnosed with PC with a PSA of 9.0. His DRE felt perfectly normal but his prostate gland volume, measured at the time of his biopsies using the transrectal ultrasound, was 90 cubic centimeters (cc). Using the formula above, $90 \times 0.066 = 5.94$ ng of PSA which could be attributed to BPH. Subtracting this from his PSA of 9.0 results in 3.06 ng of unexplained PSA that relates to PC until proven otherwise.

As an example, if Charlie had a Gleason score that was read or validated by an expert in PC pathology

and that score was (3,3), we could estimate his cancer volume using the concept of PSA leak.³¹ The higher the Gleason score, the less the PC cells leak PSA into the blood stream. A GS of 6 is associated with a PSA leak of 4.26 ng for every cubic centimeter of PC tissue. Therefore, Charlie would have a calculated tumor volume of $3.06 \text{ ng} \div 4.26 \text{ ng/cc} = 0.71 \text{ cc}$ of tumor. Such a small amount of PC is associated with an excellent chance of the disease being confined to the prostate. **In this situation, a methodical process of evaluation has led to treatment options that could involve RP, RT, Cryosurgery, Watchful Waiting or Androgen Deprivation Therapy. However, this is just the first chapter in our evaluation of such a hypothetical patient.**

PSA Leak vs. Weighted Gleason Grade

Gleason score	Gleason Grade (Average)	PSA Leak (exact)	PSA Leak (rounded off)
10	5	0.93	1
9	4.5	1.36	1.5
8	4	1.99	2
7	3.5	2.92	3
6	3	4.26	4
5	2.5	6.23	6
4	2	9.12	10
3	1.5	13.33	15
2	1	19.49	20

The PSA leak relates to the amount of PSA (ng) that enters the blood stream for each cubic centimeter (cc) of PC tissue that has a specific average Gleason grade. In a patient with all biopsy cores showing a Gleason score of (3, 3), his weighted Gleason grade would of course be 3. If a patient had four cores from the right lobe of the prostate with a Gleason score of 8, and two cores from the left lobe with a Gleason score of 6, his weighted Gleason grade would be: $4 \times 8 + 2 \times 6$ divided by total number of cores (6) = average Gleason score of 7.33 with a weighted Gleason grade of 3.67 and a PSA leak of 2.57 ng/cc.

This hypothetical story is a good one. However, PC patients may have Gleason scores of 9 or 10 with low levels of PSA and yet large tumor volumes. Charlie’s hypothetical son, Billy Darwin, when diagnosed with PC at age 54 years had the same baseline PSA of 9.0, clinical stage of T1c, but his gland volume was 20 cc and his Gleason score read by an expert was (5,4). The calculations for benign-related PSA for Billy Darwin indicate a value of $20 \text{ cc} \times 0.066 = 1.32 \text{ ng}$. His PC-related PSA would be 9.0 minus 1.32 or 7.68. With an average Gleason score of 9, his weighted Gleason grade would be 4.5 giving him a PSA leak of

1.36. His calculated tumor volume is 7.68 divided by 1.36 or 5.6 cc. This gives Billy a 34% chance of organ-confined PC based on the work of D'Amico et al^{32,33} and a 50% chance of cure with an RP based on published statistics from Stanford³⁴ relating tumor volume to successful outcomes with RP. Of course, these are only guidelines that help the Darwin's assess their status more scientifically.

The Excel software program that can be used to create worksheets to create data as that described above is currently available on the PCRI (Prostate Cancer Research Institute) web site at www.pcri.org under the menu listing of "PC Tools." Click on PC Tools, then click on "software," go down to the 4th item called "tumor volume calculator" and download that program. This is free software. The program requires inputs of PSA, gland volume, and Gleason score to calculate the PC volume. The necessity of having a reading of the Gleason score by an expert in PC pathology will be discussed later.

The Clinical Stage (CS)

The clinical stage is often confused by physicians and patients alike. This refers to the clinical impression of the amount and extent of disease **exclusive of pathology findings such as the results of biopsies or of radical prostatectomy**. The clinical stage as used today essentially reflects the findings of the digital rectal examination (DRE) of the prostate; this is essentially the T stage. Understanding that the vast majority of the urologic world equates the clinical stage with the T stage of the TNM classification is important if we are to speak one medical language. Confusing the clinical stage with the findings after pathologic biopsy or RP leads to incorrect perceptions of the extent of disease and invalidates proper strategy. The clinical stage, as it relates to the T portion of the TNM classification, is described and illustrated in "A Primer on Prostate Cancer, The Empowered Patient's Guide," a 368-page full color guide written by Donna Pogliano and yours truly. The Primer is most easily available via www.amazon.com or through the publisher, Life Extension, at 1-866-820-7457 or www.lefprostate.org.

The clinical stage is highly subjective and many physicians (including urologists, radiation oncologists and medical oncologists) do not have great skills in discerning pathology within the prostate gland. Thus, the clinical stage (CS) is the least accurate of the

three basic assessments (PSA, Gleason score, and clinical stage) that are used most often in the initial evaluation of patients. Moreover, in at least 70% of men who are newly diagnosed with PC in the U.S.A. by physicians skilled in the art of DRE, the CS reveals no evidence of PC; these patients have a CS of T1c. This is a favorable prognostic finding when present. When the CS is more advanced, it reflects more PC that may be a factor in the outcome using therapies such as RT or Cryosurgery. Such therapies are considered to be **tumor-volume dependent**. That is, a significant factor in the success of such treatment approaches relates to the amount of PC assuming the disease is organ-confined. Therefore, for at least 30% of men with PC, the CS still is hypothetically relevant in our strategy of how best to treat PC. (* Note: In contrast, RP is felt to be **tumor-extent dependent**. If the disease is not confined to the surgical boundaries of the RP procedure, the treatment will not be curative.)

Oncogenes

Numerous other biologic factors have been associated with a more advanced stage of disease. These include genes relating to tumors (oncogenes) that promote cancer cell survival. Oncogenes such as bcl-2 are associated with a more advanced clinical stage.³⁵ In addition; growth factors such as plasma levels of transforming growth factor beta-1 (TGFβ-1) have recently been reported to be associated with occult metastatic disease in patients with apparently localized PC.³⁶

However, in our initial strategy with a newly diagnosed patient with PC or for a patient with recurrent disease, we can use the basic biologic tests that are readily available and still enhance our strategic skills even if we do not have the ability to explore new studies.

Virtually all of these biologic expressions are disease manifestations as they reflect interaction between the host (the patient) and the malignancy. The PSA dynamics may relate to the rapidity of disease growth. Is the disease slow-growing or fast growing? The DRE may reflect the amount of tumor volume as well as provide a clue that part of the PSA is benign-related in those men presenting with large prostate glands without DRE evidence of PC. When we use such tools, we are listening to the biology of cancer

and enhancing our strategy of success.

This ends Part I of the Strategy of Success in the Treatment of PC.

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INTENSITY MODULATED RADIOTHERAPY TREATMENT OF PROSTATE CANCER

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OVERVIEW

It is estimated that one out of three persons in the United States will be diagnosed with cancer in their lifetimes. More than half of these patients will receive some form of radiation therapy. The goal of radiotherapy of malignant tumor is to administer a sufficient dose of radiation to kill cancerous cells within a given target volume. A high enough dose of radiation can eradicate any cancerous mass. The catch is that injury to the surrounding normal tissue limits the delivery of high radiation doses in many settings. Intensity modulated radiation therapy, or IMRT, is a refinement over existing conformal radiotherapy modalities, rather than a breakthrough technology. IMRT represents an advance in the means that radiation is delivered to the target, and it is believed that IMRT offers an improvement over conventional and conformal radiation in its ability to provide higher dose irradiation of tumor mass, while exposing the surrounding normal tissue to less radiation. IMRT may be especially useful in the treatment of concave tumors, and tumors that are surrounded by or are adjacent to sensitive normal tissue. This en-

hancement in accuracy is achieved by the delivery of thousands of tiny pencil-thin radiation beams, rather than a single large radiation beam passing through the body, and by the enhanced ability of the radiation oncologist to “map” the direction of beamlet travel so that dose distribution to cancer cells is maximized and normal tissue exposure is minimized. Because prostate cancer fits the ideal target criteria for IMRT of adjacent sensitive dose-limiting tissue (rectal and bladder), and since prostate cancer has been the most widely used application of IMRT with the longest follow-up periods, this paper will emphasize the role of IMRT in the treatment of prostate cancer.

HISTORICAL ANTECEDENTS

Radiation therapy has been used to treat cancer for over a century. The first recorded case of radiation treatment in literature occurred in January 1896; just several weeks after Nobel laureate Wilhelm Roentgen reported his discovery of the X-ray. The discovery of radioactivity and X-rays led to the knowledge that radiation could be used to damage cells. Cancer cells reproduce at a greater rate than normal cells, and thus are vulnerable to the effects of radiation. Normal cells, while also affected by radiation, have a greater ability to regenerate than cancerous cells.¹

First developed and marketed in the 1950's, the medical linear accelerator represented a technological breakthrough in the way that radiation was delivered to treat cancer. These machines operate by using microwave energy to accelerate electrons to nearly the speed of light over a short distance, usually one meter or less. As the electrons reach maximum speed they collide into a tungsten target, which releases photons as the result of the bombardment. As the photons, or X-rays, hit human tissue, they produce highly energized ions that are lethal to both malignant and benign tissue. However, unlike cancer cells, non-cancerous tissue can adapt over successive regenerative cycles, leading to the practice of administering repeated radiation treatments rather than a single massive dose.²

Radiation treatment underwent a major progression when it evolved from generic radiation of the entire pelvis to an approach known as conformal radiation therapy. The technique, known as three-dimensional conformal radiation therapy, or 3D-CRT, was introduced in the 1980's, and was the first radiation therapy that had the ability to conform the shape of the

radiation beam to that of the tumor. The objective of 3D-CRT is to irradiate a target volume that is the result of a three-dimensional study, rather than the two dimensional dose planning system it replaces. Several randomized trials have shown that, compared with conventional radiation therapy of prostate cancer, 3D-CRT reduces the radiation volume to the adjacent normal tissue, while the higher dose delivery allows for improved efficacy rates.³

Because of the proximity of the prostate to the rectum and bladder, radiation oncologists have been reluctant to irradiate prostate tumors with doses higher than 70 Gy, out of a fear of radiation toxicity. However, in many cases, 70 Gy is a suboptimal dose, either due to radio resistance, poor vascularization, or local hypoxia.⁴

3D-CRT, despite its name, cannot conform well to three-dimensional objects, largely because of the uniformity of beam strength. This can pose a significant problem in tumor control. Researchers in the field of radiation oncology estimate that approximately 30% of tumors exhibit concave features, thereby posing difficulty for treatment with conventional conformal radiotherapy.⁵

WHAT IS IMRT

IMRT is the latest technological advance in conformal radiation therapy. IMRT evolved from the inability of 3D-CRT to irradiate tumors that are concave, surrounded by normal tissue, or in very close proximity to sensitive normal tissue, without causing excessive radiation exposure of adjacent normal tissue. IMRT aims to overcome the limitations of 3D-CRT by adding modulation of beam intensity to beam shaping. In fact, it is the use of non-uniform intensity fields that most differentiates IMRT from 3D-CRT.

IMRT incorporates two distinct features over 3D-CRT; inverse treatment planning, and computer-controlled intensity modulation of the radiation beam.⁶

The conventional forward planning that is used with 3D-CRT is not feasible with IMRT. Instead, IMRT employs the use of “inverse” planning, a method that has a greater capability of integrating the very large number of possible beam profiles. This technique begins with the required dose distribution and a set of planning parameters. The planning computer then

designs the beam profiles necessary to produce their distribution.⁵

Conventional conformal beam radiation is characterized by a constant fluence. IMRT differs in that the radiation fluence varies across the beam, a phenomenon termed beam intensity modulation or BEM. Intensity modulated beams can be produced by a variety of methods, including the use of metal compensators, sequential delivery of smaller segments or sub-fields (termed the “step and shoot” method), the “sliding window” technique which uses pairs of moving dynamic multileaf collimators (dMLC), and the irradiation of the target slice by slice, termed tomotherapy.⁵

ADVANTAGES OF IMRT

IMRT allows for varying intensities of radiation to produce dose distribution that is significantly more precise than 3D-CRT. Since IMRT has the ability to deliver radiotherapy that is highly conformal to the target tumor volume, dose escalation, with the resultant improved local control and cure, is more feasible. With conventional radiotherapy, the average intensity of the radiation dose to the prostate has been 65-70 Gy. The problem is that subpopulations of prostate tumor cells are radio resistant to doses of this intensity. Doses greater than 70 Gy are needed to achieve local control, but the rates of severe complications double when the dose is escalated beyond 70 Gy. IMRT offers the potential advantage of dose escalation without a corresponding increase in radiotherapy-associated toxicity to surrounding tissue.⁷

Several potential advantages of IMRT over conventional radiotherapy include greater latitude for dose escalation which may lead to improved local control and cure, the ability to deliver differential dose rates, a possible reduction in acute and late radiation toxicity, the potential to approach any complex problem regardless of shape, and the empowerment of clinicians who use low doses of radiation to elevate doses to appropriate levels.⁸

DISADVANTAGES OF IMRT

Compared with conventional radiotherapy, there are several potential disadvantages of IMRT, including dose heterogeneity within the target that is the result of the tradeoff of higher conformality with multiple beam delivery, increased volume of normal tissue exposure that is the consequence of improved dose

distribution around the target, inefficiency of beam delivery and beam leakage that may result in a total body dose that is significantly higher than in conventional radiotherapy, prolonged treatment delivery time that is inherent in the inefficiency of the beam delivery, and the greater sensitivity of IMRT over other radiotherapies to any degree of internal movement of the targeted tumor region, which can confound calculations of dose and arbitrarily defined margins.^{6,8}

Other potential concerns over IMRT include a higher risk of error due to the complexity of planning and delivery, and difficulties in quality assurance, radiation safety, and portal verification. IMRT is time-consuming, expensive, complex, and may not necessarily offer an advantage over more conventional techniques for some patients. Long-term follow-up of patients treated with IMRT is necessary to resolve these issues.⁹

RESEARCH FINDINGS

Although IMRT has been used clinically in the treatment of tumors of the brain, breast, head and neck, liver, lung, nasopharynx, pancreas, prostate, and uterus, the primary focus of research involving IMRT in the United States has been on prostate cancer. Additionally, prostate cancer is the only application involving comparisons with conventional radiotherapy, with an emphasis on comparative morbidity between IMRT and 3D-CRT.

Zelevsky, et al.¹⁰ followed a series of 772 prostate cancer patients for a median of 24 months who were treated with a dose of either 81.0 or 86.4 Gy. 1.5% of the patients experienced moderate (grade 2) rectal toxicity and 0.5% experienced serious (grade 3) rectal toxicity. The 3-year actuarial rate of \geq grade 2 rectal bleeding was 4%. Also, they found no difference in the rate of toxicity between the two treatment groups. The 3-year actuarial PSA relapse-free survival rates among patients with low, medium, and high risk for biochemical relapse treated with 81 Gy were 93%, 84%, and 81%, respectively.

Zelevsky, et al.³ compared the acute and late toxicities of patients with locally confined to locally advanced (T1c-T3) prostate cancer receiving high-dose (81 Gy) 3D-CRT (n=61) and IMRT (n=171). The median follow-up period was 39 months for 3D-CRT and 12 months for IMRT. The authors found that

IMRT significantly reduced the incidence of acute mild to moderate rectal toxicity compared with 3D-CRT, and that there was a corresponding increase in the number of patients who did not exhibit rectal toxicity with IMRT. Additionally, there were fewer cases of moderately severe late rectal toxicity with IMRT than 3D-CRT, and there were fewer total number of cases of late rectal toxicity with IMRT.

To quantitatively evaluate the differences between IMRT and 3D-CRT, 20 randomly selected patients in the Zelefsky study³ were planned concomitantly with both methods. Histogram analysis revealed that IMRT planning resulted in a larger volume of targeted malignant tissue receiving the prescribed dose relative to 3D-CRT. The authors believe that this provides evidence that IMRT provides greater conformality in the treatment of prostate cancer than 3D-CRT. However, planning studies such as this do not provide clinical data and are no substitute for appropriate clinical trials.⁵

A study with long-term follow-up was published Zelefsky, et al.¹¹ in 2001. Although the outcome figures of IMRT were combined with those of 3D-CRT, the authors did follow 40 patients who received high dose radiotherapy delivered by IMRT for a median of 31 months. They found that 5% developed late-onset moderate rectal toxicity and 20% developed moderate urinary toxicity. The authors conclude that IMRT allows the delivery of high dose radiotherapy unattainable by 3D-CRT without significant compromise to adjacent tissue.

A study comparing the side effects of high dose (82 Gy or more) IMRT with 3D-CRT was published by Shu and colleagues.¹² At a median follow-up of 18.7 months and 30.1 months for IMRT and 3D-CRT, respectively, the authors found that IMRT produced significantly greater rates of acute rectal toxicity than those treated with 3D-CRT. However, the results were confounded by a higher degree of tumor aggressiveness among the IMRT patients, and a higher rate of whole pelvic irradiation among IMRT recipients.

In summary, the body of research of IMRT treatment of prostate cancer suggests that IMRT can achieve similar rates of efficacy as 3D-CRT, but with lower rates of acute and late-onset toxicity

ISSUES OF CONTROVERSY AND DIRECTION FOR FURTHER RESEARCH

As is often the case with any new medical technology, there is a lack of medical consensus surrounding issues such as patient selection criteria, target selection and delineation, target dose prescription strategies, and non-involved organ dose constraints that are defined for IMRT.⁹ Although there is no medical consensus on exactly which patient populations IMRT is appropriate treatment, IMRT is most likely to benefit patients with tumor targets that are concave, and where the avoidance of normal tissue irradiation is paramount. Patient selectivity is important with IMRT because of its higher cost, increased treatment time, and increased demands on physicians, physicists, and therapists relative to conventional radiotherapy. Zhen, et al.⁶ propose a set of disease and patient-related characteristics that should be considered prior to IMRT treatment. Patient-related factors include performance status, age, tolerance for prolonged daily treatment, and history of previous radiation therapy. Disease-related factors include curability with radiotherapy, potential improvement over conventional radiotherapy, histology, site or location of the tumor, and tumor motion.

Zen, et al.⁶ conclude that priority for IMRT treatment should be reserved for patients with good performance status, absence of significant co-morbidity, and reasonable life expectancy.

Third party reimbursement can be a contentious issue surrounding new medical technologies. The reimbursement policy for IMRT that is established by Pennsylvania Medicare¹³ may serve as an example of how third parties may implement coverage for IMRT for prostate and other cancers. In their policy, they state that “IMRT is considered to be reasonable and necessary in instances where sparing the surrounding normal tissue is essential and the patient has *at least one* of the following conditions:

- Important dose limiting structures adjacent to, but outside the planned treatment volume are sufficiently close and require IMRT to assure for safety and morbidity reduction.
- An immediate adjacent volume has been irradiated and abutting portals must be established with high precision.

- Gross tumor volume margins are concave or convex and in close proximity to critical structures that must be protected to avoid unacceptable morbidity.
- Non-IMRT techniques would increase the probability of grade 2 or grade 3 radiation toxicity in greater than 15 percent of radiated similar cases.
- The volume of interest is in such location that its parameters are not assessed by simple two dimensional imaging techniques but rather by three dimensional reconstructions.
- IMRT is covered when the tumor tissue lies in areas associated with target motion caused by cardiac and pulmonary cycles, and the IMRT is necessary in order to protect adjacent normal tissues.”

Additionally, they state that IMRT is not covered “in situations where sparing surrounding normal tissue is not essential.”

Often, there is the temptation to assume that improvements in technology automatically translate into improvements in patient outcome. Preliminary evidence suggests that IMRT treatment can provide similar efficacy with less acute and long-term rectal toxicity than 3D-CRT. However, the body of clinical research on IMRT treatment of prostate cancer is quite limited. Issues that need to be addressed by future research should include clinical outcome data, the establishment and refinement of patient selection criteria, optimal treatment planning and delivery, cost analysis, and impact on quality of life. Of particular interest is whether IMRT can reduce the rate of late toxicity and risk of complications that are found in conventional radiotherapy.⁶ Additionally, there is wide variation in response among tumors that are identical by location and pathological type. The factors associated with these variations should be examined so that dose modulation can be implemented.⁴

In conclusion, preliminary evidence suggests that IMRT can play a valuable role in reducing radiation toxicity to sensitive normal tissue adjacent to the targeted tumor, with no loss in efficacy. However, more comprehensive and longer-term data will be necessary before IMRT can be shown to be superior to conventional three dimensional therapy in regards to survival.

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OSTEOPOROSIS IN MEN WITH PROSTATE CANCER

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Osteoporosis means weakened bone from calcium loss over time. Calcium loss is a silent phenomenon until a bone fracture occurs. Common fracture sites from osteoporosis are the spine, rib, wrist, and hip. Osteoporotic fractures often have dire consequences. Bone fractures are associated with shortened survival in men with prostate cancer.¹ Compression fractures of the spine can be extremely painful, result in loss of height, and when advanced, result in a forward curva-

ture of the spine commonly termed the “dowagers hump.”

Osteoporosis is mistakenly perceived to occur only in females. Fully a third of all hip fractures occur in men. There are many causes of osteoporosis. Men who are slender have less bone reserve and are more predisposed. Thyroid or parathyroid hyperactivity can be implicated. Other causes of osteoporosis are excessive use of alcohol, caffeine, or tobacco; cortisone, used to treat asthma or arthritis, is another common culprit; common diuretics such as hydrochlorothiazide, a drug used to treat hypertension, can also contribute. Excess vitamin A has also been associated with osteoporosis and fractures.² Lack of exercise, lack of sunlight exposure (low vitamin D), and low calcium intake are additional potential causes.

Osteoporosis-induced bone fractures are even more frequent in men treated for prostate cancer with androgen deprivation therapy (ADT).^{3, 4} Androgen deprivation therapy reduces testosterone levels in the blood. Testosterone, and estrogen that is derived from testosterone, both inhibit excess calcium loss from bone.^{5,6}

Osteoporosis needs to be identified before a fracture occurs. Unfortunately, the most common scanning technique for diagnosing osteoporosis, the DEXA (dual energy absorption x-ray) scan, grossly underestimates bone mineral loss from the spine in men.⁷ Men over age fifty usually have degenerative arthritis of the lower back, a condition accompanied by calcium deposition in the tissues surrounding the spine. When the DEXA scan sends x-rays through this area to measure spine density, the excess calcium surrounding the spine results in an artificially high bone density reading.

Fortunately another more accurate technique of measuring bone mineral density is available called quantitative CAT scan or QCT. This scan measures the calcium density in the center of the vertebral column avoiding the problem of surrounding calcium. A lack of awareness of the DEXA scans' limitations among health care providers is common even though these limitations have been well documented in a study from Massachusetts General Hospital.⁷ This study compared DEXA and QCT in 41 men with prostate cancer who had never previously been treated with

ADT. QCT detected osteoporosis in 26 men (63%) but DEXA only found osteoporosis in two (5%)!

On the basis of this study, which was done in men who had an average age of 68, we can conclude that osteoporosis is common even in men who have never had previous exposure to testosterone-lowering drugs. Men who have a diagnosis of osteoporosis before starting ADT should be evaluated for other known causes of osteoporosis such as overactive thyroid or parathyroid glands.

Osteoporosis is common and can potentially have devastating effects. The process of reversing osteoporosis logically begins by implementing some common sense measures to reverse the underlying causes. Such measures should include starting a regular exercise program, restricting the excess use of alcohol, tobacco, or caffeine, and cutting down on the excess use of vitamin A.

Sometimes for medical reasons osteoporosis-inducing treatments like cortisone or ADT cannot safely be stopped. Studies do show that using ADT intermittently (compared to continuous ADT) prevents excess bone loss.⁸ Despite the negative impact of ADT and cortisone on bone density it appears that bisphosphonates are able to overcome these effects.^{9,10,11} We will further address this preventative effect of bisphosphonates later in the article.

Supplementation with calcium and vitamin D represents routine osteoporosis therapy. We normally recommend 1000 mg of calcium and 400 I.U. of Vitamin D. Calcium citrate is better absorbed than calcium carbonate. Epidemiological reports raising concerns about calcium causing prostate cancer have not been borne out in recent studies.^{12,21} Excessive intake of calcium is known to lower vitamin D levels, so relative vitamin D deficiency induced by excess calcium may be the explanation for the epidemiological reports reporting calcium as a cause of higher prostate cancer incidence.

Multiple studies confirm the inhibitory effect of vitamin D on prostate cancer growth.^{13,14} Vitamin D in the common form sold over the counter is not very active until it is chemically modified by the kidneys. The chemical conversion to a more active form appears to require adequate amounts of two mineral elements, magnesium and boron. As is well known,

sun exposure is also required. As it turns out, all these chemical steps can be bypassed by the oral administration of pre-activated vitamin D, which is sold in prescription form as calcitriol. Side effects from calcitriol are not common but some individuals may have elevation of calcium blood levels so this needs to be checked periodically.

Modern osteoporosis therapy has been revolutionized by a new class of drugs called bisphosphonates. Normal bone metabolism is a balance between the rate of bone breakdown and the formation of new bone. Osteoporosis occurs when the formation of new bone lags behind the rate of bone breakdown. Bisphosphonates function by slowing the rate of bone breakdown allowing the cells forming new bone to catch up.

Bisphosphonates come in both oral and intravenous forms. The oral forms are not very well absorbed though small amounts are absorbed when they are administered on an empty stomach. The most common side effect from orally administered bisphosphonates is stomach or esophageal irritation that occurs in about 5-10% of patients. To minimize esophageal irritation incurred by drug reflux, the manufacturer recommends not lying down for an hour after taking the drug. Fortunately this inconvenience has been minimized to a substantial degree by the development of agents that are effective when administered on a once-weekly basis.

The two most common oral bisphosphonates are Actonel and Fosamax. In general the drugs appear to have comparable efficacy and side effects though one study suggests that the incidence of stomach irritation may be slightly less with Actonel.¹⁵ Most studies of oral bisphosphonates have been done in women but one large study of Fosamax has been performed in men confirming its effectiveness.¹⁶ Experience in our own practice would suggest that the two products are interchangeable.

Bisphosphonates are also available in intravenous preparations. Intravenous administration has the advantage of bypassing the stomach thus avoiding concerns about stomach irritation. Also with the intravenous approach 100% of the drug gets into the system as compared to the oral preparations that are only 1 - 2% absorbed. The most common side effect, occurring in a minority of men, is a brief flu-like muscle soreness lasting a day or so. These symptoms do

not usually recur on subsequent infusions. The infusions are repeated every three months.

Aredia and Zometa are the names of the two available intravenous preparations. There seems to be generally comparable efficacy and toxicity between the two agents. Both agents have been studied in a controlled fashion to determine if they are able to prevent bone loss in men treated with ADT.^{11,22} In the case of Aredia, Smith et al studied 47 men who were randomized to either Lupron plus Aredia 60 mg every 3 months vs. Lupron alone. QCT bone density was obtained at the start of therapy and repeated after one year of treatment. There was no loss of bone after one year in the men treated with Aredia whereas the men treated with Lupron alone lost 8.5% of their trabecular bone.

Smith, et al. also performed a similar trial in 106 men who either received ADT alone or ADT plus Zometa 4 mg every 3 months. DEXA scan was used to measure bone density at baseline and after one year of treatment. Spine bone density increased by 5.5% in men who received Zometa and ADT. Bone density decreased by 2.2% in the men receiving ADT alone.

In our own practice at Prostate Oncology Specialists we have studied 30 cases where men treated with 18 months of ADT were treated prophylactically with either of the oral bisphosphonates Actonel or Fosamax. These men had baseline bone density testing with either QCT or DEXA which was repeated 18 months after starting ADT. We found that the average bone density was unchanged after 18 months of ADT.

So it appears that all forms of bisphosphonates are capable of preventing bone loss during ADT. Since accelerated bone loss can be anticipated with ADT we recommend that all men undergoing this form of therapy be administered bisphosphonates as a preventive measure during ADT therapy.

Bone density scans administered annually, preferably the QCT scan, are the standard method for detecting osteoporosis. The metabolic activity of bone can also be measured by analyzing urine or blood for the presence of excess bone breakdown products like N-telopeptide or Pylinks-D.¹⁷ These bone breakdown products are usually elevated when accelerated bone loss is present and their levels in the blood and urine should decline to normal if the treatment imple-

mented to counteract the osteoporosis is working. The urinary tests are helpful because they can be repeated soon after therapy is initiated enabling an early determination of treatment efficacy rather than waiting a whole year until the results of the next bone density scan is available.

Osteoporosis unresponsive to bisphosphonates, calcium, and activated vitamin D (Calcitriol) is uncommon but does occur. Additional modalities that can be considered to further enhance the effectiveness of the osteoporosis treatment are an increase in the bisphosphonate dose, the use of oral or intravenous fluoride, estrogen in low doses, Calcitonin, Raloxifene, and supplemental vitamin K.^{18,19,20}

Two articles published recently in the New England Journal of Medicine demonstrate that synthetic parathyroid hormone administered by injection builds bone more quickly than bisphosphonates.^{23,24} This new form of treatment would seem to represent an effective alternative to bisphosphonates especially in individuals who do not appear to be responding to bisphosphonate therapy. The treatment is administered via daily injections which are inconvenient but certainly doable.

However in prostate cancer patients there may be a more fundamental concern about the use of this new treatment. It is well known that prostate cancer has a propensity for spreading to bone. What is not so widely known is that the growing prostate cancer cells secrete a chemical substance called *parathyroid hormone-related protein*.^{25,26} This protein is processed by the cancer cells into peptides that affect the growth rate of the cancer cells. Until more information is available about the safety of this new drug it would appear prudent for prostate cancer patients to avoid the use of synthetic parathyroid hormone except in the most urgent circumstances.

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What the heck has been going on in my world? PART II

By Mark A. Moyad, M.P.H.

So, it is time to bring you up to date once again on some of the latest news-Part II. Some of it is good, some bad, and some indifferent (just like life). Keep in mind that some studies looked at preventing prostate cancer and some studies looked at changing the course of this disease after men were diagnosed with

prostate cancer. Regardless, whatever looks good for prevention may be effective for men after a diagnosis and vice versa so you should keep this in mind. Let's get started because there is a lot to talk about in the world of complementary and preventive medicine.

HEART & PROSTATE HEALTH - MOYAD SAYS "LET'S REVISIT THIS ISSUE OVER AND OVER AGAIN"

7) FISH TO REDUCE THE RISK OF METASTATIC PROSTATE CANCER???

This was a study from the Health Professionals' Follow-up Study (prospective cohort). A total of 47,882 men were followed for a mean of 12 years. A total of 2,482 cases of prostate cancer were diagnosed with 617 advanced cases and 278 metastatic cases. Men that consumed fish more than 3 times a week versus little to no weekly consumption (less than 2 times a month) had a reduced risk of prostate cancer. The most pronounced effect was a 44% reduction in metastatic prostate cancer risk (Augustsson K, et al. *Cancer Epidemiol Biomark Prev* 12:64-67, 2003). This is some good news for all us sushi lovers that have suffered for years in silence. No, I am not worried about getting an infection from raw fish, but if you do not like raw fish then feel free to broil or bake (not fry) those little guys!!! Basically, fish and fish oil pills contain 2 primary compounds called "EPA" and "DHA" and these are omega-3 fatty acids that may reduce inflammation and may have an effect on prostate and other cancers. Obviously, this research is preliminary but who cares because fish is already so heart healthy that it just makes sense to include more of this stuff in your diet. Once in a while I get questions on which types of fish contain high levels of mercury (not a good thing). Well, the FDA has mentioned that specifically 4 types of large predatory fish may have higher levels of mercury. The 4 types of fish are: 1) Shark 2) Swordfish 3) King Mackerel, and 4) Tilefish. Now, I am not necessarily a fan of those 4 fish and the FDA is not sure whether or not they actually can cause problems but we thought we would let you know who made the list. By the way, fish oil supplements (if your doctor says you qualify for these things) tend to contain little to no mercury (reported from a recent survey at www.consumerlabs.com).

8) HIGH CHOLESTEROL = HIGHER PROSTATE CANCER RISK???

A prospective study of 862 patients from 4 urological centers in Austria included 3 groups. Group 1 was patients with histologically proven prostate cancer. Group 2 was patients with no prostate cancer after 2 biopsies. Group 3 was patients with no suspected signs and symptoms of prostate cancer. Researchers found that those patients with prostate cancer had a significantly elevated total cholesterol/HDL quotient (mean = 5.21) in comparison to the group with a negative biopsy (mean = 4.71). Researchers hypothesized that a high cholesterol/HDL ratio may be a possible risk factor for prostate cancer (Sonnleithner M, Jeschke K, Bayer L, et al. *Dyslipoproteinemia as a risk-factor in prostate cancer. J Urol* 169: page 79-abstract #294, 2003).

9) DIET VS. STATINS (cholesterol lowering drugs) TO REDUCE HIGH CHOLESTEROL LEVELS?

In this preliminary 1-month investigation, researchers assigned 55 healthy men and women with high cholesterol levels to 1 of 3 treatments:

A) A very low-saturated fat diet based on whole-grain cereals and low-fat dairy foods = CONTROL GROUP.

B) The same diet above + 20 mg/d of lovastatin (Mevacor®) = STATIN GROUP

C) A diet high in plant sterols, soy protein, viscous fibers and almonds = DIETARY PORTFOLIO GROUP.

A total of 46 patients completed the 1-month study. Researchers reported that the statin or dietary portfolio treatment groups had approximately 30% reduction in LDL (bad cholesterol) & 30% reduction in c-reactive protein (CRP) versus an 8% (LDL) and 10% (CRP) reduction in the control group. Thus, in short term, patients on a specific diet may be able to reduce their cholesterol and c-reactive protein levels as much as low-dose statin drugs - wow (Jenkins DJA, Kendall CWC, Marchie A, et al. *Effects of dietary portfolio of cholesterol-lowering foods vs. lovastatin on serum lipids and c-reactive protein. JAMA* 290:502-510, 2003)!!!

10) LIFESTYLE CHANGES FOR PATIENTS WITH PROSTATE CANCER.

A total of 87 men with biopsy + prostate cancer, PSA 4-10, and Gleason scores less than 7 were randomly assigned to an experimental group (low-fat, low-calorie, vegan diet with soy and antioxidants, mod-

erate aerobic exercise, stress management, and psychosocial group support) or a non-intervention control group. After one year, mean PSA levels were reduced 3% in the experimental group but increased 7% in the control group ($P = 0.034$). The changes in PSA began to occur in as little as 3 months (Ornish D, Fair W, Pettengill E, et al. Can lifestyle changes reverse prostate cancer? *J Urol* 169: page 74-abstract #286, 2003). We will know more about this study soon (after the actual paper is published).

11) STATINS (cholesterol lowering drugs) AND THE RISK OF RECURRENCE AFTER RADIOTHERAPY

This was a study from Memorial Sloan-Kettering. A total of 905 men with clinical stage T1-3 prostate cancer were treated between 1995 and 2000 with radiation therapy. The median age was 69 years, the median Gleason was 7, and the median PSA at diagnosis was 8.2 ng/ml. A total of 153 patients (17%) were on a statin (cholesterol-lowering drugs) at the time of diagnosis. Median follow-up was 39 months after radiation therapy. Researchers observed that statin use was associated with an improved freedom from PSA recurrence ($P < 0.001$) when all 905 patients were evaluated. When analysis was limited to 592 men with intermediate or unfavorable risk prostate cancer, these patients had a significant reduced risk of 5-year freedom from PSA recurrence. Statistical analysis of all of these patients stratified by use of neo-adjuvant androgen suppression found that lots of factors could possibly affect PSA recurrence including cholesterol levels.

The bottom line is that statin use was associated with improved PSA control after high dose radiation therapy. Statins could be acting as a radiation sensitizer or may affect PSA artificially. Regardless, this is interesting data (Katz MO, Zelefsky MJ, Marion C, et al. Statin use is associated with improved biochemical outcome after high-dose radiotherapy for clinically localized prostate cancer. *Proceedings of the 45th Annual ASTRO Meeting*: page S271-abstract#1016, 2003). Again, the overall bottom line = **KEEP YOUR CHOLESTEROL LEVELS LOW-EVEN WHILE YOU ARE BEING TREATED FOR PROSTATE CANCER**. Let's just pretend that cholesterol lowering does not affect your prostate cancer - well turns out you should still benefit by lowering your risk of dying of cardiovascular disease. Therefore, lowering your cholesterol level just makes sense

when looking at the whole picture of life and trying to live longer and better!

12) REDUCED EFFECT OF ASPIRIN WHEN TAKING NSAIDS AT THE SAME TIME OF THE DAY???

Researchers performed an analysis from the Physicians' Health Study (5-year randomized trial of 325 mg every other day of aspirin vs. placebo). This study was stopped after 5-years because of a significant (44%) reduction in first heart attack in the aspirin group ($n = 22,071$ total in the study of healthy men). Among participants randomized to aspirin, the use of other Non-Steroidal Anti-inflammatory Drugs = NSAIDs (motrin, ibuprofen, ... for example) for 1-59 days per year was not associated with a heart attack, but the use of NSAIDs for 60 or more days per year was associated with an increased risk of heart attack compared with no use of NSAIDs. In other words, the data demonstrated that regular but not intermittent use of NSAIDs inhibits the clinical benefits of aspirin. Patients should be informed that regular NSAIDs use could reduce the effect of aspirin therapy for the prevention of a first heart attack. Patients should either take an aspirin before the NSAIDs (for example in the morning) or reduce their consumption of NSAIDs (Kurth T, Glynn RJ, Walker AM, et al. Inhibition of clinical benefits of aspirin on first myocardial infarction by nonsteroidal anti-inflammatory drugs. *Circulation* 108:1191-1195, 2003). Whether or not COX-2 (Celebrex, Vioxx ...) inhibitors affects the heart healthy benefits of aspirin is not exactly known. Again, the bottom line = **TALK TO YOUR DOCTOR AND TRY AND TAKE YOUR DAILY ASPIRIN (if you are taking it to reduce the risk of a heart attack) BEFORE YOU TAKE A NSAIDS...** However, taking your aspirin daily and taking motrin or other NSAIDs at the same time may not be a good idea.

13) LYCOPENE SUPPLEMENTS WITH AN ORCHIECTOMY or LHRH TREATMENT???

A total of 54 patients with metastatic prostate cancer (M1b or D2) were studied. Patients either received lycopene (2 mg twice a day = 4 mg total per day) or no supplements. At 6 months there was a significant reduction in PSA in both groups, but a larger change was observed in the lycopene group. After 2 years these changes were more consistent in the lycopene group (mean 3.01 vs. 9.02 ng/ml; $P < 0.001$). More patients in the lycopene group had a complete PSA response. Bone scans also reported a more complete

response in the lycopene group. There was also a better peak flow rate and less patients died in the lycopene group. Thus, the researchers concluded that adding lycopene supplements to orchiectomy produced a more reliable and consistent reduction in PSA level that not only reduced the tumors, but provided better relief from bone pain and lower urinary tract symptoms, and improved survival compared to orchiectomy alone (Ansari MS, Gupta NP. A comparison of lycopene and orchiectomy vs. orchiectomy alone in the management of advanced prostate cancer. *BJU Int* 92:375-378, 2003). I am not sure that I can comment on this study. I am skeptical that 4 mg of lycopene supplements per day makes such a large difference, but I think it is important to at least mention this study. If someone wants to take that exact amount of lycopene then it seems to be okay - what the heck! I am just not sure at this time if it was the lycopene pills or the other healthy things that these men did while taking lycopene or was it a combination of both of these things??? Talk to your doc about this study.

14) WEIGHT LIFTING FOR MEN RECEIVING ANDROGEN DEPRIVATION THERAPY FOR PROSTATE CANCER.

A total of 155 men with prostate cancer who were scheduled to receive androgen deprivation therapy for at least 3 months, were randomly assigned to a weight lifting program 3 times a week for 12 weeks (n = 82) or a control group (n = 73). Men assigned to weight lifting had less fatigue on activities of daily living (P = 0.002) and higher quality of life scores (P = 0.001) compared to men in the control group. Men that lifted weights had higher levels of upper body (P = 0.009) and lower body (P < 0.001) muscular fitness versus men in the control arm. The 12-week weight lifting intervention did not improve body weight, body mass index, waist circumference, or subcutaneous skinfolds. However, **LIFTING WEIGHTS SHOULD BE ABSOLUTELY RECOMMENDED IN MEN RECEIVING ANDROGEN DEPRIVATION TREATMENT FOR PROSTATE CANCER (LHRH treatment...)** because of the profound impact on fatigue and quality of life and because of many other health benefits (anti-osteoporosis) that we will write about in a future issue (Segal RJ, Reid RD, Courneya KS, et al. Resistance exercise in men receiving androgen deprivation therapy for prostate cancer. *J Clin Oncol* 21:1653-1659, 2003). Basically, lifting weights and aerobic

exercise should be equally important. One not more important than the other!!

There is so much more to discuss when it comes to the latest research on prostate cancer and we will cover this again in the next issue of PAACT (part III). I apologize, but I need to get some sleep and get the next article ready for the next issue. In the meantime, I do sleep with a clear conscience because the book that we put out several years ago seems to be supported more than ever by the latest research. If you still want to order the book, call 1-800-462-6420 (National Book Network) and ask for the ABCs of Nutrition and Supplements for Prostate Cancer by Mark Moyad. This is a shameless promotion but I am proud to say that most of the predictions in this book seem to be supported by the latest research! Now, if you do not want to spend the money you could always photocopy portions from the library or your doctor's office or you could print out some of the articles from the internet. Regardless, I wish all of you the best of health and a wonderful fall and winter and look for more recent research in the next issue of PAACT.

LAC-PAACT¹UPDATE

By Gregory H. Teufel, Esq., Chairman²

It has been a while since we have updated you on any of the doings of the Legal Advisory Committee or the progress of reimbursement fights for advanced cancer treatments. The most significant recent change is that BCBS of Texas finally issued a coverage policy for cryosurgical ablation of the prostate (CSAP). Galil Medical USA worked diligently with the Harris County Medical Society, the AUA and some physicians in Texas to support the coverage. A group of physicians led by Dr. Paul Handel met with BCBS and the outcome of the meeting was the favorable change in policy and coverage, which was effective June 13, 2003.

¹ LAC-PAACT is PAACT's legal advisory 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, I encourage you to consult a lawyer in your state, so that your specific situation and local laws can be considered.

²Gregory H. Teufel, Esq. is a partner in the Litigation Department of Schnader Harrison Segal & Lewis LLP's Pittsburgh office. The views expressed are those of Mr. Teufel personally and not of the firm.

As a side note, the policy still contains outdated information such as “A bilateral vasectomy may be performed prior to or in conjunction with the cryosurgery. A urologist and a radiologist always perform cryosurgery together. Repeated treatment sessions are not uncommon.” However, the fact that their policy now allows for coverage is fantastic. Thank you to Lisa Hayden for the update on this.

We are creating another supplement to the LAC-PAACT kit, and will include a copy of the Texas BCBS Coverage policy in the supplement. Expect the new supplement to be available by January 1. 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@schnader.com. You can also call me at work at (412) 577-5289, home (412) 421-7123, or on my cell phone (412) 596-6316, or send me a letter at Schnader Harrison Segal & Lewis LLP, Suite 2700, Fifth Avenue Place, 120 Fifth Ave., Pittsburgh, PA 15222. Please note that requests for the LAC-PAACT kit should be addressed to PAACT. Contact information for PAACT is on page 2 of this Newsletter. Please remember that this article is not legal advice and I cannot generally give you legal advice or become your personal attorney

COURT ORDERED LEGAL NOTICE

ALL PURCHASERS OF LUPRON®*

*Lupron® is an injectable prescription drug used to treat PROSTATE CANCER in men, ENDOMETRIOSIS and INFERTILITY in women and CENTRAL PRECOCIOUS PUBERTY in children.

IF YOU, OR ANYONE YOU KNOW, PAID FOR THE PRESCRIPTION DRUG LUPRON® AT ANY TIME BETWEEN 1991 AND THE PRESENT, YOUR RIGHTS (OR THE RIGHTS OF OTHERS) MAY BE AFFECTED.

Nationwide Class Action Certification

Notice is hereby given that a nationwide class has been certified in the class action lawsuit entitled Stetser, et al. vs. TAP Pharmaceutical Products, Inc., et al., No. 01-CV-5268 (General Court of Justice, Superior Court Div., New Hanover Co., N.C.), consisting of "all persons and entities in North Carolina and throughout the United States who paid any portion of the cost of Lupron® from 1991 to the present which cost was based, in whole, or in part, on the AWP (or Average Wholesale Price) for Lupron®..." (the "Class").

The Lawsuit

This lawsuit concerns an alleged fraudulent scheme and conspiracy involving the marketing, sales and distribution of Lupron®. The representative plaintiffs for the Class are Harry E. Stetser, Dale E. Nelson, and Michael deMontbrun, all residents of North Carolina and prostate cancer patients who have been prescribed and paid for Lupron®. The defendants in the case are: TAP Pharmaceutical Products, Inc., Abbott Laboratories, Takeda Chemical Industries, Ltd., Johnson & Johnson, Ethicon Endo-Surgery, Inc., Indigo Laser Corporation, Scott Hidalgo, David Jett, Christopher Coleman, and Eddy James Hack. This class action lawsuit seeks to recover over-payments for Lupron® which are alleged to have resulted from defendants' conduct. North Carolina law will apply to claims of the Class in this lawsuit. Defendants deny that they are liable, and contend that plaintiffs and the Class will be denied recovery because of numerous defenses they have raised. The Court has not yet decided whether or not plaintiffs or the Class are entitled to a recovery.

Settlements with Individual Defendants

Notice also is hereby given that proposed settlements have been reached with the four individual defendants, Hidalgo, Jett, Coleman and Hack. None of the corporate defendants has settled. While the settlements involve no payment of money, these individual defendants have agreed, among other things, to cooperate in the further prosecution of the case against the corporate defendants. A hearing on the proposed settlements will be held before the Honorable Paul L. Jones, Superior Court Division Judge, 130 South Queen Street, Kinston, NC on March 8, 2004, commencing at 10:00 a.m., to consider whether the settlements should be finally approved. Any Class member wishing to oppose the settlements, submit papers to the Court, or participate in the hearing must comply with the instructions for doing so set forth in the General Notice which may be obtained by calling the number or visiting the website below.

Your Rights and Options

If you do not want to be included in the Class, or receive any of the benefits of the class action lawsuit or the settlements, you must exclude yourself by no later than **JANUARY 8, 2004**. If you do not exclude yourself, you will be bound by any settlement or judgment in the class action. If you want, you may enter an appearance in the class action lawsuit, through your own attorney or on your own, but, you do not need to hire your own attorney to participate in the class action. Complete information about your rights, including how to exclude yourself, is set forth in the General Notice, or you may write to co-lead counsel representing plaintiffs and the Class: Donald E. Haviland, Jr., Esquire, Kline & Specter, P.C., 1525 Locust Street, 19th Floor, Philadelphia, PA 19102 or Marvin K. Blount, Jr., Esquire, The Blount Law Firm, P.L.L.C., 400 West First Street, P.O. Drawer 58, Greenville, NC 27835.

QUESTIONS? Call **1-800-LUPRONLaw** or visit www.LUPRONLaw.com
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