

HORMONE BLOCKADE VERSUS RADICAL LOCAL THERAPIES --
AND THE WINNER IS....

Triple hormone blockade as sole treatment for clinically localized or clinically nonmetastatic prostate cancer has finally been recognized as a reasonable treatment option. *Urology* 60: Supplement 3A: September 2002, is entitled "Newer Approaches to Androgen Deprivation Therapy in Prostate Cancer; Proceedings of the Second International Conference." The guest editors are Peter Carroll, M.D., Professor and Chair, Department of Urology, UC San Francisco. The other editor is Dr. Philip Kantoff, Harvard Medical School. The symposium was held in Cambridge, Massachusetts. The 18 international conference participants included some of the best known names in prostate cancer. The second article in the symposium is "Contemporary Patterns of Androgen Deprivation Therapy Use for **Newly** Diagnosed Prostate Cancer." The senior author is Dr. Peter Carroll, a urologist with a well known bias towards recommending radical prostatectomy. This article reveals some startling and unexpected trends that will probably surprise you.

"...it appears that the use of ADT (androgen deprivation therapy) is increasing for men with clinically localized prostate cancer...." Since 1995, of 1,485 patients accrued from 35 urology practices around the country, 294 of them (20%) chose ADT as their **only form** of therapy for clinically localized prostate cancer (no surgery, radiation therapy, or seeds). Hormone blockade alone was commonly used in men with low or intermediate-risk disease without evidence of metastases. In the past, only men with poor prognostic factors chose primary androgen deprivation therapy (except for our practice where men have chosen ADT for low, intermediate, or high-risk disease since 1991).

The text on page 10 of this article states the following: "A recent series advocates an alternative **primary** hormonal regimen (primary means hormone blockade alone without any

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local therapy) for men with localized prostate cancer. Leibowitz and Tucker"...(our peer reviewed, published results are summarized, and the authors conclude)...."although androgen deprivation therapy appears to be effective in many men with localized prostate cancer...." For the authors to "admit" that androgen deprivation therapy appears to be effective in many men with localized prostate cancer is a rather strong admission from urologists who have ridiculed this concept since we began using it in 1991. They are admitting that hormone blockade is effective in many men with localized prostate cancer. The fact that our prior publication, "Treatment of Localized Prostate Cancer With Intermittent Triple Androgen Blockade: Preliminary Results in 110 Consecutive Patients;" *The Oncologist*; (6; 177-182; 2001; Leibowitz, R. and Tucker, S.J.) is referenced is, of course, quite flattering. The article concludes, "although some studies suggest a benefit of early use of ADT..." the authors then caution that longer follow-up is needed, etc. They are conceding that early androgen deprivation therapy seems to be beneficial. They point out precautions regarding hormone blockade but fail to mention that radical local treatments have never been shown to prolong survival.

In this paper, we shall discuss our updated results for the first approximately 150 patients who have completed their initial cycle of triple hormone blockade, and are currently on Proscar, 5 mg once a day. We have called this Proscar or finasteride maintenance therapy. The earlier results of this study of ours were published in the April 2001 edition of *The Oncologist*. An abstract regarding this work was published in the *Proceedings of the American Society of Clinical Oncology*, Volume 20, 2001, Abstract Number 2372.

In 2002, two additional abstracts were published in the *Proceedings of the American Society of Clinical Oncology*, Volume 21, 2002, Abstract Numbers 2481 and 2486. They are entitled "Five-Year Follow-Up of Triple Androgen Blockade for Clinically Localized Prostate Cancer: Prognostic Features and Preliminary Patterns of Failure" and the other, "At What PSA Level Should Cycle Two of Hormone Blockade Commence in Men Who Refuse Local Treatment for Prostate Cancer and Are Treated With Intermittent Androgen Blockade?" These abstracts were authored by myself and Dr. Tucker.

As of November 2002, we have had to re-treat eight out of approximately 150 patients. We have had one death from prostate cancer. This yields a 99.4% five-year prostate cancer cause-specific survival. Besides the one patient who died from prostate cancer, seven patients were re-treated. All seven had at least one high-risk prognostic feature, as defined by D'Amico. Only one of the seven had one high-risk feature; one had three high-risk features, and the others had two high-risk features. There were 39 other patients in our series who had at least one high-risk feature who have not required re-treatment. High risk is defined as Gleason scores of 8 or higher, PSA over 20, or locally advanced disease. These results are far superior to any published result using radical prostatectomy, radiation therapy, or seeds.

Mayo Clinic has set up a web site for early stage prostate cancer, a decision guide, that looks at "five common treatment options." One of the five is hormone blockade. To us, this means that even Mayo Clinic now "admits that hormone blockade is a common treatment option for early prostate cancer." An article appeared in the *British Medical Journal* by Lu-Yao, G.; 2002; 325:740-743. This study examined 94,000 patients from Seattle versus 120,000 patients from Connecticut. They were studied over 11 years. Men in Seattle were 5.4 times more likely to undergo PSA testing, and 2.2 times more likely to have biopsy, compared to the Connecticut men. 6.6% of the men from Seattle had either radical prostatectomy or radiation therapy. Only 3.6% of the men from Connecticut were treated this way. Remember that the initial patient base were men without known prostate cancer. What is fascinating is that you would assume that if radical local therapies were beneficial, then the Seattle group, having almost twice as many radical procedures, should have a higher prostate cancer survival rate. However, the risk of dying from prostate cancer in Seattle was slightly higher than the risk of dying from prostate cancer in Connecticut (not statistically significantly higher). Therefore, radical treatments did not reduce your risk of dying from prostate cancer, but still caused terrible side effects. The study concludes that there is no difference in prostate cancer outcome at 11 years between more versus less aggressive approaches to screening and treating prostate cancer.

An article in the *Journal of Urology* by Moul, Judd; Volume 165; pages 469-473; February 2001 reports "our results imply

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that tumor cell spillage at surgery may be responsible for recurrence (spread) of disease." Yes, the conclusion is that surgery may be responsible for prostate cancer spreading. Dr. Thomas Stamey, noted urologist at Stanford (now retired), had pointed out that stage T1 or T2 prostate cancer untreated has a median PSA doubling time of four years, meaning it takes four years for a PSA to go from 1.5 to 3; or from 2 to 4, etc. However, the patients who fail radiation therapy or surgery have doubling times of usually less than 100 days. He commented that these patients might have been better off untreated. He additionally comments, "Thus, it is feasible that the surgeon who creates a positive margin at radical prostatectomy is similar to the radiation therapist...both convert a slowly progressive cancer into a rapidly advancing malignancy."

This same phenomenon of cancer cells being spread by the procedure is also described by Siddiqua, A., *Urology* (60; 2: 2002; pages 270-275), "Our results show that a substantial number of patients undergoing brachytherapy have iatrogenic (that means the doctor caused it) dissemination of prostate cancer cells in their bloodstream caused by the insertion of needles in the prostate gland."

In an interview with Paul Lange, urologist from Seattle, is a quote, "The argument that prostate cancer is a systemic disease is gaining ground from a variety of sources." Systemic means disease outside the prostate, such as in the bones, for example. Dr. Chodak, urologist from the University of Chicago, is quoted in *Urology*; 60; 201-208; 2002, regarding hormone blockade alone for localized prostate cancer. "Some patients chose this approach because of the effect on PSA level" (We remind the reader that all of the men treated with triple hormone blockade/Leibowitz protocol, reached unmeasurable PSA levels of less than 0.1), **"and because none of the local therapies has been shown to prolong survival."**

Dr. J. Talcott, writing an editorial in the *Journal of the National Cancer Institute*, Volume 94; Number 6; March 20, 2002; pages 407-409, "During the last decade, physicians have begun to treat men with asymptomatic early prostate cancer with hormone blockade alone." In fact, 27% of men in a study conducted between 1995 and 1997 chose hormone blockade alone for primary treatment of early (nonmetastatic prostate cancer).

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Back in 1981, Dr. David Byar from the National Cancer Institute concluded, "The most important conclusions seem to be that some prostate cancers spread early, and that in the future (remember, he wrote this in 1981), some systemic treatment (such as *triple hormone blockade*/Leibowitz protocol) should be used in addition to, **or instead of** the operation. The italics have been added by me.

The definition of triple androgen blockade/Leibowitz protocol refers to men with clinically localized and/or clinically nonmetastatic prostate cancer who have never had prior hormone blockade and have never received local therapy. They are treated with 13 months of Lupron or Zoladex, three Casodex a day (not one), and Proscar 5 mg once a day. Following this, the men must be maintained on Proscar 5 mg once a day, so-called Proscar maintenance therapy.

Before Casodex became available, we used flutamide, two every eight hours. Any other combination is not triple hormone blockade/Leibowitz protocol. Similarly, men who have recurred after prior local therapy or prior hormone blockade should not expect the same success rates that we achieve with triple hormone blockade/Leibowitz protocol. The men who recur after prior hormone blockade and/or local therapy and are treated with triple hormone blockade usually achieve unmeasurable PSA while on treatment. However, in most men, PSA's will begin to rise six to 36 months later.

At the end of 2001, when our work was first referenced in a major cancer journal, we made a slide stating "hormone blockade alone is now recognized as an appropriate treatment option for so-called clinically localized prostate cancer." It has taken ten years from the time Dr. Leibowitz first began to recommend triple hormone blockade/Leibowitz protocol as sole treatment for localized prostate cancer for an article published in the *Journal of the National Cancer Institute* to recognize hormone blockade alone as a legitimate treatment option for men with so-called early prostate cancer. During those ten years, he has gone from being ridiculed to being called a pioneer. The journey from Maverick to Maven was long, painful, and often discouraging, but ultimately vindication tastes absolutely delicious. Readers familiar with some of his earlier papers will appreciate that hormone blockade as an acceptable treatment

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option is what we refer to as the "Platinum and Diamond Standard" for treating early prostate cancer.

Finally, let us compare our results to watchful waiting and to radical prostatectomy.

In the September 12, 2002 issue of the *New England Journal of Medicine*, an article by Holmberg, Lars, Volume 347; #11, reports on a prospective randomized trial comparing radical prostatectomy with watchful waiting for early prostate cancer. >From 1989 through 1999, 695 men with newly diagnosed prostate cancer, stages T1b, T1c, or T2, were randomly assigned to watchful waiting or radical prostatectomy. During a median 6.2 years of follow-up, there was no significant difference between surgery and watchful waiting in terms of overall survival. There were fewer prostate cancer deaths on the radical prostatectomy arm, but the overall survival was not statistically different.

Of note is that men assigned to radical prostatectomy were treated on relapse with immediate hormone blockade, while those on watchful waiting had delayed therapy. Since many believe that early hormone blockade improves survival, this would bias the study against watchful waiting. We would point out that in the watchful waiting group, there were 21 Gleason 8-10's; only 14 in the radical prostatectomy group. There were more Gleason 7's in watchful waiting arm than the radical prostatectomy arm. Follow-up PSA results are not given. Obviously anyone with a rising PSA after radical prostatectomy would be considered a failure, but these results are not given. The authors also stressed that their results were obtained primarily in a group of men with clinically-detected prostate cancer, rather than the much more commonly PSA-detected prostate cancer that we now have. Only 10% of their patients were PSA-detected. In fact, one of their conclusions is that in men with cancer detected by PSA screening, the baseline risk of death from prostate cancer may be even lower since men survive years longer the earlier you diagnose their prostate cancer. If you only diagnose the disease when it has spread to the bones, survival is much shorter than PSA-detected cases. This means that for the first five to eight years after PSA-detected cases, most men will not die from prostate cancer, even without treatment. Any possible benefit from surgery

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would not be apparent for several more years. Thus, the absolute benefit of radical treatment, if any, may be even less pronounced for patients diagnosed by PSA screening (the way prostate cancer is usually diagnosed today in the USA) than the way men were diagnosed in this study.

The authors point out there were the expected, well documented side effects from surgery such as impotence and incontinence. They remind us that at six years of follow up there is **no** difference in overall survival comparing watchful waiting to radical prostatectomy. Even in this study with all of its biases, the findings comparing radical prostatectomy to watchful waiting require that 17 patients undergo a radical prostatectomy in order to prevent one death from prostate cancer over an eight-year period. The authors emphasize that this is the best possible outcome. But as of the time of publication, the chances of death from any cause are the same whether you were assigned to watchful waiting or radical prostatectomy.

We then did a comparison of radical prostatectomy from this series versus our triple hormone blockade/Leibowitz protocol results. We recommend triple hormone blockade, not watchful waiting. Therefore, compare radical prostatectomy to triple hormone blockade/Leibowitz protocol. We treated 115 patients. They treated 347. Since their series was three times larger than ours, multiple our results by three to correspond to their results. Our average follow-up was 60 months. Their's was 72 months. We had one prostate cancer death. They had 16. Since they had three times more patients than we did, they had 13 excess prostate cancer deaths compared to our treatment. Only one of our patients developed distant metastases; 35 of the radical prostatectomy series were found to have metastatic disease. That means 32 extra patients developed mets compared to our treatment. We have had to re-treat seven patients. They have re-treated at least 40. This translates into twice as many failures for radical prostatectomy compared to our treatment. Our baseline PSA was 12.7; theirs was essentially the same -- 13. All of our patients had known recorded Gleason scores. Forty-six of their's did not even have a known Gleason score. Our average baseline Gleason score was 6.6. Their's was unknown because 46 were missing.

We conclude that the results of triple hormone blockade/Leibowitz protocol are far superior to the radical prostatectomy results as reported in the *New England Journal of Medicine* in September 2002. Our noninvasive treatment

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approach with (almost always) reversible side effects is, to us, the obvious preferred treatment for clinically localized prostate cancer. Avoid radical local treatments with permanent side effects, and with results that are far inferior to ours. We acknowledge that in order to prove this result, a prospective randomized trial would be necessary. We urge urologists and radiation therapists to do this. But do not use just any hormone blockade. Use the hormone blockade treatment that has the highest success rate for any published protocol, triple hormone blockade/Leibowitz protocol.

In the series just reported, "almost half the men in the radical prostatectomy group had urinary leakage at least once a week." In fact, 62% of the men reported at least some leakage, and 43% required regular dependence on some form of protective aid for their incontinence. None of the patients in our series had urinary incontinence. 80% of men in the radical prostatectomy group reported erectile dysfunction. Side effects from triple hormone blockade/Leibowitz protocol are essentially always reversible with a rare elderly patient reporting significant persistent erectile dysfunction.

In late 2001, articles on prostate cancer began to acknowledge hormone blockade as an acceptable treatment option for men with clinically localized prostate cancer. It is gratifying and satisfying to see that other doctors are accepting this treatment option and are beginning to allow some of their patients to be so treated. As Winston Churchill so aptly put it, "this may not be the beginning of the end, but it is the end of the beginning." Hormone therapy for clinically localized prostate cancer is a treatment option whose time has finally arrived.

As 2002 draws to a close, we recognize that the pendulum is swinging our way. Each year more men will learn of this option; will insist on this form of therapy, and more doctors will eventually recommend triple hormone blockade/Leibowitz protocol as their treatment of choice for clinically localized carcinoma of the prostate. Around the world men are discovering that finally there is a highly successful noninvasive treatment option with reversible side effects that successfully treats prostate cancer without leaving men incontinent and/or impotent.

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As always --

Be happy,

Be well,

Live long and prosper,

DR. BOB

DR. STEVE

****** None of the above should be construed as medical advice or consultation, and anything discussed in this paper is meant for information only. All medical treatments, consultations, decisions and recommendations can only be made by the patient and his/her treating physician.

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