
1997
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April

(Revised)

**"THE FACTS, DOC,
JUST THE FACTS"**

I have just reviewed a timely article. Here are some quotes and paraphrases from it: "Recently, a number of urologists have begun to question the basically unchallenged role of radical prostatectomy in treating early prostatic cancer." Additional data that may be useful in considering this matter are supplied herein: "Studies of the incidence of microscopic cancer in men not seeking medical aid for other conditions have revealed a high incidence of unsuspected tumors. The remarkable unaggressiveness of the tumors reported in this series suggest that they may be representative in part of the same phenomenon: Had these patients not needed (for example, a PSA, or transurethral resection), it is improbable that most of these tumors would have been discovered during the patient's lifetime." The article continues: "A review of four other recent series from the literature, combined with the present series, all of stage I prostate cancer not treated by radical prostatectomy indicates that the overall number of patients who have died of prostatic cancer is only 1.9%." Of course, the period of follow-up was different in the various series (in this particular series, the follow-up was about five plus years). The paper goes on to report that, "It seems clear to us from our study and other published series that radical prostatectomy is unjustified as a recommended form of therapy for patients with incidently found microscopic prostatic cancer, that is, for patients with stage I cancer. A large proportion of these patients will not die of prostatic cancer." And finally, the paper concludes: "These results suggest that the role of radical prostatectomy for stage I cancer of the prostate should be carefully reconsidered."

What is most remarkable is that if I asked the reader to try to predict how many months ago this paper may have been published, I don't believe you would even be close to guessing the publication date. This is an article that appeared in the *Journal of Urology*, the author David P.

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Byar, entitled "Survival of Patients with Incidentally Found Microscopic Cancer of the Prostate." It was published in Volume 105, December **1972**, pp. 908-913. Hard to believe!! Twenty-five years ago, 1972, not 1997.

This paper studied 148 patients who had their prostate cancer diagnosed by TURP (roto-rooter job) and refused radical prostatectomy. The men were treated **only** with hormone blockade, specifically estrogen or orchiectomy. By the time this paper was written, 72 of the 148 men had died. In 22 of them, an autopsy was permitted. In only one of the 22 patients was residual prostate cancer found. This tells us that 21 of the 22 men were apparently cured of their prostate cancer with hormone blockade alone. None of these patients had allowed radical prostatectomy. Hormone blockade alone got rid of all of their prostate cancer in the prostate and everywhere else. No cancer was found anywhere at autopsy. "Show me the cancer." You can't because it was all gone.

Additionally, deaths from prostate cancer by assigned treatment: placebo, zero deaths from cancer of the prostate; estrogen, zero deaths; orchiectomy, zero deaths; orchiectomy plus estrogen, zero deaths from prostate cancer. Over five years of follow up and yet in all of the men with stage I prostate cancer who **refused** surgery, there were no deaths from prostate cancer. Remember the Wayne State autopsy data: 27% of men in their 30's have prostate cancer; 34% of men in 40's have it. Remember that about 80% of men in their 80's have it. All told, about 40% of men have prostate cancer at autopsy; only two or three% die from it. Most of us die with it.

At the 1997 session of the American Society of Clinical Oncology meeting in the educational session, "Controversy in the Management of Early Prostate Cancer," the speakers concluded that, as of today, appropriate treatment options for patients with clinically localized prostate cancer include radical prostatectomy, radiation, or watchful waiting. I was the first audience participant allowed to comment. At the conclusion of the presentation, I grabbed for the microphone, hurling women, children and religious leaders aside, so that I could be the first to comment. I pointed out that since

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watchful waiting is an acceptable treatment option today, then surely one year of triple androgen blockade must also be an appropriate treatment option. Not one of the over 500 to 800 cancer specialists in the audience argued with me. My conclusion stood as stated.

Looking at the results for seed implantation, the following article appeared in the *Journal of Urology*, July 1997. This article reported results from the original 1,078 patients treated by Dr. Willett Whitmore. These were men with clinically localized prostate cancer; they were treated with retropubic I-125 iodine implantation. Of course, seed specialists will point out that these patients were treated between 1970 and 1987, and our technology has vastly improved and, therefore, you should not consider these results; throw this darn study out; we are doing a whole lot better job today, or something to that effect. However, I would point out that if the urologists who essentially invented this procedure were permitted to operate on 1,078 patients and did these procedures at Memorial Sloan-Kettering in New York, certainly these patients and their physicians were led to believe that this treatment was as good as radical prostatectomy (they may be right; especially since I believe results from radical surgery are just as poor as the results reported from seed implants.....).

In order to keep treating this many patients, preliminary results had to look pretty good. However, at 15 years of follow-up, if one considers all of the 1,078 patients brought to the operating room, one finds that less than 14% of them have control of their disease. I submit that if Dr. Whitmore can only control 14% of patients with clinically localized prostate cancer by radical local treatment, then radical local treatment just doesn't work. The other 86% failed with recurrence of their prostate cancer.

We are just on the verge of having others acknowledge that we have been doing far, far too many radical local procedures (see my recent paper, "Angiostatin and Why Local Therapy Fails to Cure So Many Men"). At a lecture in Santa Monica, Dr. Stan Brosman, noted urologist, pointed out that the number of radical prostatectomies will fall by at least one-third in the next 12 months. As you know, if I had it my way, radical prostatectomies would fall by 99% plus.

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I am actually mystified at how great the marketing effort has been to convince patients and physicians that we should be doing radical local procedures when there is no data to support this. Until such a time as radical local treatments are found **to be both necessary and effective**, and found to improve upon the results of one year of triple androgen blockade, I shall not recommend them. It would seem to be fairly easy to show anyone how wrong I am simply by producing the articles that show, in a prospective randomized study, that radical local treatment is both necessary and effective. The 1972 article asked for such a study. A quarter of a century later and there is no proof that radical local treatment is both necessary and effective. The reason might be that it is not necessary and effective. How much longer should we continue to do these treatments before someone sticks their head out of a window and yells, "We're mad as Hell and we're not going to take it any more."?

Clearly, we are diagnosing many patients who, in the absence of PSA, would not have prostate cancer diagnosed. We know that 80% of men in their 80's have prostate cancer at autopsy; only 7 or 8% develop a symptom of it in their lifetime, and only 2 or 3% die from it. If we can identify all 80% of men with it, should we be doing radical prostatectomies on all of them when we don't even know that radical prostatectomy would be necessary for the small number of men who actually could benefit from it? We know that radical local treatments are associated with far greater toxicity than is admitted and PSA failure free survivals are a lot closer to the percent that Willett Whitmore's study just demonstrated, rather than the 80 or 90% so-called success rate that others claim for their radical local treatments. I would point out that if you do seed implants, or any other radical local treatments on patients with PSA's in the single digits and Gleason scores of 6 or less, that these men will recur at a much later date than men not so carefully selected. If you then use actuarial projections and have relatively short follow-ups of three to five years, your figures will look quite successful. However, we know from the Mayo Clinic study of men with A2 prostate cancers, that between the tenth and fifteenth year, men continue to recur at a steady rate, without demonstrating a shoulder or plateau to the disease free survival curve. Only 35% of men in that study were

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PSA failure free at 15 years and failures continue to occur after 15 years. It is my belief that radical local treatments done on men with low PSA's and low Gleason scores will show high failure free survivals during those first few years, but then failures will be identified several years later and the long-term results will probably be no better than a 25-33% survival with undetectable PSA's. These are probably the same men who would not have died from prostate cancer if left alone.

Additionally, if you use the ultrasensitive PSA methodologies currently available, rather than arbitrarily stating that PSA's up to 0.2 equals cure, then I believe a much more realistic failure free survival percentage will be found (meaning far

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fewer men than stated in Pat Walsh's series will actually be found to have PSA failure free survivals). It is my belief that less than one-third of men will have PSA failure free survivals at 10 to 15 years.

An article appeared in *The New England Journal of Medicine*,

July 31, 1997, Volume 337, Number 5, by Bolla, et al., which reported the results for men randomized between radiation

therapy alone and radiation therapy plus hormone blockade. The results were startling; 79% five-year survival for patients receiving hormone blockade plus radiation, and only 62% for those treated with radiation therapy alone. More importantly, PSA failure-free survival was only 48% with radiation alone; whereas, it was 85% with radiation plus hormone blockade. The median follow-up is only 45 months, so I feel quite certain that many more patients in the radiation arm will, of course, fail. What this study clearly demonstrates is that hormone blockade is quite beneficial in the treatment of prostate cancer. These were men with locally advanced prostate cancer. This study does not demonstrate any benefit from the addition of radiation therapy. I have argued for the past four years that a hormone blockade alone arm is necessary in order to determine whether radiation therapy offers any additional

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advantage over hormone blockade alone. In fact, the editorial reviewing this article appears on page 340. Dr. John Blasko, who is one of the best known seed implanters in the world, comments that older studies hint that treatment for locally advanced disease with **ONLY** androgen ablation may be as efficacious as androgen ablation combined with radiation. This, of course, is exactly what I am saying; that studies have not demonstrated any benefit to radiation therapy when added to hormone blockade.

I am starting to see others in the community begin to acknowledge the extraordinarily high failure rate from any radical local treatment, and they are beginning to wonder whether hormone blockade alone might not be the best way to treat our patients. An article in the August 1997 *Journal of Urology*, Volume 158, pages 319 to 325, has some fascinating information on page 323. A table is shown with the percent five year actuarial biochemical control of PSA. This table shows that the biochemical control ranges from a low of 5% to as high as 89%; in another category of patients, from 24% to 100%; in another category, 45% to 92%. These wildly divergent "success rates" are explained in the body of the paper. The explanation follows: "Depending on which definition of biochemical control was used (based on definitions from three of the **largest academic institutions in the radiotherapy literature**), statistically significant differences in overall treatment outcome were detected attributable **only** to the definition chosen." What this means is the various so-called success rates were simply dependent on how the author in each of the different articles defined success. Some of them defined success as PSA's less than one; some as less than 1.5; others as less than 4 and others as clinical local control. Therefore, the radiation therapy literature from the three largest academic institutions in radiotherapy medical literature can claim success rates of 100% when their definition of success is clinical local control of the prostate, but in the same article, if they use PSA's of less than 1; the success rate drops to 24%. In order to be cured after radiation therapy, most of us would want the PSA to drop to less than 0.5 and to remain there. I submit that if we utilize ultrasensitive PSA's, we will find that the true cure rate is much closer to 24% than to 100%.

Additional evidence that confirms the ineffectiveness of

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radiation therapy alone is provided by a study reported by Laverdiere, J. in the *International Journal of Radiation Oncology*, 1997; Volume 37 (2: 247-252). His study randomized

118 patients with clinical stage B or C prostate cancer to three different arms. In arm one, external beam radiation alone; arm two, the same radiation preceded by three months of Lupron and flutamide; and arm three, three months of Lupron and flutamide, followed by the same radiation therapy, but Lupron and flutamide continued during radiation therapy and for an additional six months after radiation (total treatment with combined androgen blockade, not triple hormone blockade, 10.5 months). Biopsies were obtained on all patients two years following radiation. Arm one, radiation alone, 65% of men had prostate cancer on their biopsy; arm two, with three months of hormone blockade, only 28% had prostate cancer; and with ten and a half months of hormone blockade plus radiation, only 5% of men had prostate cancer on biopsy. This study clearly shows that hormone blockade is necessary for men with prostate cancer and further proves that ten and a half months of hormone blockade (in my opinion, 13 months would be ideal) is far superior to only three months of hormone blockade. The same pattern was shown with regard to PSA failures.

M.D. Anderson recently reported that with radiation therapy alone, the failure rate at five years was 82%; with radiation therapy plus androgen blockade, the failure rate was only 15%. This result appears in *Clinical Oncology Alert*, Volume 12, Number 10, page 74, October 1997. I believe these radiation therapy results all conclude the same thing; radiation therapy alone is almost worthless; hormone blockade is highly effective. None of these studies tell us that radiation therapy adds anything to hormone blockade, since that question was not addressed. My own strong feelings are that, in all probability, most if not all of these men would have done just as well with hormone blockade alone, but again, that is opinion. Since 2000 or 2001, we recommend 12 doses of weekly, low-dose, very well-tolerated chemotherapy utilizing Taxotere/Emcyt/carboplatinum, along with 13 months of triple hormone blockade for men presenting with one or more high-risk negative prognostic factors.

My feelings are stronger than ever, and I believe that

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almost every month additional literature is published which will contribute to the downfall of the use of radical local treatments. As I have emphasized time and time again in the various papers I have written, no prospective randomized study has ever demonstrated radical local treatment to be both necessary and effective. Therefore, as of Thanksgiving 1997, **"the best local treatment is systemic treatment."**

My longest follow-up to date is over six years for a patient with a PSA of 34, treatment only with hormone blockade, and then Proscar, 5 mg once a day, so-called finasteride maintenance therapy. He has been off his Zoladex and antiandrogen for over four years (since September 1993) and his PSA is about 2. He never had any local treatment; one cycle of hormone blockade alone has been all he has needed. In all of the other patients I have treated for clinically localized prostate cancer, I have one patient with a PSA as high as 4.2; all of my other patients have PSA's between 0.1 and approximately 2. No patient has had to be re-treated; hence, all of these patients received initial up front 13 months of hormone blockade, followed by finasteride maintenance, and are not even on intermittent androgen blockade, since they have not yet had to be re-treated. I guess, therefore, that my preliminary results would be a 100% success rate, since I have not had to re-treat anyone.

I would urge that all men with clinically localized prostate cancer (and, in fact, all men with any stage prostate cancer) start with triple androgen blockade, and they can then spend the next 13 months figuring out what, if any, local treatment they desire, unless they have previously had local therapy and/or prior hormone blockade.

Now that you are armed with this additional information regarding treatment options for clinically localized prostate cancer, I urge you to ask your urologist, radiation therapist, implant specialist and/or cryotherapist to give you a written estimate of the probability of cure for your proposed treatment. Tell him/her you want in writing the word "cure rate" written. Have him write down the definition of cure. Do not accept the term "success," since as I have pointed out in this paper, the definition of success depends; the doctor could be talking about local control of the prostate, and that is his definition of success. You believe that

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"success" means cure. After all, if your prostate area is fine but prostate cancer has spread to your bones, you would not call this "success," but some prostate cancer articles would. This is not how you would define cure. Insist also on getting a copy of the medical references that will substantiate the cure rates quoted by your physician. Make sure the expectations of PSA failure free survival are given to you, and the PSA value the doctor is using for PSA failure free survival is shown to you and written down in your medical record. Ask for a copy of this medical record.

If you get all of the facts, then I believe your treatment choice for clinically localized prostate cancer will be quite obvious. Insist upon:

The Facts, Doc,

Just The Facts.

And as always --

Be happy,
Be well,
Live long and prosper,

BOB LEIBOWITZ, M.D., AKA DR. BOB