

# Carcinoma of the Prostate: The Great Widow-Maker\*

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The percentage of urological cancers is considerable. Of all of the cancer deaths in our country, 10% are urological; in men alone, 18% are urological. It is immediately obvious that a very important aspect of this specialty is the treatment of cancer.

Of the 18% urological deaths among males, more than half are due to cancers of the prostate. When a patient is seen with evidence of a metastasizing cancer and a search is made for the primary site or source, there is always a hope that it will be cancer of the prostate, because we can do a great deal for this cancer that cannot be done in many other cancers.

A comparison of the various urological cancer deaths will show that cancer of the prostate is the most frequent. Second is carcinoma of the bladder, followed by kidney tumors. In comparing cancer of the prostate with other cancers in older men (men over 75), prostatic carcinoma is the most common cause of cancer deaths. If figures for cancer of the colon, rectum and stomach are combined, the resulting figure is slightly in excess of that for prostatic tumors. The impressive fact is that cancer of the prostate is the most significant cause, makes the most widows, of all the cancers among older males. With every passing decade, the number of cancers that one finds in any autopsy series of older people increases steadily. It does not increase among the people with cirrhosis, perhaps because of the increased circulating estrogens in older people who have hepatic cirrhosis. If men were to live for an indefinite period of time, practically all of them would die of cancer of the prostate. The secret weapon is the rectal examination to detect the prostatic nodule before it has developed to a more advanced stage.

Dr. Charles Huggins' classic cross sections of the prostate (4) showed that the cancerous, dark area is almost always in the posterior lamella against the rectum where the rectal finger can easily palpate the nodule. It is universally recognized that rectal palpation of the nodule will disclose cancer in only 50% of the cases. Nevertheless, in the 50% where cancer exists, the extent of the cancer is usually more than one would suspect from what one can feel. Recently, I have had it brought to my attention very forcefully that an asymmetry of the prostate without any particular increase in firmness may be worthy of great attention. I have had several patients who related that their internist had detected an asymmetry two or three years prior to biopsy and diagnosis. The instrument we use for biopsies is one developed by Dr. Ralph Veenema.

This instrument can be used with local anesthesia, but it is much easier with pentothal anesthesia. We prefer the Veenema instrument, however, since it gives a substantial fragment of tissue as compared to the Silverman or Vim-Silverman needle biopsies. Inadequate specimens may prevent the pathologist from rendering a diagnosis. We also want larger fragments because we grow the biopsies in tissue culture. This gives not only a dimension of additional size, but also gives an opportunity to experiment with that patient's cancer to see what medications act best against it and to see how it might differ from others.

Of the prostate tumors biopsied, 11% were confined to the prostate. Bone scans, bone surveys, and marrow acid phosphatases have shown that 55% of the prostate cancers have extended locally. There is still another substantial group that has extended beyond the confines of the pelvis. The treatment varies in these different groups. It is the first group that is amenable to radical excision; the second group may be amenable to radiotherapy plus hormone therapy. For the third group, one must

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depend upon hormone therapy and hopefully, in the next few years, immunotherapy.

Only 13% of patients with prostatic cancer were detected at an operable stage. The periodic rectal examination is a campaign which we must all wage. It affords the greatest chance of success for making a contribution in preventive medicine. The executive physical examinations that many companies sponsor is one of the best programs in the area of prevention. Occasionally, we find cancer in the chips from a transurethral prostatectomy which we did not suspect from rectal palpation. Then we have the dilemma of whether cancer has been left in the capsule, and we may resect a little more after a while to see whether we have chips. A few patients have undergone radical prostatectomy. Since radical prostatectomy is difficult technically following transurethral prostatectomy, we resort to radiotherapy plus hormones or just hormones alone. Following radical prostatectomy, we administer antiandrogen treatment in the form of castration and estrogens for every patient who will take what we consider to be our best advice. We have a substantial number of cases treated in this way and are awaiting the 20-year follow-up to compare with surgery alone.

When suprapubic or retropubic enucleation reveals cancer, we are better able to determine whether all of the tumor has been removed. If so, there is no need to go back and do a radical procedure. Frequently, when the patient has been through a big operation, he is not anxious to undergo further operative therapy. We are building some experience with radiotherapy after enucleation. One of our worries was that strictures might be more common and indeed be a bad feature of this type of therapy, but this has not turned out to be true.

We prefer the radical retropubic prostatectomy. We do not perform radical perineal prostatectomies except for instructional purposes or for a particular case where it seems to be indicated. With the radical perineal prostatectomy, there is no opportunity to investigate for nodal metastasis.

The first and classical study that Nesbit and his group (5) compiled indicated that stilbestrol increased the five-year survival of patients with prostatic cancer. Orchidectomy was a little better and the combination was better than either one alone. The Veterans Administration report (2) has indicted stilbestrol therapy as a cause of coronary artery disease, phlebitis, and perhaps cerebral artery disease. In the wave of shock and enthusiasm on

their part they have gone overboard and have discouraged a number of physicians from using stilbestrol.

Castration, however, is a more certain way of obtaining an antiandrogenic effect and has none of the drawbacks that stilbestrol itself might have. We combine hormone therapy, or antiandrogens with castration. Castration is not of great importance to most of our patients. Their sex life has almost ended by the time we see them for their cancers, and they do not mind trading a better life expectancy for castration. Bony metastases of considerable extent will clear remarkably with antiandrogen treatment, and likewise, pulmonary metastases have cleared.

Drawing on Dr. Huggins' experience (3), we have an interesting bit of information. A patient with metastases from a cancer of the prostate, proven by biopsy, was given stilbestrol by Dr. Huggins. He was left with just one or two metastases. Dr. Huggins then performed an orchidectomy and the nodules disappeared. Thus we have two different modes of action with these two agents. A combination will be more effective than either one alone. It is not just an additive but it is a different action.

A patient with cancer of the prostate which had obstructed the ureter was benefited by radiotherapy in shrinking the prostate. He was given 6,000 r of radiotherapy to the prostate area and the obstruction was relieved. The enthusiasts for this particular method of therapy, and particularly Dr. Malcolm Bagshaw (1), have put together a very large number of patients treated more or less with radiotherapy alone. Their success rate has been so good that they tell us that radiotherapy is curative. Raimey (6), however, has produced at least a dozen cases where he has biopsied the prostate after radiotherapy and the cancer appeared exactly as before radiotherapy. He argues that the cancer is not cured. Bagshaw replies that it looks like cancer but is not cancer and will not grow. Time will tell whether radiotherapy is really effective. Supervoltage therapy and perhaps larger doses and better targeting are improving results and the question is whether radiotherapy is as good as radical prostatectomy.

The Veterans Administration study suggests that conservative therapy is as good as radical surgery, but my view, after reviewing all of the studies, is that we do not yet know whether radiotherapy is indeed as good.

The next question concerns combining radiotherapy with antiandrogen therapy. Will that be as

good as a radical operation? At this moment, we do not know. We do know that if we remove the tumor, at least we are rid of the major part of the focus. The question remains, what about the cells that are spilled or that have migrated away? In reply to that question, one can demonstrate various experiments where a large mass of cancer treated by any modality has no great chance of shrinking. If the large tumor mass is removed and you leave behind only a few cells, then you may indeed kill those few cells by whatever supplementary means you use. We must look in the future to taking out the mass of cancer and then successfully treating what is left behind by immunological, hormonal means or by x-ray. We must think in terms of combination, and in my mind it is not entirely clear whether the radiation therapy plus hormone treatment is as good as surgery alone or surgery plus hormone treatment.

Occasionally, there will be a massive cancer and the resectoscope will be necessary to tunnel an opening through it. This can be done and supplemented by other treatments. Another modality for this problem is freezing the prostate. We insert a cryoprobe much in the same location as the resectoscope sheath. The temperature is dropped to minus 170° F and the mass of prostate freezes completely solid. It looks like a ball of ice, and literally, it is a ball of ice. Over the course of the next few weeks, the prostate will then slough. A catheter may have to remain in place for quite a long time while the gelatinous slough is removed. Later, there will be a very satisfactory tunnel through the middle of the prostate, whether it is benign or malignant.

There has been some suggestion that the very act of freezing will set up an immune reaction in the body wherein the body will attempt to reject, not only the frozen prostate, but also perhaps the metastases. There is some encouraging evidence of this, and we have research going on presently in this field. We have been freezing the prostate three times, a so-called triple-freeze, and this is alleged to improve the immunological response and is a new dimension that is worth testing. It is not certain that it will be as good as we would like but, nevertheless, bone pain does diminish.

If the prostate tumor appears to be resectable, we prefer to use the suprapubic approach. Our operation involves dividing the urethra just beyond the apex, dividing the vasa, dissecting the seminal vesicles down to their tips and dividing the vessels. We take the fascia around the seminal vesicles pur-

posely because we have found that this is the first route of extension of the disease outside of the prostate. We also remove a cuff of bladder.

We take pieces of tissue from a benign area and pieces from the cancerous area and grow them in a medium that is laced with radioactive food in the form of thymidine and cytidine. We then make a radioautograph of this and determine the DNA and RNA synthesis rates in these various areas. We find a very clear picture of benign activity in the benign areas and a very clear picture of greater activity (five or six times as much mitosis) in the cancerous area. Dr. Myron Tannenbaum, one of our researchers, has found that the area surrounding the cancer was as active as the cancerous area. This surprised him, and he then subjected the cells from this area to a higher magnification and discovered some very interesting material in what we refer to as the demilitarized zone, just outside the cancer.

The cancers of the prostate are histologically so much like cancers of the breast that we run a lot of parallel work in the two fields. Dr. Tannenbaum looked at cancers of the breast and found the same virus-like material in them. Turned on edge, the rods of the material look more target-like. Looking at the cancers themselves in both the breast and in the prostate, he found the virus-like material in the lumen of the prostate and the breast. A different kind of virus-like particle, the so-called "C" particle has been found in the milk of a mouse with breast cancer as well as in the semen of her mate. A similar "C" particle has been found in the semen of one of our patients with cancer of the prostate. We are now heavily involved in antibody testing of all of our patients and their wives to see if there is any possible relationship between cancers of the prostate in men and cancer of the breast or genitalia in their wives. We studied 5,000 men and found 186 men with cancer of the prostate, where the wife had been living and having intercourse with him for at least two years before the diagnosis of cancer of the prostate was made. We found 8-9% of the wives of those patients had cancer of the breast. When one compares this with the expected incidence of such a group, it is 500 times more. From this very carefully controlled group, it was found that the controls had an incidence of less than 1%—a finding of more than just passing interest. From this work we now advise that all of the wives of patients with cancer of the prostate have a very careful breast examination, cervical Pap smear and ovarian examination at least every six

months. We have been cautious about stirring up a lot of anxiety where it might be unfounded, but knowing these facts and saying nothing would not be right either. We consider it advisable to be cautious in the campaign of encouraging the wives of men with cancer of the prostate to be examined more carefully and conscientiously than wives in the general population.

It is possible to take a time-lapse picture of a cancer cell and see what happens as it begins to divide. First, a refractive outer coat appears as the cell goes from the resting configuration to the stage where it is about to divide. The chromosomal material begins to shape into a spindle and starts to divide. Then the spindle forms very decidedly and some minutes later, there are two sets of chromosomes, divided and beginning to pull apart. They pull apart further, and two cells begin to form, now having a configuration more like the resting phase. If you know how many frames per second or per minute are involved in these changes, you can time the intervals between each of these phases. We usually take two-to-four frames per minute. The cancer cells take longer to divide than the normal cells, but the cancer cells go through this procedure much more often than the normal cells. An eye dropper can be used to add various anticancer medications to the culture to see how the course of events can be influenced. If the mitotic process stops, one can see in what phase it stops. The anticancer agents can be labeled and observed as they go into the cell. If the particles are fine enough and are hooked up to an immunological apparatus, it is possible to discover where they went in the cell. The technical aspects of this procedure pertain to the fact that some drugs go into the cell wall, some into the mitochondria, some into the nucleus, and other drugs act on the nucleolus. If one is using multiple drugs, it is helpful to have different modes of action. We have done this with the Wilms' tumor drugs and have sorted them to determine the actions of the different medications and have been able to obtain some information about the different modes of action and the most effective combinations. In spite of this technical apparatus, we still find the most important single case-finding factor influencing the successful treatment of this prostate cancer to be the periodic rectal examination.

Another aspect of scientific advancement is the fact that the cancers have caused the development of various immunological changes in the blood stream. Sometimes various antigens and antibodies

are present. There has been a rekindling of enthusiasm about this. Certain carcinomas of the bowel and certain embryological pieces of bowel give off antigens into the blood that can be measured quite easily. We have discovered that in various urological cancers this same antigen, called a cancer-associated antigen or a carcinoma embryonic antigen, is detectable. We have demonstrated that in various samples of prostate from various samples of the patient population, we would find an increased and measurable amount of tumor-associated antigen that would not be of any value as a screening test because it was not always positive. Yet it did have value as a test of failure of treatment. If one surgically removed the prostate in a cancer patient and the test became negative, that was a good sign. If the test remained positive following surgery, one would know that all of the tumor had not been removed. Therefore, one might be more vigorous with the antiandrogenic or irradiation treatments. We have used it as an index of failure in radiotherapy cases where the first portal was mapped out and treatment included the prostate only. If the test remained positive, then we knew we had failed to kill all of the cancer and we then irradiated to a larger field. Thus the test does have some usefulness even in its present crude form. The obvious implications are that we may be able to develop an antigenic test specifically for the prostate. This is what we are working on and I am sure others are investigating it also. This field is of considerable importance and interest.

We have used the same tumor-associated antigen, hooking it onto a bridging-type of enzyme substance, onto which can be hung a color, namely a reddish-brown color. If the tumor is positive with this antigen, we can treat the patient with this material and the cancerous areas will turn a very distinctive color. In a lymph node where the cancer is not obvious and where, by ordinary investigation, that is light microscopy, it may not be possible to tell that these areas are cancerous, this test will show that the node is very specifically cancerous.

The same technique might be applied to the Pap smear to ascertain whether there are cancerous cells in tissues. With the electron microscope, one can tell for sure, but you cannot scan wall-to-wall with the electron microscope. With the antigen, it would be possible to pinpoint the areas that turned red and go directly to them with the electron microscope. We may be able to apply our greater scientific capability to the clinical staging of the cancer and thus

bring about a more specific and accurate staging and treatment. The implications of this are considerable.

Our only protection against cancer of the prostate and its rapid growth is the annual physical examination. We know that various cancers divide at different rates. We do not know the reasons for all of the differences. We do not even know why one person develops a prostatic cancer and the next does not. The fact that it is endocrinologically dependent, the fact that it is possible to survey what goes on in great detail through the capabilities that we have makes the urological specialty very valuable in the cancer area.

We are able to study the rate of growth, regression or improvement of solid tumors of the kidney through pyelography, aortography and angiography better than other fields. Epithelial tumors of the bladder can be observed with the cystoscope and biopsied periodically to follow the efficacy of treatment or to get specimens for study. Hormone-dependent therapy in cancer of the prostate gives us more leverage and opportunity to study the activity of cancer. The advances that have been accomplished, in fact some of the great success stories of cancer, have been urological. I think the prostate was certainly the bellwether of all the demonstrations that a hormone-dependent cancer could be influenced. I think it is part of our responsibility as urologists to

realize that we have this opportunity. I know that all of you share with me this enthusiasm to do everything we can and to be in a position for contributing more than any other specialty to the study of cancer.

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