Review of Focal Therapy *for* Localized Prostate Cancer

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Prostate cancer is the most common, non-cutaneous malignancy diagnosed in men. It is the sixth leading cause of death in men worldwide according to the American Cancer Society. The incidence of prostate cancer can vary up to 50-fold between countries and is likely due to Prostate Specific Antigen (PSA) screening.[1] With the advent of PSA screening, developed countries have had a significant increase in the number of early, localized prostate cancers diagnosed.

Standard options to treat localized prostate cancer include active surveillance, surgery, and radiation. Each of these modalities has associated morbidity but a high likelihood of cure. Therefore, individualized treatment of a patient is the primary goal to minimize the morbidity for each patient.

Modern pathologic data indicate that focal therapy – which limits treatment to the cancerous area alone – can be a curative treatment option. This concept, in practice, is in its early stages. With improvements in imaging modalities that allow the delineation of areas of tumor and improvements in delivery of therapy, focal treatment of localized prostate cancer may help maximize cancer therapy and minimize treatment morbidity. Multiple options for treatment of localized prostate cancer exist. We will review the rationale and current focal treatment options for localized disease.

PSA and prostate cancer detection

The initiation of PSA screening in the United States led to a significant increase in the diagnosis of prostate cancer, with the incidence of prostate cancer almost doubling between 1989 and 2002. A recent study reported the incidence of prostate cancer increased by 22% in a screened cohort of patients over a control group. Despite increased detection, the prostate-cancer mortality was equal between the groups at seven years.[2] Studies evaluating prostate cancer diagnosed at autopsy for death unrelated to prostate cancer show up to a 40% incidence of incidental prostate cancer.[3] These findings support many of the claims that prostate cancer is being over-detected and therefore, over-treated. In essence, many patients will receive treatment and the subsequent morbidity with no survival or quality of life benefit.

Active Surveillance

Active surveillance has emerged in recent years as an acceptable option for patients with low volume, low grade prostate cancer or who have significant medical problems that are more likely to impact their quality and length of life. Multiple active surveillance trials are on-going. The goals of these trials are to determine prognostic indicators for distinguishing clinically significant prostate cancer from latent cancers. Unfortunately, there are no reliable and sensitive techniques to determine which prostate cancers will require treatment and which ones will be clinically insignificant. Given that prostate cancer accounts for over 250,000 deaths globally per year and that the limited ability to determine which patients will be affected, most patients elect treatment and accept the side effects of current therapy.

Stage migration and tumor focality

With PSA screening and subsequent stage migration [see Insights 12(4)], a decrease in median tumor volume has been observed.[4][5] Evaluation of radical prostatectomy specimens reveals that up to 38% of organs have unifocal (a single focus) disease sites.[6] Even in patients with multifocal tumors, the tumor volume has decreased significantly over the past two decades. Ohori *et al* [7] demonstrated that the mean volume of prostate tumors was two centimeters or less and the most of the volume arose from the indexed, diagnosed tumor. The rationale for focal therapy is based upon these findings that tumor burden in modern prostate cancer patients is smaller and may respond appropriately to more conservative treatment with the aim of minimizing the side effects from current standard treatments.

Identifying focal disease: imaging and biopsy

The main concern with focal therapy is the ability to accurately target and destroy a tumor that will be clinically significant. In order to target the tumor, its size, location, and – ideally – biologic potential must be accurately and reproducibly demonstrated. Initial strategies to map prostate cancer tumors were based upon saturation biopsies. Schulte *et al* [8] reported that contemporary twelve-core prostate biopsies are able to reliably diagnose cancers, but fail to provide consistent localization of tumors to specific areas of the prostate. More recent developments include the addition of three-dimensional ultrasound prostate mapping which Onik *et al* [9] report is well tolerated and provides more accurate staging than traditional twelve core biopsies. It is apparent that taking more samples, over 40 core biopsies, will improve accuracy of staging, but the addition of grid mapping should improve the reproducibility of identifying the target tumors. *(Continued on page 4)*

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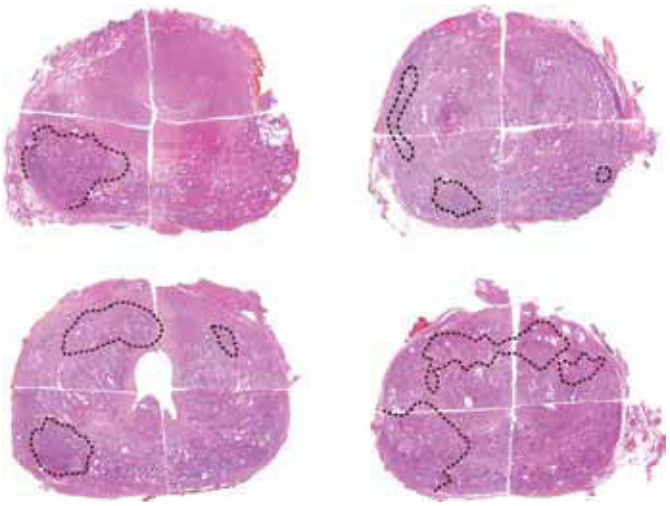

Focal treatments require careful prostate mapping to determine where the cancer is located.

In addition to mapping biopsies, imaging modalities have been employed to improve localization of tumors. Ideally, Dynamic Contrast-Enhanced Magnetic Resonance Imaging (DCE-MRI) can be used to prospectively identifying prostate cancer and eventually eliminate the need for biopsies. But until accuracy is improved, biopsies must be used in conjunction with imaging. Recently published studies assessed the accuracy of MRI as compared to pathological specimens for peripheral zone tumors found MR spectroscopy and T2-weighted MRI to be similar at 58% and 60% by AUC [*area under the curve, a measure of the accuracy of a test on a scale of 0 to 100% - ed.*].[10] Additional reports increase the specificity to 94% and sensitivity to 86%of MRI with an AUC of 0.87 if the tumors are larger than 0.5cc. Studies are currently on-going to improve the MR spectroscopy and MRI for detection of small tumors and can be used as a toll to follow patients treated with focal therapy.

Despite the advances in prostate mapping and imaging, reliable localization of tumor remains problematic. In combination, these tools can help identify patients who would benefit from focal therapy, but is not perfect in its current state of technology.

FOCAL THERAPY WITH ENERGY ABLATIVE TECHNIQUES

HIFU (High Intensity Focused Ultrasound)

Focal energy therapies are being evaluated for primary treatment of localized and focal prostate cancer. HIFU relies upon coagulative necrosis from elevated temperatures to destroy tissue. Using the focused ultrasound energy converted to heat, a precise demarcation between treated and untreated tissue is expected. This technology is exploited in other solid organ tumors, including liver, renal, and pancreatic cancers. A recently released article from England reports no evidence of disease in 92.4% of 172 patients treated with HIFU with only a short follow-up period.[11] The study is limited by follow-up and the longer term morbidity is not completely evaluated. It does provide encouraging results; more long-term data on oncologic effectiveness is pending the completion of current trials.

Cryotherapy

Improvements in administration of cryotherapy have made it applicable to focal therapy and not merely a salvage treatment option for prostate cancer. Cryotherapy relies upon cell membrane disruption from freezing causing necrosis and thrombosis. The third generation of needles allows for more precise areas of freezing to minimize secondary structural damage. Initial data is difficult to evaluate because many of the studies include salvage therapy and patients with higher risk disease or on concurrent hormonal therapy. Cryotherapy has been shown effective in treating prostate cancer, but more mature and long term data is needed. Formal studies evaluating its use in a focal setting are ongoing. Also, the evaluation of morbidity of erectile dysfunction associated with the newer technology is pending.

Photodynamic Therapy (PDT)

Photodynamic Therapy is a treatment that uses a drug, called a photosensitizer or photosensitizing agent, and a particular type of light. When photosensitizers are exposed to a specific wavelength of light, they produce a form of oxygen that kills nearby cells. Each photosensitizer is activated by light of a specific wavelength. This wavelength determines how far the light can travel into the body. In the first step of PDT for cancer treatment, a photosensitizing agent is injected into the bloodstream or taken as an oral agent. The agent is absorbed by cells all over the body, but stays in cancer cells longer than it does in normal cells.

For newer treatments of the prostate, the drug is activated in the prostate by low-power laser light, delivered using optical fibers. The fibers are placed within needles in the prostate, guided by transrectal ultrasound and a perineal template. The photosensitizer in the tumor absorbs the light and produces an active form of oxygen that destroys nearby cancer cells. Some forms use a transurethral light source. In addition to directly killing cancer cells by necrosis, PDT appears to shrink or destroy tumors in two other ways. The photosensitizer can damage blood vessels in the tumor, thereby preventing the cancer from receiving necessary nutrients. In addition, PDT may activate the immune system to attack the tumor cells. Initial studies are small, but report minimal morbidity at early follow-up. PSA values decrease, but few of the studies are in a primary treatment setting.[12]

Electroporation (IRE)

Irreversible electroporation is a tissue ablative technique to produce cell necrosis. IRE is considered nonselective but acts on the cell membrane only (leaving structural components intact). IRE requires larger magnitude and duration of electric pulses and there is a concern for surrounding thermal damage. The extent can be measured with real-time electrical impedance tomography.[13] There are no published data, but news reports state biopsies taken from five treated patients' prostates were normal two weeks after treatment. The patients had no side effects. Trials are expected to continue to develop clinical data on the technology's therapeutic effectiveness. Clinical trials on its use in melanoma and pancreatic cancer are accruing.

Conclusion

With the advent of PSA screening and subsequent stage migration, developing therapies to treat localized prostate cancer with minimal morbidity is paramount as patients are presenting at younger ages with lower risk disease. Although in its infancy, focal therapy is rapidly expanding and the technology is improving. With improvements in localization of biologically active tumors, the ability to effectively treat focal areas of the prostate is advancing.

Concerns regarding focal therapy are not unfounded given the limitations of current diagnostic and risk assessment tools. Therefore, the strategies for developing focal therapies must include allowing for whole gland therapy following focal therapy, minimizing the side effects to a *(Continued on page 6)*

John F. Ward, M.D.

Dr. Ward earned his medical degree at Georgetown University School of Medicine. He completed his general surgery training and Urologic training at the Naval Medical Center San Diego and went on to a Urologic Oncology fellowship at the Mayo Clinic (Rochester, MN). He served 18 years in the Navy and was the first chief of Urologic Oncology for the Nevada Cancer Institute before being recruited to join the faculty at M. D. Anderson Cancer Center. Dr. Ward has over 50 peer reviewed research articles and numerous book chapters. He is the recipient of many honors and awards throughout his career and is a sought after speaker on an array of topics which deal with the treatment of men with prostate cancer. He is a Diplomat of the National Board of Medical Examiners and a Fellow of the American College of Surgeons. He is certified by the American Board of Urology and is a member of several professional societies.

Dr. John Ward believes that it is important to limit the side effects of cancer treatments while meeting the primary goal of curing the cancer. Dr. Ward finds that cryotherapy is an effective cancer treatment, with the advantages of a same-day or overnight hospital stay, minimal discomfort and excellent cure rates. With regard to cryotherapy, he points out, "Urinary incontinence is a very rare event. In the future, I hope cryo can be shown as an effective means of performing a 'male lumpectomy' removing only the cancerous prostate tissue."

lower level than current surgery or radiation treatments, and demonstrable oncologic control of clinically relevant tumors.

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COMMENTARY

Focal Therapy *for* Prostate Cancer

Stanley Brosman, M.D.
and
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Patients often ask: "Why treat the whole prostate when the cancer is only in one part? Can't you just take out a part of the prostate or just radiate some of it?" These questions have intrigued a number of investigators who have begun to study this issue. Information regarding the location of the cancer and its grade has been compared to the pathologist's findings after a prostate has been removed by surgery. In some cases there is good correlation but in many others there is more cancer and often of a higher grade than what was predicted from the biopsy. To deal with this issue, better imaging with the color Doppler ultrasound and MRI with spectroscopy have been used. Saturation biopsy of the prostate where 30 or more cores are obtained have helped to increase the possibility of accurately localizing the cancer.

The purpose of focal therapy is to treat the cancer and minimize the potential side-effects associated with surgery, radiation therapy or medical therapy to halt testosterone production. When you examine the patients who meet all of the criteria for focal therapy, small tumors located in one area, grade 3 only, no more than two positive cores and a PSA less than 10, you have to wonder how many of these patients need any treatment. There will always be the possibility of side-effects regardless of the type of therapy. This is the group of men who are presently confounded by the choice between active surveillance and a more complex whole-gland treatment. As better and more accurate diagnostic tools become available, the role for some type of focal therapy may become clearer. Right now, some will consider this as an investigational method, but review of limited literatures show good cancer control with high rate of preserving urinary continence and sexual potency utilizing cryoablation as a technique. Larger scale with long-term follow-up study is necessary to draw a meaningful conclusion.

COMMENTARY

Active Surveillance *for* Localized Prostate Cancer

Stanley Brosman, M.D.

The concept of observing patients following a diagnosis of prostate cancer has been around more than 50 years. The hypothesis is that by following a protocol of active surveillance for men with favorable risk (low risk), localized prostate cancer, and over treatment of clinically insignificant prostate cancer would be reduced while retaining the option of definitive therapy for those men in whom there is evidence of cancer progression. The second caveat is that by following this strategy, there would be no decrease in survival and these men would not experience, or at