Recent Advances in Targeted Cryosurgery for Prostate Cancer

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Localized prostate cancer traditionally has been treated with radical surgery, external beam radiation therapy, and brachytherapy. However, each treatment can result in a substantial risk of significant morbidity (Oncology, 1999;13:985 90), and patients may be at significant risk for primary treatment failure or biochemical recurrence in the high risk prostate cancer patients even with apparent clinically localized disease. Some recent studies showed a minimal survival benefit between no treatment and radical prostatectomy. Consequently, watchful waiting slowly is gaining wide acceptance as a viable management alternative in certain patient population (Eur Urol, 1998;34(Suppl 3):33 6; J Clin Oncol, 2003;21:4001 8). The decision to treat prostate cancer with surgical or medical modalities versus watchful waiting requires a careful assessment of the risks and benefits, if any, for that patient. Therapeutic decisions for organ confined prostate cancer become easier when the complications and side effects of treatments are reduced. However, many patients who choose the watchful waiting approach eventually end up seeking treatment.

Percutaneous cryosurgery of the prostate has emerged from being an experimental treatment modality to becoming one of the good tools available to urologists for the treatment of prostate carcinoma. Since the approval of prostate cryoablation by Medicare, USA, in 1999 as a viable therapeutic option in the management of prostate cancer, there has been a significant resurgence in the level of interest and enthusiasm for the procedure. Several large studies demonstrated that

targeted cryoablation of the prostate provided a long term, durable response with regard to disease control (Cancer, 1997;79:963 74; Urology, 2001;57:518 23). In addition, cryoablation is associated with a lower incidence of overall morbidity compared with radical surgery and radiotherapy (J Cancer Res Clin Oncol, 2003;129:676 82). Indications for the use of this approach initially were limited to salvage procedures after radiation therapy. Recently published, multicenter trial (J Urol, 2003;170:1126 30) showed reasonable short term success with procedure as a primary cryotherapy for prostate cancer. Recent advances in the technology for cryoabaltion have produced significant decreases in the associated complications and morbidity.

Since the first published application of cryosurgery to the prostate cancer in 1964 (Invest Urol, 1964;14:610 9), cryoablation has undergone many advancements to make it available as a legitimate treatment modality for prostate cancer. With recognition of cryosurgery as a therapeutic option by the American Urological Association in 1996, there has renewed interest in this technology. In the study published in 1982 (Urology, 1982;19:37 42) 229 patients were followed for up to 10 years after cryosurgery. Comparisons of these patients were made with patients who underwent radical prostatectomy and received radiation therapy. The authors found similar survival rates for all treatment modalities. Cryosurgery showed advantages in the treatment of large, bulky tumors. However, difficulties with monitoring of the freezing process, due to unavailability of yet to be developed technology, resulted in major complications, such as urethrocutaneous and rectourethral fistula, at much higher rates compared with the rates among men who received the other treatment modalities. These complications initially limited the acceptance of cryosurgery as a treatment modality for patients with prostate cancer.

Advances, such as improved TRUS of the prostate and the development of urethral warmers, significantly have reduced the rates of complications, such as incontinence, urethral sloughing, and fistulas. The development of the third generation cryosurgery included two more advances. This system signaled the transition from liquid nitrogen to gas driven probes in which pressurized gas can be used to both freeze (argon gas) and actively thaw (helium gas) the prostate, using the Joule Thomson effect, in which different gases undergo unique temperature changes when depressurized, according to unique gas coefficient. This transition from liquid to gas permits the use

of smaller diameter probes. This new generation cryotechnology allows to use ultrathin cryoprobes for direct transperineal placement through a brachytherapy like template, without using tract dilatation and insertion kits.

at 29 69% for patients in the moderate risk and high risk groups.

With results from the studies described above showing disease control with cryosurgery similar to that achieved with radiation therapeutic modalities, the focus of investigators shifted to reducing the complications associated with this technology as well as improving disease control by gaining better control over total ablation of the prostate. However, total gland ablation is associated with significantly higher impotence rates compared with radiation therapy and radical surgery (Cancer, 1999;86:1793 1801).

The rationale for adjuvant or neoadjuvant androgen deprivation therapy in high risk patients is the theory that these patients can eventually fail after definitive therapy because they already have local or distant micrometastatic disease at the time of diagnosis. On this basis, improving local control of disease will have very little impact on recurrence free survival. There is also the distinct possibility that some patients likely develop metastatic disease due to inadequate local treatment. Adjuvant or neoadjuvant androgen deprivation therapy in high risk patients, thus, has become an important strategy. When combined with radiation, a short course of androgen deprivation therapy appears to improve local regional control as well as distant metastatic disease in patients with T2 4 disease. Long term adjuvant hormonal therapy in addition to radiation therapy also appears to improve survival in patients with Gleason scores>7 (Int J Radiat Oncol Biol Phys, 2001;50:1243 52, Int J Radiat Oncol Biol Phys, 2001;49:937 46). In a recently reported multicenter series on 122 patients in a pooled, multinstitutional analysis using third generation cryosurgery, seventy one percent of the high risk patients in their study remained free of biochemical recurrence at 12 months of follow up. The most common complication was scrotal swelling and pelvic pain (5.9%). Those patients had no episode of infection or fistula.

Most of the data available on outcomes after cryosurgery of the prostate have been from patients who failed radiation therapy, with PSA levels and biopsies that were indicative of locally recurrent prostate carcinoma. Given the technical challenge and reported surgical morbidity of salvage radical

prostatectomy, cryoablation rapidly found a role as an alternative salvage procedure. Although it is not without complications and inherent challenges, modern cryosurgery has been performed safely for locally recurrent prostate cancer following radiation therapy, especially in older patients and those with some morbidities, but with an acceptable operative risk. Biochemical NED rates in salvage cryosurgery have varied according to the definition of biochemical failure. Five year biochemical NED has been reported to be 40% in one series (J Clin Oncol, 2002;20:2664), whereas in other series with different parameters for failure the reported rates are 40% to 74% at 2 years (J Urol, 2001;166:1333). Predictors of a favorable outcome are preoperative PSA less than 10 ng/ml, Gleason score less than 8 and clinical stage less than T3 as well as the lack of preoperative hormonal use.

Recently, new advances in cryosurgery using third generation cryotechnology have allowed its extension as a primary treatment in patients with T1 3 prostate cancer. Because high risk patients often are regarded as poor candidates for radical prostatectomy, the third generation cryosurgery offers these patients another good treatment option in addition to radiation treatment.