



TITLE: Cryoablation of the Prostate for the Treatment of Primary and Recurrent Localized Prostate Cancer

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CRYOABLATION OF THE PROSTATE FOR THE TREATMENT OF PRIMARY AND RECURRENT LOCALIZED PROSTATE CANCER

INTRODUCTION

The California Technology Assessment Forum has been asked to review the scientific literature on the safety and efficacy of cryoablation of the prostate for the treatment of primary and recurrent localized prostate cancer.

BACKGROUND

In 2004, approximately 230,000 new patients were diagnosed with prostate cancer and about 30,000 men died from the disease (<http://www.nci.nih.gov>). This makes prostate cancer the most common malignancy in men in the United States after skin cancer and the second most common cause of cancer death, second only to lung cancer (Katz and Rewcastle, 2003). Every American man is estimated to have a 1 in 5 chance of developing prostate cancer at some time during his life (Drachenberg, 2000). In spite of these figures, there is ongoing controversy surrounding the role of screening for prostate cancer and the appropriate treatment for men diagnosed with early stage disease. Recommendations for the use of prostate specific antigen (PSA) testing in screening for prostate cancer have been advanced by the American Cancer Society and the American Urological Association (<http://www.cancer.org>; <http://www.urologyhealth.org/adult/index>). However, the U.S. Preventive Services Task Force (USPSTF) has concluded that the evidence is insufficient to recommend for or against routine screening for prostate cancer using PSA testing or digital rectal examination (DRE). The USPSTF found good evidence that PSA screening can detect early-stage prostate cancer but mixed and inconclusive evidence that early detection improves health outcomes. Screening is associated with important harms including frequent false-positive results and unnecessary anxiety, biopsies and potential complications of treatment of some cancers that may never have affected a patient's health (Harris and Lohr, 2003).

In spite of the uncertainty, more men are being screened for prostate cancer and are diagnosed earlier in the course of their disease. These patients and their physicians are faced with an increasingly complex set of options for treatment. The main treatment options for localized prostate cancer are radical prostatectomy (RP), radiotherapy including external beam radiation therapy (EBRT), brachytherapy, three dimensional conformal radiation therapy (3D-CRT), intensity modulated radiation therapy (IMRT) and in some circumstances, watchful waiting. For some men, techniques such as proton beam radiotherapy, high intensity focused ultrasound, thermotherapy, laparoscopic radical prostatectomy, HDR-iridium 192 brachytherapy and cryotherapy may be attractive treatment options. Unfortunately, there are virtually no randomized clinical trials that compare these options. In the only randomized clinical trial (RCT) to date, 695 men with early prostate cancer were randomized to either watchful waiting or RP. After a median follow-up of 6.2 years, RP reduced disease-specific mortality, but there was no significant difference in overall survival between the two groups (Holmberg *et al.*, 2002).

Approximately 13% to 35% of patients with stage T1, T2 localized disease will develop local recurrence by 10 years (Chen and Wood, 2003). Locally recurrent prostate cancer following radiation therapy or other treatment has an aggressive natural history. Local recurrence of prostate cancer after radiation therapy is often associated with the development of distant metastases and ultimately death. Although some patients have micro-metastatic disease beyond the reach of any further local therapy, others appear to have persistent localized disease only, as suggested by persistently undetectable serum PSA in approximately 1/3 to 1/2 of patients following salvage prostatectomy (Pisters *et al.*, 1997). These data suggest that a subset of patients with locally recurrent disease may be cured by further aggressive local treatment.

The optimal approach to treatment of local recurrence remains uncertain. Salvage surgery (RP or radical cystoprostatectomy), salvage cryoablation, salvage brachytherapy or endocrine therapy by androgen deprivation, are the currently recognized treatments for locally recurrent prostate cancer. Androgen ablation is the best treatment for men with systemic recurrence, but it is not curative.

Cryoablation of the Prostate

Cryotherapy, or cryoablation, is a minimally invasive surgical technique that induces the localized destruction of tissue by extreme low temperature. The goal of cryoablation is the destruction of all prostatic tissue. It was first introduced by Soanes *et al.* (1968), as an alternative to RP or radiation therapy in the late 1960s, in the treatment of benign prostatic hyperplasia and prostate cancer. The technique went out of favor due to a high incidence of complications such as sloughing of urethral tissue and development of fistulas, until the early 1990's when technological advances made it possible to more effectively ablate the prostate with fewer complications.

Although some variation exists, the basic technique of cryoablation is consistent across institutions. Cryotherapy is performed under local or general anesthesia. Multiple cryoprobes are placed through the perineum directly into the prostate. The cryoprobes are specially designed to conduct a continuous flow of liquid nitrogen or high pressure argon gas to the tip. This produces very cold temperatures very rapidly, freezing the prostatic tissue in an expanding or spherical fashion around each probe. Generally two freeze/thaw cycles are used. Transrectal ultrasound (TRUS) is used to monitor the freezing process. TRUS is used in real time throughout the procedure. In addition, TRUS clearly delineates the leading edge of the ice balls forming in the prostate during the procedure, allowing the surgeon to accurately limit the extent of the ice ball's growth, thereby minimizing any freezing damage to structures which are close to or surround the prostate. By keeping the prostatic urethra warm during cryosurgery, with urethral warming devices via urethral or supra-pubic catheters, the rates of urethral sloughing can be minimized. The patient is discharged home with a urethral catheter in place and is treated with prophylactic antibiotics. (Shinohara, 2003; Schmidt, 1997; Onik *et al.*, 1993; Baust *et al.*, 1997; Benoit *et al.*, 2000). Cryosurgery techniques continue to evolve. Second generation cryosurgery was marked by the development of TRUS guidance and urethral warming. More

recently, “third generation” cryosurgery, first described in 1997, saw the introduction of gas driven probes that both freeze the organ with argon gas and thaw with helium gas. This allowed for the use of thinner probes through a brachytherapy template (Han and Beldegrun, 2004).

Current recommendations are for the PSA to be obtained every three months for the first year after treatment and then every four to six months. The PSA declines gradually after the procedure and will nadir at three months if the outcome is likely to be successful. Unlike following RP, the PSA will likely remain detectable albeit at low levels even following a successful ablation (Shinohara, 2003).

There are currently three main indications for prostate cryoablation: 1) primary localized therapy for high risk patients who refuse or are not candidates for other definitive treatment; 2) salvage therapy for patients who have local recurrence after radiation therapy or surgery; 3) palliation (i.e. the debulking of large local lesions even in the face of widespread metastases) (de la Taille and Katz, 2000). Potential complications of cryoablation include erectile dysfunction, which may be seen in 50-95% of patients (Han, 2004), incontinence, tissue sloughing, pain, recto-urethral fistula, urethral stricture, penile numbness, small bowel obstruction and hydronephrosis.

To be eligible for salvage cryotherapy following radiation treatment, patients should have biopsy-proven prostate cancer, a complete evaluation to rule-out occult metastatic disease and a reasonable life expectancy. It may be difficult to definitively rule-out metastatic disease since pelvic imaging may overlook pelvic nodes and TRUS can be difficult to interpret after radiation treatment (Schellhammer *et al.*, 1997). Patients at high risk of lymph node involvement (i.e. PSA > 20ng/mL or Gleason score > 8), in spite of negative imaging, may undergo regional lymph node dissection to confirm the absence of regional spread.

This review primarily focuses on the role of cryoablation in salvage therapy, but will also update the recommendations from the Blue Cross Blue Shield Association Technology Evaluation Center review of cryoablation for the primary treatment of clinically localized prostate cancer released in September, 2001. That review concluded that cryoablation for the primary treatment of clinically localized prostate cancer did not meet TEC criteria.

TA Criterion 1: The technology must have the appropriate regulatory approval.

Several cryoablation systems have received 510K clearance from the FDA. These include: The CryoPlan System (Cryomedical Sciences, Inc., Crofton, MD); The Cryocare™ Surgical System (Endocare, Inc., Irvine, CA); the Seednet system (Galil Medical Inc., Westbury, NY).

TA Criterion 1 is met.

TA Criterion 2: The scientific evidence must permit conclusions concerning the effectiveness of the technology regarding health outcomes.

The Medline database, Cochrane clinical trials database, Cochrane reviews database, and the Database of Abstracts of Reviews of Effects (DARE) were searched using the key words "prostate", "cryotherapy", "cryoablation", cryosurgery" and "salvage". The search was performed for the period from 2001 through April 2005. The bibliographies of systematic reviews and key articles were manually searched for additional references. Further references were obtained when relevant from experts in the field, manufacturers and professional societies. The abstracts of citations were reviewed for relevance and all relevant articles were reviewed in full.

To date, there have been at least 11 studies of cryoablation of the prostate for localized recurrent prostate cancer after radiation therapy, published in peer-reviewed journals. Since September 2001, there have been several studies published in peer reviewed journals on the primary treatment of localized prostate cancer. All of these studies consist of Level 5 evidence case series without control subjects. The evidence that exists from case series is limited by short follow-up times and heterogeneous patient populations. There are no studies that compare outcomes of primary or salvage cryoablation with salvage prostatectomy or with any other primary or salvage treatment modality.

Outcomes assessed in these trials include clinical exam findings (such as DRE), serum PSA (often converted to biochemical disease-free survival (bDFS), presence/absence of disease on ultrasound guided biopsy and side effects/complications. Follow-up times were limited to two years or less in many of the studies. This is inadequate, given the generally slow progression of the disease and the fact that many of the patients also received adjunctive hormonal therapy.

One area of controversy is the method for ascertaining clinical benefit from therapeutic strategies that are applied to this population. The majority of published studies focus on bDFS as a primary endpoint. Recently, some authorities argue that the preferred end point of clinical benefit is prostate cancer-specific survival (Scher *et al.*, 2004). Trials must accurately assess and enroll patients with localized, recurrent prostate cancer as well as follow-up relevant outcomes after treatment. Inclusion criteria should consist of a positive biopsy and negative metastatic work-up.

There is also inconsistency in the literature on the assessment of patient complications from cryoablation. This information was often extracted from retrospective chart review or from non-validated surveys. Careful tracking of short and long-term complications and side effects is critical to compare the risks/benefits of various treatments.

In sum, the existing literature is limited to case series, often with short follow-up times and insufficient information about the patient populations and complications of treatment. Therefore, the scientific evidence does not permit conclusions concerning the effectiveness of the technology regarding health outcomes.

Levels of Evidence: Level 5.

TA Criterion 2 is not met for primary or salvage treatment.

TA Criterion 3: The technology must improve the net health outcomes.

Randomized Clinical Trials

There are no randomized clinical trials of primary or salvage cryotherapy.

Case Series: Cryosurgery for Recurrent Prostate Cancer Following Radiation Therapy

Bahn *et al.* (2003) report on a seven-year retrospective analysis evaluating the morbidity and bDFS of cryoablation for failure after radiation therapy. Between 1993 and 2001, 59 patients who had been previously treated with radiation therapy and had rising serum PSA values underwent salvage cryoablation of the prostate for localized, histologically proven, recurrent prostate cancer. Serial serum PSA testing was performed and biopsies were taken at 6, 12 and 24 months; again at five years; and any time the PSA rose above 0.5 ng/mL. The combined post-salvage bDFS rate using a PSA cutoff of 0.5 ng/mL and 1.0 ng/mL was 59% and 69%, respectively. Patient biopsies showed no evidence of residual or recurrent disease, so presumably all failures were secondary to distant metastases. The bDFS in this small series is similar to that reported for salvage RP.

Chin *et al.* (2003) report on histopathological findings on 106 patients who underwent 110 cryoablation procedures for biopsy proven, clinically localized radiation failure. Post-cryoablation, patients were followed with TRUS guided biopsy done at 3, 6, 12 and 24 months. They found that 15 patients (14.2%) were positive, the majority within one year. Of interest is that a significant percentage of patients (up to 42%) had evidence of residual viable prostatic glandular tissue on repeat biopsy, implying that “vigilant long term follow-up is mandatory” in these patients.

Izawa *et al.* (2002) report on 131 patients who had received definitive radiation therapy and underwent salvage cryotherapy between July 1992 and January 1995. Of these, 37 patients had received various combinations of XRT, hormonal therapy and systemic chemotherapy. Post-cryotherapy consisted of DRE and PSA determination every three months for a median follow-up of 4.8 years. The five year disease free survival was 57% for patients with a pre-cryotherapy PSA level of ≤ 10 ng/mL but only 23% for those with a PSA level > 10 ng/mL. The authors conclude that the subset of patients cured by cryotherapy appears to be small.

Chin *et al.* (2001) performed 125 cryoablation procedures on 118 patients with local recurrence after full dose radiotherapy. Of the 118 patients, 71 had been on hormone therapy before cryoablation and there were ten patients who had undergone prostatic transurethral resection. Follow-up included serial PSA and biopsy (83% overall compliance) at 6, 12 and 24 months. On biopsy follow-up, 3.1% (23 of 745) of the cores were positive. These were obtained from seven patients in the total salvage cryoablation population. All seven patients underwent second cryoablation. They found that 97% of patients had PSA nadirs below 0.5ng/mL, but at median follow-up of 18.6 months, only 34% of patients remained below this level. Serial biopsy revealed that at 24 months, 50% of patients has residual viable glands and 24% had residual viable stroma. Serious complications included four recto-urethral

fistulas (3.3%) and “severe” incontinence (6.7%). Predictors of biochemical failure included Gleason score of eight or greater before radiation and stage T3/T4 disease. The authors conclude that cryoablation is an “acceptable” treatment option for those patients in whom radiation has failed so long as “vigorous” patient selection criteria are adopted.

de la Taille *et al.* (2000) evaluated 43 patients who underwent salvage cryoablation between October 1994 and 1999. All patients had biopsy proven recurrent prostate cancer and a negative metastatic work-up, including lymph node dissection, and had received three months of combined hormonal treatment prior to cryoablation. bDFS was defined as a PSA value < 0.1 ng/mL. The mean follow-up was 21.9 months. At 12 months, they report a bDFS of 66%. Complications, determined by chart review, included urinary problems (14%), obstruction due to necrotic tissue requiring transurethral resection (5%), rectal pain (11%), perineum swelling (5%) and UTI (4%).

Ghafar *et al.* (2001) used an argon based cryotherapy system to treat 38 men for recurrent prostate cancer after radiation therapy. All patients had PSA > 0.3 ng/mL above the post radiation nadir, biopsy proven disease and a negative bone scan. They report bDFS rates of 86% at one year and 74% at two years. Reported complications include incontinence (7.9%) and perineal/rectal pain (39.5%), lasting one to two weeks.

Pisters *et al.* (1997) evaluated the efficacy of cryoablation in 150 patients who had prior radiation, hormonal therapy and/or systemic chemotherapy between 1992 and 1995. Overall, 45 patients (31%) had persistently undetectable PSA. Patients with a history of radiation therapy only, who underwent a double freeze-thaw cycle (the current standard), had a negative biopsy rate of 93% over an average follow-up of ten months. Major complications included urinary incontinence (73%), obstructive symptoms (67%) and impotence (72%).

Cespedes *et al.* (1997) conducted a retrospective chart review to report on complications following cryoablation of 143 patients for treatment failure after radiation therapy. They report that, of the patients who had the procedure done with a urethral warming device (the current standard), 28% had persistent incontinence and 9% had urinary obstructive symptoms.

Schmidt *et al.* (1998) report on 21 patients; 86% had negative biopsies following the procedure and PSA levels were normal in 67%. Miller *et al.* (1996) retrospectively studied cryoablation in 33 men who failed radiotherapy between 1990 and 1994. They report an overall negative biopsy rate of 79% over one year. Bales *et al.* (1995) report on cryoablation in 23 men from 1992 to 1994. At 17 months, the bDFS (defined as PSA < 0.3 ng/mL) was only 11%, leading them to conclude that cryoablation following radiation therapy should be considered experimental.

Case Series: Cryosurgery for Primary Treatment of Localized Prostate Cancer

Prepelica *et al.* (2005) report on 65 consecutive men with prostate cancer with high-risk features and negative metastatic evaluations who underwent primary cryosurgery between January 1998 and April 2002. High risk was defined as either a PSA ≥ 10 or a Gleason score ≥ 8 or both. The median patient age was 72 years, median Gleason and PSA were 7 and 21.70 and median follow-up was 35 months. Many patients (68%) received neoadjuvant androgen-deprivation therapy for three months. At two years, 94% and 81% of patients had a PSA nadir < 4.0 ng/mL or < 1.0 ng/mL, respectively. A six year Kaplan-Meier analysis revealed an 82% ASTRO survival probability (ASTRO failure = 3 consecutive increases in PSA level) and a PSA nadir < 4.0 ng/mL of 50% and < 1.0 ng/mL of 35%. Eight patients underwent biopsy and one had evidence of recurrent disease. They report a low rate of complications (it is unclear how this information was collected) with 3% complaining of rectal pain, urinary retention and incontinence. Rates of erectile dysfunction are not reported. The authors conclude that cryosurgery offers high risk patients another treatment option in addition to radiation therapy and that longer follow-up is needed.

Han *et al.* (2003) report on 106 patients with at least 12 months of follow-up. The mean age was 70 years and the study population was evenly divided between high and low risk (Gleason ≤ 7 , PSA ≤ 10) patients. One-third received preoperative hormone therapy. At 12 months, 75% remained free of biochemical recurrence; 42 (78%) of low risk patients and 37 (71%) of high risk patients had a PSA of 0.4 ng/mL or less. Complications included tissue sloughing (5%), incontinence (8%), pelvic pain (6%), penile tingling/numbness (6%) and impotence (87%). The authors conclude that longer follow-up of PSA and survival is necessary before conclusions are reached about the efficacy of this technique.

Donnelly *et al.* (2002) report results from a "prospective, pilot study" in which 76 patients were treated with 2nd generation cryoablation (10 patients received two treatments and one patient received three treatments) and followed-up for a minimum of 36 months. Mean age was 65 years, mean PSA at entry was 9.7 ng/mL and mean Gleason was 7. At five years, PSA was < 0.3 ng/mL for 60% (n=13) of low risk patients, 77% (n=23) for moderate risk patients and 48% (n=40) for high risk patients. At PSA < 1.0 ng/mL the rates were 75%, 89% and 76%, respectively. Complications included tissue sloughing in 4% requiring TURP of the necrotic tissue and incontinence in one patient. At three years, 53% of patients had become impotent and 72% who remained potent required the use of sildenafil or prostaglandin.

Bahn *et al.* (2002) report on 590 consecutive patients who underwent cryoablation at a single institution from 1993 to 2001. Mean follow-up was 5.4 years and mean age was 71 years. Using a PSA of 0.5 ng/mL as the cut-off, they report at seven years 61% of low risk, 68% of medium risk and 61% of high risk patients remain free from biochemical relapse. At 1.0 ng/mL, the seven year disease free rates were 87%, 79% and 71%. Of the 547 patients who underwent at least one biopsy, the rate of positive biopsy was 13%. The most common complication was

impotence (95%) with 5% recovering potency over one to two years. About 16% were considered incontinent and TURP was performed in 5.5%. The authors conclude that their results are comparable or superior to those achieved with conventional radiation therapy. Of note, at seven years, data is reported on 196 of the 590 patients originally enrolled; approximately 2/3 of the patients in each risk group appear to have been lost to follow-up.

Aus *et al.* (2002) report on 54 patients with a mean follow-up of 58 months. Mean age was 68 and mean PSA was 26. Progression free survival defined as a PSA < 1ng/mL or a negative biopsy was 39%. Fourteen out of 50 patients biopsied (28%) had cancer remaining in their prostates. Complication rates were high with 15% undergoing TURP, 17% developed strictures and one fistula formation. The authors of this Swedish study report that they discontinued their use of cryoablation because of high complication rates and poor outcomes.

Ellis (2002) reports on the experience from a community practice in the treatment of 75 patients. While they achieved a PSA nadir of ≤ 0.4 ng/mL in 84% of the population, follow-up was too short to draw meaningful conclusions from this study.

Patient Risks

There are a number of potential short and long-term risks to the patient undergoing cryoablation of the prostate. These risks include impotence, incontinence, tissue sloughing, pain, recto-urethral fistula, urethral stricture, penile numbness, small bowel obstruction and hydronephrosis. Impotence is seen in most patients following cryoablation, though some younger patients may be able to regain potency up to two years following treatment (Bahn *et al.*, 2002). Incontinence rates following primary cryotherapy vary from 4% up to 27% (Han *et al.*, 2003). Tissue sloughing and subsequent urethral obstruction and/or stricture have become much less common following the introduction of urethral warming devices (Cespedes *et al.*, 1997). A recent study of quality of life and sexuality of men 12 months after primary cryosurgery found that most quality of life measures returned to baseline after treatment. As other studies report, however, they found that only 13% of men had regained erectile functioning at 36 months (Robinson *et al.*, 2002). In spite of these problems, a survey of patients who had undergone cryoablation at one institution found that patient reported complications compared favorably to those reported for RP and external beam radiation (Badalament *et al.*, 1999). With the introduction of second generation cryosurgery in the 1990s and with the advent of urethral warming catheters and improved surgical technique, serious complications of cryosurgery have significantly decreased, though impotence continues to be the most common and bothersome complication (Rees *et al.*, 2004).

As with salvage surgery, the side-effects for patients undergoing salvage cryotherapy appear to be more severe than for those who have undergone cryoablation as a primary therapy (Anastasiadis *et al.*, 2003). In a retrospective comparison of quality of life and symptoms following primary and salvage cryotherapy, Anastasiadis *et al.* (2003) reports incontinence rates of 5.9% and 10% and severe erectile dysfunction in 86% and 90% in the primary and salvage groups, respectively. Impotence, rated secondary to salvage cryoablation, is difficult to determine from the

literature as most patients have pre-existing dysfunction, but those patients who have maintained potency are likely to lose it following salvage cryoablation. The rates of incontinence appear to be significantly higher in patients who have cryoablation following radiation with more than 3/4 of patients affected (Chin *et al.*, 2001; Ghafar *et al.*, 2001; Long *et al.*, 2003). A serious potential complication of salvage cryosurgery is recto-urethral fistula. The rate of recto-urethral fistula is generally reported to be between 0% and 3%, but one series showed that it was as high as 11% (Long *et al.*, 1998). Likewise, perineal pain and urinary tract infection are also more prominent in patients who undergo salvage treatment compared to primary treatment (de la Taille and Katz, 2000).

Some experts raise concern about the feasibility of safely accomplishing whole gland ablation while avoiding potential morbidities such as rectal or urethral injuries. A temperature of -40° is needed to assure complete destruction of the affected tissue and a very steep temperature gradient is required along a very short distance. This may be difficult to achieve. New techniques are still being tested that allow for effective treatment, while protecting vulnerable adjacent tissue (Cytron *et al.*, 2003).

Recent technological innovations have increased interest in cryoablation for the treatment of localized prostate cancer. This is particularly true for patients with recurrent disease following radiation for which there are few viable options for cure. To date, there is insufficient evidence to conclude that primary or salvage cryoablation is as effective as RP. All studies to date are retrospective case series often describing the experience of a single institution. In addition, these studies have used different definitions of biochemical failure and clinical risk and have not tracked patient morbidities in a consistent manner. There continue to be technological advances in cryosurgery that in more recent series have led to improved outcomes and decreased complications and morbidity. Ideally, randomized clinical trials should be conducted so that safety and effectiveness of cryoablation can be assessed along with the other commonly used treatment modalities.

TA Criterion 3 is not met for primary or salvage treatment.

TA Criterion 4: The technology must be as beneficial as any established alternatives.

The optimal treatment for patients with primary prostate cancer or for those with a recurrence after definitive treatment of localized primary prostate cancer is uncertain. Although some men have micro-metastatic disease that has disseminated beyond the reach of further local therapy, others have persistent localized disease with the potential for long-term disease free survival. Patients who recur after radiation treatment have a much higher likelihood of developing metastases and death from prostate cancer.

Options for patients who recur after surgery include various forms of radiation including brachytherapy, hormonal therapy, chemotherapy or continued observation. Options for men with post-radiation recurrence include salvage RP, hormonal treatment, chemotherapy, cryoablation and rarely, brachytherapy. Further external beam radiation is

generally not an option due to the increased frequency of radiation-induced complications (Corral *et al.*, 1996). Of these treatments, only RP and cryoablation can be considered potentially curable treatments for men with recurrent disease following definitive radiation treatment.

Overall, salvage prostatectomy following radiation treatment has reported survival rates of between 60% and 70% at five years and between 30% and 40% at 10 years (Steinberg, 2000). The largest salvage prostatectomy series with the longest follow-up found a 10-year cancer specific survival rate of about 70% (Amling *et al.*, 1999). Lerner (1995) reports that 65% of men undergoing salvage RP were disease free at 60 months, with a PSA < 0.2 ng/mL. The ten-year cancer specific survival rate in the prostatectomy group was 72%. A recent review reports that salvage RP offers five-year biochemical relapse-free rates between 55% and 69%. They conclude that cryosurgery biochemical response rates vary according to the definition of failure but they are generally lower than those of salvage RP (Touma *et al.*, 2005).

Higher complication rates are reported with salvage compared to primary RP including rectal injuries, bladder neck contracture and urinary incontinence. These rates have improved, however, with the advent of newer surgical techniques. The rate of rectal injury in salvage RP is between 0% and 19%, compared with a rate of 1% in primary RP. The mean bladder neck contracture rate is 18% in all salvage prostatectomy series reporting the rate, comparable to that of primary RP. The mean rate of incontinence for salvage RP is 45%, compared to a rate of incontinence for primary RP of between 5% and 31%, depending on the definition used. Other, less frequent surgical complications of salvage prostatectomy are urethral transection, fistula, urinary extravasation, wound infection and sepsis. Medical complications are deep vein thrombosis, pulmonary emboli, myocardial infarction and lymphedema (Touma *et al.*, 2005).

As found with cryoablation, strict criteria for patient selection may be the key to successful outcomes in salvage RP. In one report (Gheiler *et al.*, 1998), 40 men underwent salvage RP following radiation therapy and biopsy-proven local recurrence. When stratified by the serum PSA at presentation, the three-year bDFS rates were significantly better for men with serum PSA < 10 ng/mL, compared to those with higher values (68% vs. 26 %). In general, salvage RP should only be considered for carefully selected men who had organ-confined disease prior to the original RT and still have clinically organ-confined disease. With strict criteria, relatively few patients (one recent review quoted 2%-5%) may be eligible for salvage prostatectomy (Steinberg, 2000).

Androgen deprivation is standard treatment for metastatic prostate cancer and is often initiated in men with local recurrence in an attempt to improve response. Therapeutic responses are typically limited, however, and the optimal timing of hormone therapy for men with advanced prostate cancer is controversial. In addition, the value of hormone therapy for men with recurrent local disease, following local therapy, is unknown because no randomized trials have been conducted in this group. Hormone therapy including traditional hormone monotherapy (LHRH agonists,

orchiectomy), complete androgen blockade or nontraditional oral therapies is commonly used in this group of patients and appears to provide a modest survival benefit. Hormone therapy is not curative, however, so it is not an alternative to RP or cryoablation in these patients. Instead, it is often used as an adjunctive treatment in many of the salvage cryoablation trials (Corral *et al.*, 1996).

While acknowledging the deficiencies in the literature, salvage cryoablation offers patients with locally recurrent prostate cancer, who are candidates for definitive therapy, a less invasive alternative to salvage prostatectomy. It is the only non-surgical treatment that has the potential for cure and may be the only feasible treatment available for some patients who are not surgical candidates, particularly older patients and those with significant co-morbidities. Although RP offers the patient the best chance of long-term disease free survival (Touma *et al.*, 2005; Pisters, 2003), with appropriate patient selection, cryosurgery offers a reasonable alternative. Evidence from case series and expert opinion suggests that salvage cryoablation is beneficial in selected patients with preoperative PSA of < 10 ng/ml, Gleason score of < 8 and clinical stage < T3. Salvage prostatectomy for localized radiation failure is the preferred option for the patient with a life expectancy of at least 10 years, pre-radiation and preoperative PSA of < 10 ng/ml and localized preoperative stage, with the understanding that complication risks are higher than with primary RP (Touma *et al.*, 2005). Although most experts agree that RP offers the patient the best chance of long-term disease free survival (Touma *et al.*, 2005; Pisters, 2003), with appropriate patient selection, cryosurgery is a reasonable alternative for some patients who otherwise would be candidates for palliative therapy only.

Unlike men with recurrent prostate cancer following definitive treatment with radiation, men with primary localized prostate cancer have well established treatments to choose from. Although there are few randomized trials to inform this choice, both RP and radiation therapy have years of accumulated experience to support their use as first line treatments. As new technologies emerge, they should be tested against these “gold standard” treatments. While results from case series appear promising, patients should be directed to well-established therapies until there is data from randomized trials that support the use of other new and emerging technologies.

TA Criterion 4 is not met for primary or salvage treatment.

TA Criterion 5: The improvement must be attainable outside the investigational settings.

Improvement in outcomes has not been definitively demonstrated in investigational settings for primary cryoablation, so is not attainable outside of these settings

Salvage cryoablation has been shown to be beneficial outside of investigational settings when applied to selected patients, so the improvement would be attainable outside of these settings.

TA Criterion 5 is not met for primary treatment.

TA Criterion 5 is met for salvage treatment.

CONCLUSION

Technological developments have rekindled interest in cryotherapy as a viable alternative to surgery or radiation therapy. Outcomes have now been reported as long as seven years from treatment (Bahn *et al.*, 2003; and 2002) and in some series compare favorably with prostatectomy and primary radiation therapy. However, to date, there is not a single randomized clinical trial of cryoablation compared with these standard treatments. Cryosurgery studies largely have been retrospective examinations of single-institution experiences. Moreover, disparate definitions of clinical risk, biochemical failure, continence and potency have been used in these studies. Although evidence from case series appears promising, the extent to which evidence from case series can be generalized is uncertain. With longer follow-up cryoablation may not compare favorably with surgery. The finding from Chin *et al.* (2003), that a significant percentage of patients had viable prostatic tissue after cryoablation, is concerning and implies that longer term follow-up is required to ascertain the true effectiveness of cryoablation as a curative therapy. Patients with primary localized prostate cancer have well established treatment options available to them. This is not the case for patients who are candidates for salvage treatment.

Salvage cryoablation offers patients with locally recurrent prostate cancer, who are candidates for definitive therapy, a less invasive alternative to salvage prostatectomy. It is the only non-surgical treatment that has the potential for cure. Additional radiation is not acceptable as these tumors are likely to be resistant to this radiation treatment, and because re-treatment brings a higher risk of radiation induced complications. Salvage prostatectomy is technically challenging and can have significant morbidity. Because radiation may disrupt tissue planes, it may be difficult to assess normal tissue from those containing cancer cells, leading to positive margins in up to 40% of patients (Onik, 2001). In addition, salvage prostatectomy is associated with several serious intra-operative and perioperative complications including rectal and urethral injury, hemorrhage, bladder neck contractures, fistula formation and chronic incontinence. Hormonal therapy offers patients control of their disease and prolonged survival, but is not curative. Cytotoxic chemotherapy is not curative and usually is administered as palliation at late stages of disease.

Salvage prostatectomy for localized radiation failure is a the preferred option for the patient with recurrent localized prostate cancer and should be offered to patients with a life expectancy of at least 10 years, pre-radiation and preoperative PSA of < 10 ng/ml and localized preoperative stage, with the understanding that complication risks are higher than with primary RP (Touma *et al.*, 2005). Salvage cryoablation should be offered as a viable alternative to RP in selected patients. Although RP offers the patient the best chance of long-term disease free survival (Touma *et al.*, 2005; Pisters, 2003), with appropriate patient selection, cryosurgery is a reasonable alternative for patients with preoperative PSA of < 10 ng/ml, Gleason score of < 8 and clinical stage < T3. Given the relative paucity of alternatives for patients who experience biochemical progression after radiotherapy, cryosurgery may also prove a good alternative for those patients whose tumors appear to remain localized despite progression. Evidence from randomized trials would help address the uncertainty as to which patients are optimal candidates for salvage

cryoablation. Evidence from several series suggests that patients with serum PSA > 10, Gleason score > 8 and patients previously treated with hormonal therapy were less likely to benefit from salvage cryoablation. As future studies emerge, patients with very low risk of disease progression may be candidates for active surveillance alone, whereas those with more aggressive tumor characteristics could receive early multimodal therapy. Clear criteria as to which patients are likely to benefit from salvage prostatectomy, cryoablation, or are not good candidates for either option, should be derived from randomized trials.

While salvage cryotherapy does not meet all of the CTAF criteria, patients with localized, recurrent, low to moderate risk disease who are not surgical candidates due to advanced age or comorbidity, should be offered cryosurgery if it is available in an established cryosurgery center. Since cryoablation is a technically demanding procedure with a steep learning curve (Long, 2003), it is critical that clear criteria be established that identify cryosurgery “centers of excellence”.

Currently, patients with recurrent, localized prostate cancer have few treatment options. If they are not candidates for salvage RP, the only other option that offers the potential to cure them of their disease is salvage cryoablation. Although randomized trials have not been conducted, existing evidence suggests that salvage cryosurgery offers the potential for long-term disease free survival for a significant number of patients.

Patients and their physicians deserve evidence from well-designed randomized trials to help them make what may be life and death decisions about treatment. While evidence from existing case series is promising, the ultimate place of cryoablation in the treatment armamentarium for patients with locally recurrent prostate cancer remains uncertain.

RECOMMENDATION

A) Cryoablation for the treatment of primary and recurrent localized prostate cancer does not meet CTAF Technology Assessment Criteria 2 through 5 for safety, effectiveness, and improvement in health outcomes.

- B) In light of the available evidence in support of salvage cryoablation for recurrent localized prostate cancer following definitive radiation therapy, and the limited potentially curative treatment options currently available to these patients, salvage cryoablation should be considered for patients with recurrent localized prostate cancer who are not candidates for salvage radical prostatectomy.

June 15, 2005

The California Technology Assessment Forum panel voted unanimously to adopt the recommendation.

RECOMMENDATIONS OF OTHERS

Blue Cross Blue Shield Association (BCBSA)

In 2001, the BCBSA Technology Evaluation Center Medical Advisory Panel determined that cryoablation of the prostate did not meet criteria as a primary treatment of clinically localized prostate cancer.

Centers for Medicare and Medicaid Services (CMS)

On July 1, 1999, CMS determined that cryosurgery of the prostate gland is safe and effective, as well as medically necessary and appropriate, as primary treatment for patients with clinically localized prostate cancer, Stages T1-T3.

On July 1, 2001, CMS determined that salvage cryosurgery of the prostate for recurrent cancer is medically necessary and appropriate only for those patients with localized disease who have failed a trial of radiation therapy.

California Urological Association (CUA)

The CUA has provided an opinion statement in favor of the use of this technology. A representative attended the meeting to provide testimony.

Association of Northern California Oncologists (ANCO)

The ANCO does not have an opinion or position specific to this technology.

Medical Oncology Association of Southern California (MOASC)

The MOASC has provided an opinion in support of the use of this technology.

ABBREVIATIONS USED IN THIS ASSESSMENT:

USPSTF- U.S. Preventive Services Task Force

PSA- Prostate Specific Antigen

DRE- Digital Rectal Examination

TRUS- Transrectal Ultrasound

bDFS- biochemical disease-free survival

EBRT- External Beam Radiation Therapy

ASTRO- American Society of Therapeutic and Radiation Oncology

3D-CRT- Three-dimensional Conformal Radiation Therapy

IMRT- Intensity Modulated Radiation Therapy

TURP- Transurethral Resection of the Prostate

LHRH- luteinizing hormone releasing hormone

XRT- X-ray Therapy

RP- Radical Prostatectomy

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