Salvage Cryosurgery in Prostate Cancer

a report by
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Radiation is a common form of therapy for patients with newly diagnosed and localized prostate cancer. It has been estimated that nearly one-third of newly diagnosed prostate cancer patients will choose one form of radiation therapy as their primary treatment. Despite modifications of delivering radiation to the gland such as intensity modulation, 3D conformal, and computer-assisted brachytherapy, a significant number of these patients will have a rise in their serum prostate-specific antigen (PSA) value some time after radiation has been administered. Urologists are often called upon to manage patients with rising PSA values and radiation-recurrent cancer.

According to the recent literature, the frequency of biochemical failure with external-beam radiotherapy ranges from 20 to 66%.[1–8] However, in the past many investigators used different definitions of biochemical failure. In 1997, the American Society for Therapeutic Radiology and Oncology (ASTRO) defined biochemical failure as three consecutive PSA level rises separated by three- to four-month intervals (ASTRO panel consensus statement). More recently, the Phoenix consensus definition, PSA nadir plus 2ng/ml or more, was introduced.[9] Since rising PSA levels can occur with both local and metastatic disease, an elevation does not necessarily imply that the patient has local recurrence. In addition, a PSA level elevation may be due to benign causes. These factors make it difficult to clearly define a locally salvageable population. Only approximately one-third of patients with biochemical failure will have local recurrence.[10] If local recurrence is detected early, salvage therapy is feasible. Recent advances in both technology and the technique of salvage cryosurgery have led to the ability to eradicate these tumors with a reduction in morbidity.

Aaron E Katz, MD, is an Associate Professor of Clinical Urology and Vice Chairman of Urology at Columbia University Medical Center. He is also Director of the Center for Holistic Urology, which performs basic research and conducts clinical trials investigating the role of natural therapies within urology. Dr Katz is recognized as an expert in the field of prostate cryosurgery. In the early 1990s he began using cryosurgery to cure prostate cancers, and his pioneering work in advancing the technology helped Medicare approve of this therapy for treating radiation-recurrent tumors. He has also applied cryosurgery to the treatment of small kidney tumors, and performed the ablation both percutaneously and laparascopically. Dr Katz has published numerous articles, written chapters for medical textbooks, and directed courses at both regional and national levels. Dr Katz also developed a novel blood test that can detect small numbers of prostate cancer cells in the blood. The test, reverse transcription polymerase chain reaction (RT-PCR), was the first to allow urological cancers to be staged using a molecular assay.

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Scientific Background

Clinically based cryosurgical procedures grounded on well-recognized scientific principles support physician-managed destruction of radiation recurrent tumors of the prostate.[11–13] When performed with multiprobe devices and advanced imaging techniques, cryosurgery has yielded predictable and effective results in the long-term treatment of prostate adenocarcinoma in the primary setting.[14–16]

Prostate geometry dictates cryoneedle/cryoprobe (CN/P) placement: CN/P are placed to support thermal homogeneity at approximately -40°C throughout the prostate. Following template-assisted, ultrasound-guided placement of CN/P, the physician directs freezing from anterior to posterior in the gland. This sequencing supports clear visualization and control of the ablative process under transrectal ultrasound (TRUS).

The main principle of prostate cryosurgery is a thermal therapy that extracts heat (thermal energy) from the targeted tissue, resulting in a series of destructive effects. It has long been recognized that the tissue response from cold injury, which can range from inflammation to total destruction, depends on the severity of freezing. The lesion created by freezing is characterized by coagulation necrosis in the central region with a surrounding, relatively thin, peripheral region in which cell death is apparent. Under ultrasound, the ice ball can be clearly seen as a large hypoechoic region. The outer edge of the ice, which is the warmest part of the ice, can be monitored as it appears as a hyperechoic rim.

Salvage Cryosurgery

Salvage cryosurgery for curative intent should be strongly considered in men who have failed radiation therapy. The most appropriate candidates have documented persistent organ-confined prostate cancer, a PSA <10ng/ml, and a negative metastatic evaluation.

Patient Selection

Prostate-specific Antigen Levels

The optimal time for intervention in a patient whose post-radiation treatment increases PSA is unclear. A temporary rise in PSA levels after brachytherapy commonly occurs around 20 months after treatment.[17] This 'bounce phenomenon' has also been described in patients following external-beam radiotherapy.[18] Although there is no consensus among urologists or radiation oncologists as to when to intervene, if it is determined that salvage therapy is indicated the clinician should consider variables such as pre-existing medical conditions, patient age, and patient preference.

If the PSA level rises above the nadir level or the patient is deemed to have failed clinically based on any currently employed evaluation tool (ASTRO, Phoenix, PSA doubling time/velocity), a prostate biopsy should be performed if there are no contraindications to further therapeutic intervention. The Partin table for predicting pathological stage does not apply to post-radiation therapy patients. The patient with a PSA of 10ng/ml following radiation should not be considered to have the same pathology as a non-radiated patient with a PSA of 10ng/ml. According to Spiess et al., a PSA level >10ng/ml at the time of diagnosis of local recurrence and a PSA doubling time ≤16 months will predict a poor prognosis for salvage cryosurgery.[19] If PSA doubling time is ≤6 months, there is a significantly higher risk for metastasis even if local disease is confirmed by biopsy.[20]

Prostate Biopsy

When a biopsy is performed, multiple cores should be obtained and the pathologists should be informed that the patient has had previous radiation therapy, since there are definite pathological changes that can occur post-radiation. Benign glands affected by radiation can mimic cancerous glands, and special staining with high-molecular-weight keratin may be necessary to make a correct diagnosis.[21] Radiation therapy may not eradicate cancer immediately, i.e. malignant glands may remain as they slowly undergo apoptosis. Such severely affected cancer cells may remain in the prostate for as long as 36 months after radiation therapy. Therefore, a positive biopsy prior to 36 months after radiation treatment can be extremely difficult to interpret. Consequently, an experienced reading of the post-radiation biopsy specimen is essential. As with biopsies in the non-radiated patient, there are no definite guidelines specifying the number of cores that should be obtained. Recent literature has indicated that extended biopsy strategies enhance the detection of cancer and that sextant biopsies are no longer considered adequate.[22]

In addition to the prostate biopsy, a biopsy of both seminal vesicles (SV) is recommended in this setting of potential radiation failure. Cancer-invaded seminal vesicles may appear normal on imaging after radiation therapy. The incidence of SV involvement in the patient with a rising PSA level after radiation with locally recurrent disease is much higher than in the non-radiated patient. Pathological results from salvage radical prostatectomy series reveal that the rate of SV involvement can be as high as 42%.[23] Those patients with SV invasion will have a poorer prognosis in general despite successful local treatment of the prostate gland. In the presence of SV involvement, prostate salvage cryosurgery as monotherapy is not likely to be successful, and the use of hormonal/chemotherapy approaches in these patients is likely to improve outcomes.

Metastatic Work-up

If a prostate biopsy reveals recurrent cancer in the gland, a metastatic evaluation including nodal imaging of the abdomen and pelvis as well as a bone scan should be performed. Open or laparoscopic biopsy of the pelvic lymph nodes may also be considered for high-risk patients. The lymph node positivity rate in patients from the salvage radical prostatectomy series ranges from 11 to 40%. The role of the capromab pendetide scan in patients undergoing salvage cryosurgery has not been extensively studied, but may play a role in the patient with high-volume disease or where the PSA doubling time is less than six months. Prostate size is less of a problem when considering salvage cryosurgery as the prostate of radiated patients loses volume after radiation therapy. A prior history of transurethral resection of the prostate (TURP) is a relative contraindication for salvage cryosurgery, especially if there is a large TURP defect present, as these patients are at increased risk for urethral necrosis, leading to sloughing and urinary retention. The same is true for the patient who has a history of a prior open prostatectomy for benign disease.

Patient Selection Summary

Currently, there are no clearly defined guidelines to aid in the proper selection of patients for salvage cryosurgery. The optimal candidates for the procedure are men who have pathological evidence of locally recurrent disease without clinical evidence of metastatic disease, a PSA ≤4ng/ml,[24] a PSA doubling time somewhere greater than 12–16 months, no evidence of SV invasion, and a life expectancy >10 years.[25]

Technical Considerations and Modifications

Salvage cryosurgery can be performed in the patient with recurrent disease following external-beam radiotherapy as well as interstitial prostate brachytherapy, although the latter are clearly more difficult due to the interference with the previously placed seeds. Previously placed radioactive seeds can be visualized quite well under TRUS and may cause some confusion as their sonographic appearance is similar to the tip of the cryoneedles, especially in the transverse view. Placing the needles in the sagittal plane can overcome this difficulty, since the length of the cryoneedles can be easily followed in this view. Due to the previous radiation, the gland may be adherent to the anterior rectal wall, diminishing the thickness of Denonvilliers' fascia. This needs to be assessed by TRUS prior to freezing so the surgeon can determine how to appropriately place the posterior cryoprobes and the Denonvilliers' thermocouple. If the space between the anterior rectal wall and posterior prostatic capsule is less than 5mm, it may not be possible to drive the temperatures down to -40°C safely, and freezing should be terminated when the leading edge of the ice ball has extended just beyond the capsule, even if the target temperature of -40°C is not reached. Double freeze–thaw cycles have significantly better outcomes in terms of biochemical failure-free and local recurrence-free survival rates compared with one freeze–thaw cycle.[26]

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When counseling patients for any salvage procedure, the risks of urinary incontinence need to be addressed. The placement of a thermosensor to monitor the temperature of the external sphincter can reduce the potential of thermal injury to this muscle. The thermosensor is introduced through the perineal skin and advanced until the impression of the tip of the thermocouple can be seen in the sphincter. The placement can be documented by TRUS or cystoscopy. There is no documented evidence of benefit from hormone therapy prior to salvage cryosurgery except for down-sizing purposes.

Treatment Outcomes

Biochemical Outcomes

Over the past decade several institutions have published their salvage cryosurgery results. Many of the published series from the early 1990s had significant numbers of complications.[26,27] Despite the inability to adequately control the ice formation and target the gland in this 'early' cryosurgery period, follow-up PSA values and biopsy data from these series indicate that the introduction of lethal ice could eradicate radioresistant, locally aggressive cancer. The high morbidity presented in these reports could be attributable to a number of factors. For one, the use of thermocouples was not yet available. In addition, there was a period of time when the US Food and Drug Administration (FDA) banned the urethral warming device and, as a consequence of inadequate warming, urethral sloughing was prevalent, resulting in pain, urinary retention, and incontinence. Furthermore, early studies were performed using a liquid-nitrogen-based system that limited the ability to control the growth of the ice ball. This, coupled with improper cryoprobe placement, led to the development of rectal fistulas.

> The use of pressurized argon gas, multiple probes (a maximum of eight), and thermosensors has produced better results compared with liquid-nitrogen-based systems for locally recurrent cancer.

Second-generation cryosurgical equipment led to significant advances in the technology. The use of pressurized argon gas, multiple probes (a maximum of eight), and thermosensors has produced better results compared with liquid-nitrogen-based systems for locally recurrent cancer. Although there has been no established set of parameters to define success or failure after salvage cryosurgery, persistent disease diagnosed by prostate biopsy and a PSA cut-off value of 0.1–0.5ng/ml are commonly used to define outcomes.

Published series have demonstrated promising results for this treatment approach. Using two freeze–thaw cycles, Cespedes et al. achieved a biopsy-negative rate of 93% and a biochemical failure-free survival rate of 66% in a series of 150 patients mainly treated using the first-generation liquid-nitrogen-based system.[28] However, these results came at the price of high complication rates. Patients with pre-operative PSA levels >10ng/ml or Gleason scores ≥8 were most likely to experience disease recurrence. Bahn et al. reported seven-year salvage biochemical failure-free rates of 59 and 69% using cut-off values of PSA <0.5 and <1.0ng/ml, respectively, in 59 patients.[29]

De la Taille et al. reported a biochemical failure-free survival rate of 66% at 12 months in a series of 43 salvage patients, with low complication rates.[30] In their experience, a PSA nadir of >0.1ng/ml following treatment predicted eventual recurrence. Ghafar et al. used an argon-based cryosurgery system to treat 38 patients with biochemical recurrence after radiation.[31] They reported PSA nadirs <0.1ng/ml in 81.5% and biochemical disease-free rates of 86 and 74% at one and two years, respectively.

In another recently published large series also employing an argon-based system, Chin et al. performed cryosurgery on 118 patients with recurrent disease after radiation therapy, including five who had received permanent interstitial implants. They reported negative biopsies in 94% of these patients; the seven who had persistent disease underwent a second ablation procedure. In this series, 97% of patients had PSA nadirs <0.5ng/ml, and 34% remained below this level with a median follow-up of 18.6 months (68% had PSA <4ng/ml, and 10 patients developed metastatic disease).[32] As in the Pisters et al. study, pre-procedure PSA levels >10ng/ml, Gleason score ≥8, and stage 3/4 disease predicted biochemical failure.

The third-generation cryosurgery system is equipped with a maximum of 30 smaller 17-gauge needle-like probes. Using this device, Creswell et al. reported a 67% biochemical failure-free rate as defined by PSA levels <0.5ng/ml for 20 salvage cryosurgery patients.[33] Han et al. also reported a 74% biochemical failure-free rate at one year with the third-generation system.[34]

Complications

Recent advances in technology have significantly reduced the complication rates associated with salvage cryosurgery. In the past, incontinence rates following salvage cryosurgery exceeded 70%,[26] but current studies being performed by de la Taille, Ghafar, Chin, and Han report rates of less than 10%. Despite these improvements, incontinence rates in the salvage setting are still higher than those following primary cryosurgery. Rectourethral fistula was also reported to occur more frequently in salvage cases; however, recent studies report that this serious complication has been virtually eliminated (rate of 0–3%). Although rectal fistula is currently rare, rectal pain has been reported.

In a series of 35 patients studied by de la Taille who underwent cryosurgery of the prostate with an argon-based system, 37% who had prior radiation therapy had pain compared with 12% of patients who underwent primary cryosurgery. In a later study, Donnelly et al. reported that rectal pain occurred in 17% (eight of 46) of salvage patients.[35] The cause of the pain is unknown but may be related to an ischemic event that occurs near the anterior rectal wall. After radiation, there may be reduced blood supply to this area, and introducing lethal ice may elicit further devascularization. de la Taille, Ghafar, and Han reported urethral sloughing and obstruction in 5–10% of patients. Even with the current technologies and techniques, impotence rates remain high at more than 80%.

Quality of Life

There are two series reporting quality of life data in patients undergoing salvage cryosurgery with third-generation devices. Robinson et al. assessed quality of life using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-C30 instrument and the Prostate Cancer Index in 46 patients at baseline and at 24 months following salvage cryosurgery.[36] Quality of life returned to pre-operative levels by 24 months in all domains, with the exception of urinary and sexual functioning. At 24 months, 29% of patients

reported urinary bother as a moderate to big problem, and 56% reported sexual bother as a moderate to big problem. Thus, impairments in long-term quality of life following third-generation salvage cryosurgery seem to be limited to the sexual and urinary function domains.

Anastasiadis et al.[7] compared quality of life in 51 primary cryosurgery patients with quality of life in 31 salvage cryosurgery patients using the EORTC QLQ-C30 instrument.[37] The overall quality of life scores were high in both groups. Primary cryosurgery patients reported higher physical (p=0.005) and social (p=0.024) functioning than salvage patients. Sexual function, urinary symptoms, and incontinence were more common in the salvage patients. These results are not surprising and are analogous to the higher complication rates reported in patients undergoing post-radiation salvage radical prostatectomy compared with primary radical prostatectomy. It is important to note that there are no reports comparing quality of life before and after other local salvage therapies such as salvage radical prostatectomy or salvage brachytherapy. Thus, it is not possible to directly compare the quality of life outcomes of the various local salvage treatments.

Cost to the Healthcare System

There are limited data regarding the costs of salvage cryosurgery to the healthcare system. The costs of salvage cryosurgery are similar to those of primary cryosurgery. Two studies evaluating the cost of primary cryosurgery demonstrate that it is significantly less expensive than either radical prostatectomy or external beam radiotherapy. It is also important to consider how the costs of salvage cryosurgery compare with the costs of alternative treatments. Patients with biochemical recurrence after radiation therapy typically have a long lifespan. Even when the PSA doubling time is less than 12 months, approximately 50% of patients will live for longer than five years after biochemical relapse. Costs of hormonal therapy are significant, and it is conceivable that salvage cryosurgery may actually save money by either eliminating or delaying the need for hormonal therapy in some patients. There is an urgent need for careful economic modeling to assess the cost-effectiveness of salvage cryosurgery relative to alternative treatments.

Summary

Cryosurgery guided by ultrasound and temperature monitoring is an effective therapy for recurrent localized prostate cancer after radiation therapy. Refinements in the surgical technique and equipment have resulted in significantly less morbidity than previously reported while maintaining durable PSA results. Salvage cryosurgery is a reasonable option for selective patients with locally recurrent prostate cancer, and should be strongly considered early for patients defined as radiation failures. ■

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