Selection of Salvage Cryotherapy Patients

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Radiation therapy is a main form of therapy for patients with localized prostate cancer. Despite advances in delivering radiation beams to the gland, urologists will be faced with managing patients with rising prostate-specific antigen values and radiation-recurrent cancer. If the cancer is detected early, salvage therapy can be initiated. Recent modifications in the technique of salvage cryosurgery have led to the ability to eradicate these tumors with a decrease in morbidity. The management and selection of these patients, as well as the results of salvage cryoablation, are discussed in this article.
[Rev Urol. *2002;4(suppl 2):S18–S23*]

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Key words: Prostate • Cryosurgery • Argon • Failed radiation

Radiation therapy for localized prostate cancer is a main 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 in methods of delivering radiation to the gland, such as intensity modulation, 3-D conformal, and computer-guided seed implantation, a number of these patients will have a rise in serum prostate-specific antigen (PSA) values in the years after radiation. According to the recent literature, the rate of biochemical failures has ranged from 20% to 66%.[1,2]

Many investigators in the past have differed with regard to their definition of biochemical failure. This issue has been addressed elsewhere in this supplement. In 1997, the American Society for Therapeutic Radiology and Oncology defined biochemical failure as three consecutive PSA rises separated by 3–4-month intervals. What has not been established is the number of patients with recurrent prostate cancer. As PSA itself is not a cancer-specific protein, there are several reasons besides cancer for a PSA rise in the radiated patient.

The optimal time for intervention is unclear.

Patient Evaluation

When PSA rises in the radiated patient, the optimal time for intervention is unclear. Most radiation oncologists feel that PSA can fluctuate within the first 18 months. A recent study demonstrated a "bounce phenomenon" in patients undergoing seed implantation.[3] The investigators found that many patients can have a fluctuation in the serum PSA level following brachytherapy and that this may be due to localized prostatitis. Currently there is no consensus among urologists or radiation oncologists on when to intervene. Our practice has been to wait at least 18 months following radiation. When considering salvage therapy, the clinician needs to take into account other variables, such as preexisting medical conditions, age of the patient, and patient preference. It has been our practice to perform a biopsy of the prostate if PSA rises above the nadir level and there are three consecutive rises. In addition, a history, physical examination, urinalysis, and urine culture should be obtained prior to the biopsy to evaluate the possibility of a lower urinary tract infection or prostatitis.

If a biopsy is undertaken, multiple cores should be obtained, and the pathologists need to be informed that the patient has had previous radiation. There are definite pathological changes that can occur post-radiation, and the pathologist assigned to the case should be informed so that radiation changes can be discriminated from cancer. As with biopsies in the nonradiated patient, there are no definite guidelines as to how many cores should be obtained. Recent literature has indicated that more cores enhance the detection of cancer,[4] and sextant biopsies are no longer adequate. In our experience, performing a prostate biopsy is no different in the radiated patient, and we have not found any additional complications in these patents.

In addition to the prostate biopsy, we routinely perform a seminal vesicle (SV) biopsy on each side. The reason for SV biopsy is for pathological staging. The incidence of SV involvement in the patient who has a rising PSA and recurrent disease is much higher than in the nonradiated patient. Pathological results from salvage radical prostatectomy series reveal that the rate of SV involvement can be as high as 40%.[5] This can be critical when evaluating these patients, and it has been my practice to initiate hormone therapy alone without additional local therapy in those cases with SV involvement. The patient with a PSA of 10 ng/mL following radiation should not be considered to have the same pathology as a nonradiated patient with a PSA of 10 ng/mL. It may be that the classic Partin nomogram tables should not be applied to these patients. Although this nomogram has been reasonably powerful in predicting pathological stage in the nonradiated patient, this may not be the case with the radiated gland. Pathological data from patients who underwent a salvage radical prostatectomy shows organ-confined rates ranging from 10% to 30%, and the rates of SV invasion are high (30%–40%).[6,7]

Currently there are no defined guidelines for urologists to follow that would enable them to select patients for salvage cryoablation properly. The optimal candidates for the procedure would be those patients who have a locally recurrent cancer without clinical evidence of metastatic deposits. Salvage cryosurgery can be performed under spinal anesthesia or general anesthesia. Patients with a prior history of transurethral resection of the prostate (TURP) should be excluded from cryosurgery, especially if there is a large TURP defect present, as these patients are at increased risk for sloughing and urinary retention.

Salvage cryosurgery can be performed under spinal anesthesia or general anesthesia.

If a prostate biopsy reveals recurrent disease in the gland, a metastatic survey should be performed. It has been our practice to obtain a computed tomography scan of the abdomen and pelvis, as well as a bone scan. There may be a role in performing an open or laparoscopic biopsy of the

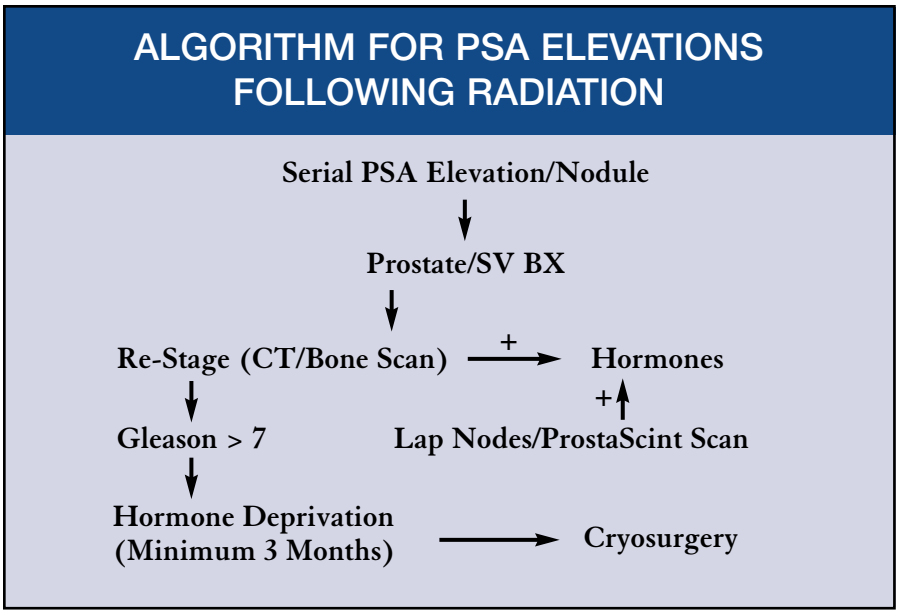


Figure 1. *Diagram of the algorithm for serum prostate-specific antigen (PSA) elevations following radiation. LAP, laparoscopic; SV, seminal vesicle; BX, biopsy.*

pelvic lymph nodes (see the algorithm in Figure 1). If we look at the lymph node positively in these patients from the salvage radical prostatectomy series, it appears that between 20% and 40% of these patients will have prostate cancer metastases to the lymph nodes.[7] We would caution novice laparoscopic surgeons that dissection of these nodes can be technically difficult, because there can be adherence to the pelvic side wall and external iliac vessels. The role of the ProstaScint scan is unknown for clinically staging these patients, but this scan can be helpful in select cases for patients who do not want to undergo a staging pelvic node dissection.

Salvage Cryoablation: Technical Modifications

The technical aspects of performing cryoablation are outlined in Dr. Donnelly's article in this supplement. There are some additional technical comments that need to be addressed in relation to the salvage cryosurgical patient. Salvage cryoablation can be performed in the patient with recurrent disease following external beam radiation as well as brachytherapy. The previously placed radioactive seeds can be visualized quite well under transrectal ultrasound (TRUS) and may cause some confusion, because their appearance sonographically is similar to the tip of the cryo needles, especially in the transverse view. This can be overcome by monitoring and placing the needles in the sagittal plane. In this view, the length of the cryo needles can be easily followed. The gland may be adherent to the anterior rectal wall due to the previous radiation, diminishing the thickness of the Denonvilliers' fascia. This needs to be assessed by TRUS prior to freezing, so the surgeon can determine how to place the posterior cryoprobes and the Denonvilliers thermocouple appropriately. It has been our practice to use androgen deprivation for 3 months prior to salvage cryoablation. We have found that routine use of hormones has led to a decrease in the overall size of the gland but has also increased the space between the anterior rectal wall and the posterior prostatic capsule, allowing the cryosurgeon a few additional millimeters of working space below the gland. If the space between the anterior rectal wall and posterior prostatic capsule is less than 5 mm, it may not be possible to drive the temperature down to –40°C safely, and freezing should be terminated when the leading edge of the iceball has extended just beyond the capsule, even if the target temperature of –40°C is not reached.

When counseling patients for any salvage procedure, the risks of urinary incontinence need to be addressed. Most recently we have placed a thermocouple device in the external sphincter. The placement of this thermocouple is performed with the aid of a flexible cystoscopy. The thermocouple 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 cystoscopy as well as by TRUS. The use of the external sphincter temperature probe has led to a dramatic reduction in urinary incontinence after salvage cryoablation. We recommend that cryosurgeons routinely use this thermocouple and maintain temperatures in the sphincter above 15°C. It has also been our practice to continue urethral warming in the recovery room for 2 additional hours following the procedure. This will reduce the urethral slough rate; we have not seen this potential complication since we began practice.

Salvage Cryosurgery: Results

The U.S. Experience

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.[8] Despite the inability to adequately

control 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 at the time of these reports. In addition, there was a period when the urethral warming device was banned by the U.S. Food and Drug Administration. Without proper warming, urethral sloughing was prevalent, and patients developed pain, urinary retention, and incontinence. Furthermore, several of these studies were performed using a liquid nitrogen–based system. Although the delivery of extremely cold temperatures into the gland was rapid, the ability to control the growth of the iceball was limited, and improper placement of cryoprobes led to the development of rectal fistulas.

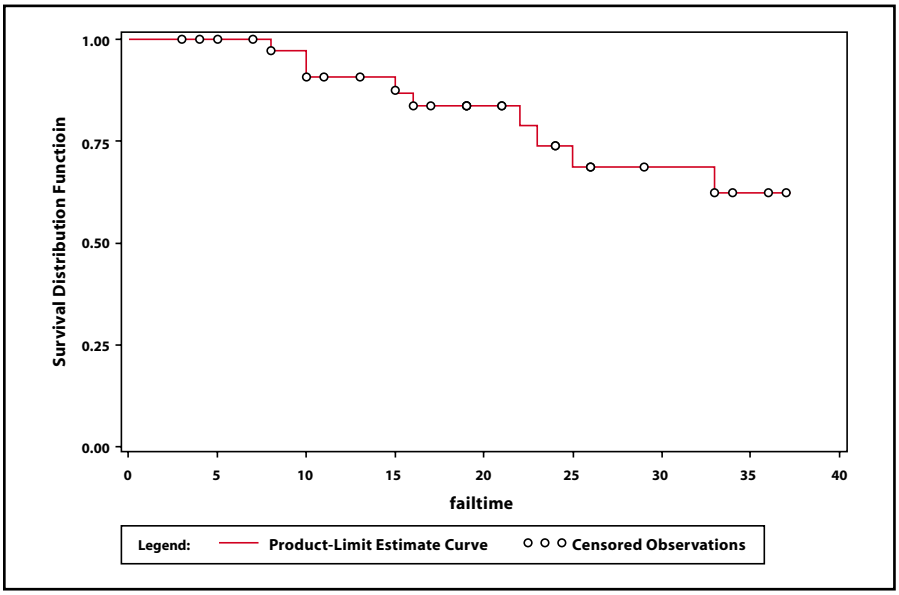
Table 1
Complications After Cryosurgery

Complication	Number (%)
Incontinence	3 (7.9)
Urinary tract infection	1 (2.6)
Hematuria	3 (7.9)
Obstruction	0 (0)
Perineal/rectal pain	15 (39.5)
Urethral sloughing	0 (0)
Rectal fistula	0 (0)
Swelling	4 (10.5)

Data from Ghafar et al[14]

The second generation of cryosurgical equipment has led to significant advances in the technology. As described elsewhere in this supplement, the use of the routine flow of the argon gas has led to the generation of recent publications on salvage cryoablation. All the patients had biopsy-proven recurrence without metastatic spread. Patients underwent cryosurgery using the Cryocare unit (Endocare, Irvine, CA). Multiple thermocouples were used. All the patients received 3 months of hormone deprivation. The mean follow-up for these patients is 21 months. Although there has not been an established set of parameters to define success or failure after salvage cryosurgery, we have designated a PSA cutoff value of 0.3 ng/mL. In our experience, 65% of the patients are able to remain free of biochemical recurrence at 3 years (Figure 2).

Figure 2. *Biochemical recurrence for patients was defined as a serum prostate-specific antigen (PSA) rise of 0.3 ng/mL or more above their PSA nadir. Reproduced, with permission from the publisher, from Ghafar MA, Johnson CW, de la Taille A, et al. Salvage cryotherapy using an argon based system for prostate cancer locally recurrent after radiation therapy: the Columbia experience.* J Urol. *2001;166:1333–1338.*



Urinary incontinence rates have been reduced over the past few years following salvage cryosurgery (Table 1). Our recent experience with the use of the external sphincter thermocouple has decreased the rates to less than 5%. This is much lower than the reported incontinence rates after a salvage radical prostatectomy. In a similar fashion, the dreaded complication of rectal fistula is near 0%, and this is due to the high accuracy of the modern day TRUS combined with temperature monitoring at the anterior rectal wall. Although we

Table 2
Results of Salvage Cryosurgery Studies

Author	Type	N	INC	Obstruction	Rectal injury	US	BRFS
Miller et al[9]	Cryo	33	9%	4%	0%	5.1%	40%
Pisters et al[10]	Cryo	150	73%	67%	NA	NA	31%
Lee et al[11]	Cryo	46	9%	NA	8.7%	NA	53%
Cespedes et al[12]	Cryo	107	28%	14%	NA	NA	NA
Chin et al[13]	Cryo	118	6.7%	8.5	3.3%	5.1	35%
Ghafar et al[14]	Cryo	38	7.9%	0%	0%	0%	74%

Cryo, cryosurgery; NA, not available; INC, incontinence; US, urethral sloughing; BRFS, biochemical-recurrence-free survival.

have not experienced any rectal fistula to date, rectal pain can occur in around 20% of patients. 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 in the area. Initial management should consist of warm baths and anti-inflammatory agents. Rarely the pain can persist for more than a few weeks. If this should occur, we have found the use of nitroglycerin suppositories to be very helpful.

The second generation of cryosurgical equipment has led to significant advances.

It has been our practice to place a suprapubic catheter (SPC) during cryosurgery, although a Foley may be employed. One of the advantages of the SPC is that patients can monitor their voiding and residual urine volumes at home. The majority of the patients will have their SPC removed in a week's time. Urinary frequency and urgency are common in the first few weeks after salvage cryosurgery and can be managed with anticholinergics. In addition, penile and scrotal edema can occur in 15%–20%. This usually resolves in a week.

The Canadian Experience

A group of cryosurgeons in Western Ontario, Canada, recently published their long-term experience with sal-

Main Points

- Between 20% and 66% of these patients will have a rise in serum prostate-specific antigen (PSA) values in the years after radiation therapy for localized prostate cancer.
- A biopsy of the prostate can be considered if the PSA rises above the nadir level and there are three consecutive rises; a history, physical examination, urinalysis, and urine culture should be done first to evaluate the possibility of a lower urinary tract infection or prostatitis.
- Seminal vesicle involvement in the patient who has a rising PSA and recurrent disease is much higher than in the nonradiated patient and can be as high as 40%.
- Androgen deprivation for 3 months prior to salvage cryoablation can lead to a decrease in the overall size of the gland and also increases the space between the anterior rectal wall and the posterior prostatic capsule, allowing the cryosurgeon more working space below the gland.
- An external sphincter temperature probe to maintain temperatures in the sphincter above 15°C can cause a dramatic reduction in urinary incontinence after salvage cryoablation.
- Continuing urethral warming in the recovery room for 2 additional hours following the procedure will reduce the urethral slough rate and hence pain, urinary retention, and incontinence.

vage cryoablation. In their study, 125 patients with biopsy-proven radiation recurrent disease underwent cryoablation using an argon-based system. The study included routine biopsies on these patients after cryosurgery. The overall negative biopsy rate was 97%. This included biopsy data from over 700 tissue cores, with a median follow-up of 18.6 months. Urinary incontinence was found in 6.7% of the cases, and 3% had rectal fistulas. The results of the salvage cryosurgery studies are summarized in Table 2. The authors concluded that salvage cryotherapy can be performed with acceptable morbidity; with regard to cancer control, salvage cryotherapy deferred the need for endocrine therapy and resulted in a significant number of negative biopsies.

Summary

Cryosurgery guided by ultrasound monitoring is very effective clinical therapy for recurrent localized prostate cancer after radiation therapy. It is less invasive than salvage radical prostatectomy and causes fewer side effects. Refinement in the surgical technique and use of the argon-based system with thermocoupling may result in less morbidity than previously reported. ■

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