

Locally Recurrent Prostate Cancer After Initial Radiation Therapy: A Comparison of Salvage Radical Prostatectomy Versus Cryotherapy

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Purpose: We compared the treatment outcomes of salvage radical prostatectomy and salvage cryotherapy for patients with locally recurrent prostate cancer after initial radiation therapy.

Materials and Methods: We retrospectively reviewed the medical records of patients who underwent salvage radical prostatectomy at the Mayo Clinic between 1990 and 1999, and those who underwent salvage cryotherapy at M. D. Anderson Cancer Center between 1992 and 1995. Eligibility criteria were prostate specific antigen less than 10 ng/ml, post-radiation therapy biopsy showing Gleason score 8 or less and prior radiation therapy alone without pre-salvage or post-salvage hormonal therapy. We assessed the rates of biochemical disease-free survival, disease specific survival and overall survival in each group. Biochemical failure was assessed using the 2 definitions of 1) prostate specific antigen greater than 0.4 ng/ml and 2) 2 increases above the nadir prostate specific antigen.

Results: Mean followup was 7.8 years for the salvage radical prostatectomy group and 5.5 years for the salvage cryotherapy group. Compared to salvage cryotherapy, salvage radical prostatectomy resulted in superior biochemical disease-free survival by both definitions of biochemical failure (prostate specific antigen greater than 0.4 ng/ml, salvage cryotherapy 21% vs salvage radical prostatectomy 61% at 5 years, $p < 0.001$; 2 increases above nadir with salvage cryotherapy 42% vs salvage radical prostatectomy 66% at 5 years, $p = 0.002$) and in superior overall survival (at 5 years salvage cryotherapy 85% vs salvage radical prostatectomy 95%, $p = 0.001$). There was no significant difference in disease specific survival (at 5 years salvage cryotherapy 96% vs salvage radical prostatectomy 98%, $p = 0.283$). After adjusting for post-radiation therapy biopsy Gleason sum and pre-salvage treatment serum prostate specific antigen on multivariate analysis salvage radical prostatectomy remained superior to salvage cryotherapy for the end points of any increase in prostate specific antigen greater than 0.4 ng/ml (HR 0.24, $p < 0.0001$), 2 increases in prostate specific antigen (HR 0.47, $p = 0.02$) and overall survival (HR 0.21, $p = 0.01$).

Conclusions: Young, healthy patients with recurrent prostate cancer after radiation therapy should consider salvage radical prostatectomy as it offers superior biochemical disease-free survival and may potentially offer the best chance of cure.

Key Words: prostatic neoplasms, radiotherapy, salvage therapy, prostatectomy, cryotherapy

Abbreviations and Acronyms

bDFS = biochemical disease-free survival

DSS = disease specific survival

OS = overall survival

PSA = prostate specific antigen

RRP = radical retropubic prostatectomy

SCT = salvage cryotherapy

SRP = salvage radical prostatectomy

Submitted for publication November 21, 2008.
Study received institutional review board approval.

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† Financial interest and/or other relationship with Endocare.

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§ Financial interest and/or other relationship with Endocare, EDAP, Gen Probe and Andro Dx.

THE first indication of prostate cancer relapse after primary radiation therapy with curative intent is typically an increasing PSA, which precedes clinically detectable recurrent disease by 3 to 5 years on average.^{1,2} It has been estimated in the United States alone that just fewer than 50,000 men will have a PSA recurrence after initial radical prostatectomy or radiation therapy.³ In the absence of salvage therapy at least three-quarters of men will have clinical evidence of recurrent disease within 5 years after an increase in PSA is detected.² Hormonal therapy is often administered as systemic therapy but it is noncurative. However, cure is possible for patients with isolated local recurrence who undergo salvage local therapy. Several reports have documented the efficacy and complications of salvage local therapies including radical prostatectomy, cryotherapy and brachytherapy.^{1,2}

SRP and SCT have been used longer than brachytherapy and, thus, longer term followup data are available for these therapies. The 5-year biochemical disease-free survival rate for patients undergoing SRP has been reported to be 61%⁴ whereas that of SCT has been reported to be 42%.⁵ Although the long-term bDFS for SRP appears to be higher than that of SCT, a direct comparison of the efficacy of these salvage therapies is difficult due to differences in the clinical features of the patients in these reports. Specifically tumor grade, tumor stage and pre-salvage PSA have been shown to have profound prognostic significance in patients undergoing salvage local therapy. Furthermore, in many of the reports patients received hormonal therapy in combination with salvage local therapy, which makes a direct comparison of the efficacy of the local therapy difficult to assess.

To date there has not been a direct comparison of the efficacy of salvage local therapies in which patients were stratified by known prognostic parameters. We compared the outcomes of patients undergoing SRP vs SCT, stratifying by extent of prior therapy, pre-salvage PSA and tumor grade.

MATERIALS AND METHODS

Patient Eligibility

The Mayo Clinic and M. D. Anderson have extensive experience delivering salvage local therapy for recurrent prostate cancer after initial radiation therapy. Therefore, our study population was composed of patients from these institutions. The Mayo Clinic experience with salvage radical prostatectomy and the M. D. Anderson experience with salvage cryotherapy have been previously reported. These reports provide a detailed description of patient selection, salvage treatment, followup and complications.⁴⁻⁸ Patients undergoing SCT were treated with the second generation

Cryomedical Sciences liquid nitrogen based equipment using a single or double freeze-thaw technique.

Study Design

This study was performed under a protocol that was separately approved by the institutional review board of each institution. Participation was limited to patients who received radiation therapy alone with curative intent for treatment of clinically localized prostate cancer. Patients who had received hormonal therapy before or after salvage (until biochemical failure) were excluded from analysis to facilitate a direct comparison of the impact of the 2 salvage local therapies without the influence of hormonal therapy. Patients were required to have a pre-salvage PSA less than 10 ng/ml and a post-radiation therapy biopsy proven Gleason score 8 or less. When available the biopsy specimens that established recurrent prostate cancer after radiation therapy were centrally reviewed by a single urological pathologist (TJS) and patients with Gleason sums of 9 or 10 were excluded from analysis. If the post-radiation therapy biopsy slides were unavailable for review but the institutionally reported Gleason grade was 8 or less, the patient was included in the final study population. Patients with large volume, clinical stage T3 or T4 disease were excluded as were those with nodal or bone metastasis. Combined these clinicopathological criteria define a favorable risk, post-radiation therapy group likely to have locally recurrent disease alone (low risk of subclinical metastatic disease) and for whom the likelihood of successful salvage should be high. The SRP and SCT databases at the Mayo Clinic and The University of Texas M. D. Anderson Cancer Center were searched to identify patients meeting these selection criteria.

Patient records were assessed for clinical outcomes including biochemical failure, disease specific survival and overall survival. Because there is no standard definition of biochemical failure after SCT, in both groups biochemical failure was assessed by 2 definitions of 1) a single PSA 0.4 ng/ml or greater, a standard definition reported by Amling et al commonly used for patients undergoing radical prostatectomy,⁹ and 2) 2 increases above the post-salvage therapy nadir PSA which has been used in a salvage brachytherapy report.¹⁰ Since SCT performed with the double freeze-thaw technique has been associated with improved biochemical outcomes compared to the single freeze-thaw cycle, a separate analysis limited to double freeze-thaw cases was conducted.⁷ Nadir PSA was defined as the lowest PSA reading after salvage local therapy (typically recorded 3 months after salvage local therapy). Patients were considered to have died of prostate cancer if they had metastatic disease and an increasing PSA before death. Patients who died without apparent metastatic progression were classified as deaths from other causes.

Statistical Analysis

Comparisons of clinical and pathological features between the groups were made using the chi-square test or the Wilcoxon rank sum test as appropriate. The bDFS, DSS and OS rates were analyzed using Kaplan-Meier actuarial methodology. The log rank test was used to evaluate the significance of differences between

actuarial curves. The Cox proportional hazards model was used to test for survival differences after adjusting for clinical features with p less than 0.05 on 2-tailed analysis considered statistically significant.

RESULTS

Of the 88 patients undergoing SRP at the Mayo Clinic between 1990 and 1999, 42 met the study criteria. Of the 160 patients who underwent SCT at The University of Texas M. D. Anderson Cancer Center between 1992 and 1995, 56 met the study criteria. We excluded a large number of patients from study who received hormonal therapy before or after salvage therapy to enable us to examine the results of the salvage therapy alone (without the confounding influence of hormonal therapy). We also excluded patients with Gleason 9 or 10 disease on biopsy after radiation because many of these patients have subclinical metastatic disease. Finally we excluded patients with bulky T3 cancers or those with lymph node or bone metastasis. The demographic, clinical and pathological features of these patients are presented in [table 1](#). There was no significant difference in patient age between the study groups. The post-radiation therapy biopsy was available for review by a single pathologist for 32 (76%) of the SRP cases and 53 (95%) of the SCT cases, and was used to confirm a Gleason score of 8 or less. Patients in the SCT group tended to have higher grade tumors than those in the SRP group ($p = 0.003$). Median followup was somewhat longer in the SRP than in the SCT series (median 7.8 and 5.5 years, respectively, $p < 0.0001$).

The treatment outcomes for patients undergoing salvage local therapy are shown in [figures 1 to 6](#). The bDFS rate was better for the SRP group using both definitions of biochemical failure (single PSA 0.4 ng/ml or greater—SCT 21% vs SRP 61% at 5 years, $p < 0.001$, [fig. 1](#); 2 increases above nadir—SCT 42% vs SRP 66% at 5 years, $p = 0.002$, [fig. 2](#)). When the SCT group was limited to patients undergoing a double freeze-thaw procedure, those undergoing SRP had a better bDFS rate by the stringent 0.4 ng/ml or greater definition (at 5 years SCT 24% vs SRP 61%, $p = 0.001$, [fig. 3](#)) and a trend toward improved bDFS by the 2 increases above PSA nadir definition (at 5 years SCT 47% vs SRP 66%, $p = 0.132$, [fig. 4](#)). OS was better in the SRP series (at 5 years SCT 85% vs SRP 95%, $p = 0.001$, [fig. 5](#)), possibly because the SRP series may have been selected to be healthier. There was no significant difference in DSS between the 2 groups (at 5 years SCT 96% vs SRP 98%, $p = 0.283$, [fig. 6](#)). After adjusting for post-radiation therapy biopsy Gleason sum and pre-salvage treatment serum PSA on multivariate analysis SRP remained superior to

Table 1. Demographic characteristics and clinical features of patient groups

	SCT		SRP		p Value
No. pts	56		42		
Age at surgery (rounded):					0.7153
Mean (SD)	67.9	(5.81)	66.7	(6.19)	
Median (range)	67.0	(56.0–82.0)	67.5	(54.0–76.0)	
Median yrs followup (range)	5.5	(0.7–8.1)	7.8	(1.7–15.4)	<0.0001
No. prior therapy (%):					0.0701
External beam radiation	50	(89.2)	39	(92.9)	
Brachytherapy	1	(1.8)	3	(7.1)	
External beam radiation + brachytherapy	5	(8.9)	0	(0)	
No. clinical stage (%):					0.1269
T1c	5	(9.8)	1	(3.8)	
T2	23	(45.1)	18	(69.2)	
T3	23	(45.1)	7	(26.9)	
Unknown	5		16		
Median pre-salvage ng/ml PSA (range)	5.4	(0.0–9.9)	4.0	(0.3–9.6)	0.1192
No. pre-salvage ng/ml PSA (%):					
Less than 4	21	(37.5)	19	(45.2)	
4+	35	(62.5)	23	(54.8)	
No. worst Gleason score (%):					0.0026
Missing	4		3		
5	1	(1.9)	5	(12.8)	
6	12	(23.1)	14	(35.9)	
7	22	(42.3)	16	(41)	
8	17	(32.7)	4	(10.3)	
No. freeze-thaw cycles (%):					
1	28	(50)	Not available		
2	28	(50)			
Nadir ng/ml post-salvage PSA:					0.0002
Mean (SD)	0.7	(1.57)	0.1	(0.73)	
Median (range)	0.0	(0.0–7.3)	0.0	(0.0–4.5)	
% Pre-salvage biopsy surface area pos for Ca:					0.3950
No.	39		31		
Median	5.0		7.5		
Q1, Q3	4.0, 15.0		3.0, 20.0		
Range	(0.0–75.0)		(0.0–50.0)		

SCT for the end points of any increase in PSA 0.4 ng/ml or greater (HR 0.24, $p < 0.0001$), 2 increases in PSA (HR 0.47, $p = 0.02$) and overall survival (HR 0.21, $p = 0.01$) as shown in [table 2](#).

DISCUSSION

Our study is the first to our knowledge to directly compare 2 different salvage therapies for locally recurrent prostate cancer after initial radiation therapy with patients stratified by PSA and tumor grade. We convincingly demonstrated that SRP offers superior bDFS compared to SCT regardless of whether biochemical failure is defined as a PSA of 0.4 ng/ml or greater, or 2 increases in PSA above the nadir. There were no statistically significant differences in the DSS rate. The OS rate for patients treated with SCT was lower than that for SRP, most likely because SCT is less invasive than SRP and was offered to patients

Comparison of Salvage RRP to Salvage Cryosurgery

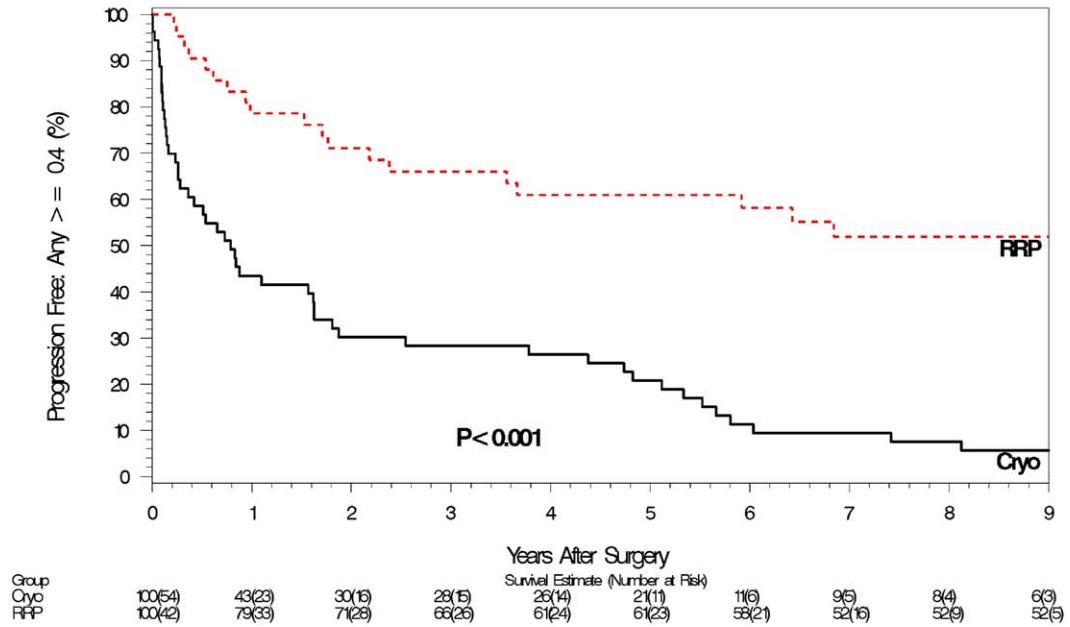


Figure 1. bDFS defined as PSA 0.4 ng/ml or greater in all patients undergoing salvage local therapy

with significant comorbidities who were likely not candidates for SRP. As a result there was a higher rate of death from causes other than prostate cancer in patients undergoing SCT.

We attempted to minimize confounding features by limiting the cohort to patients with Gleason sum 8 or less, PSA before salvage therapy less than 10 ng/ml and a prior history of radiation

Comparison of Salvage RRP to Salvage Cryosurgery

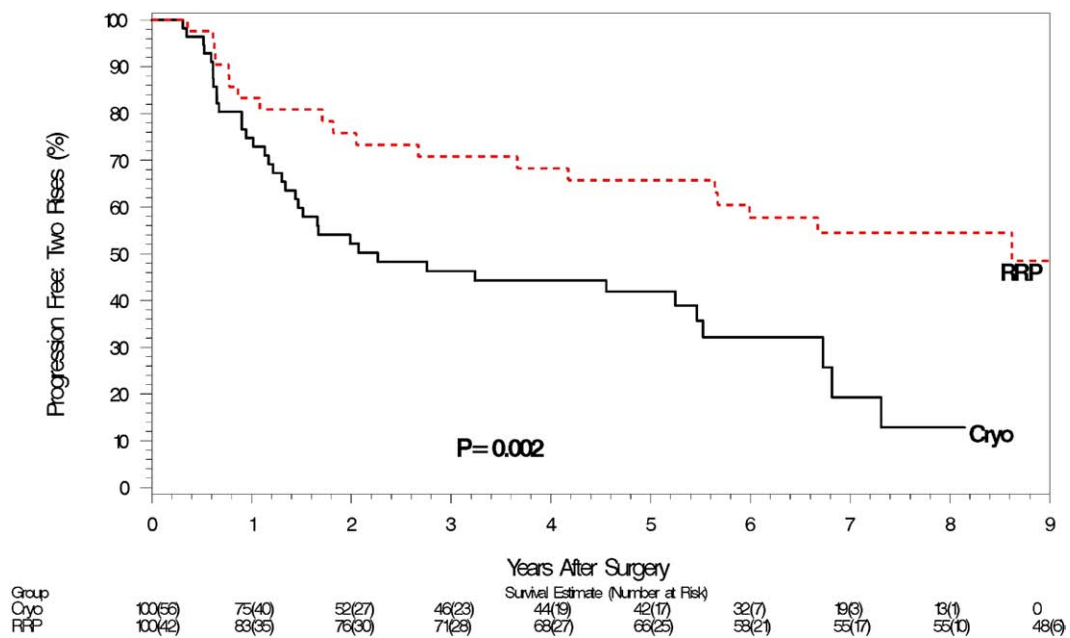


Figure 2. bDFS defined as 2 increases in PSA above nadir in all patients undergoing salvage local therapy

Salvage RRP vs Two-Cycle Salvage Cryosurgery

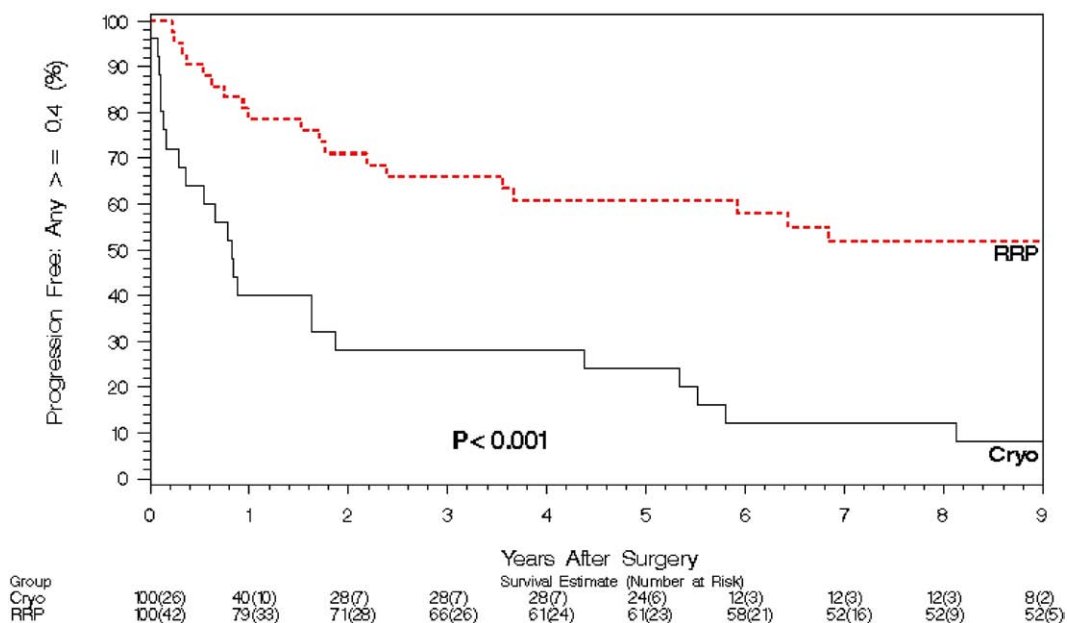


Figure 3. bDFS defined as PSA greater than 0.4 ng/ml in SRP group compared to patients undergoing double freeze-thaw cycle SCT

therapy alone. Therefore, we used the extent of prior therapy, pre-salvage PSA and tumor grade to create a relatively homogeneous study population, and then used Cox regression modeling to account for the remaining differences, thereby facilitating a valid comparison of the 2 salvage treatments. Because none of the patients in this study were treated with hormonal therapy until biochemical failure after salvage therapy, we were able to conduct a direct assessment of bDFS outcome without the confounding influence of hormonal therapy. Several reports have shown that the bDFS rate of patients treated with SCT or SRP is better for those with a pre-salvage PSA of less than 10 ng/ml.^{4,5,8} Therefore, we restricted the comparison to patients with a pre-salvage treatment PSA of less than 10 ng/ml. Although tumor grade is another powerful prognostic factor for patients undergoing post-radiation therapy salvage treatment, outcome is compromised primarily in patients with Gleason score 5 elements (high grade cancer) in the post-radiation therapy biopsy specimen. Therefore, we restricted the study group to patients with a post-radiation therapy biopsy Gleason score of 8 or less. In our study 87% of the post-radiation therapy biopsies were reviewed by a single pathologist. In the remaining cases the outside biopsies were not available for review and the institutionally reported Gleason score was used. Although tumor grade was signif-

icantly higher in patients treated with SCT than in those treated with SRP, we do not believe that this difference accounts for the observed differences in bDFS. We used a Cox regression model to account for differences in Gleason score and pre-salvage PSA. The Cox model demonstrated significant differences in bDFS and OS in favor of patients treated with SRP, although these differences were slightly less than with the unadjusted models. Furthermore, our earlier reports show similar bDFS rates for patients undergoing SCT with a Gleason score between 6 and 8.^{5,8} Thus, by limiting our study population to a favorable risk cohort defined by extent of prior therapy, pre-salvage PSA and tumor grade, and then using Cox regression modeling to account for any remaining differences in PSA and tumor grade, we are confident that the observed difference in bDFS between treatment groups is real and that our conclusion that SRP offers superior bDFS is valid.

When these patients were treated there were differences in practice patterns at the 2 institutions. At M. D. Anderson SCT was the preferred salvage treatment modality between 1992 and 1995 and, therefore, there were few SRP cases performed during this era. The approach at M. D. Anderson changed in 1995 to favor SRP in younger healthy patients, and now approximately half the patients at M. D. Anderson undergo SRP and the other half undergo SCR.

Salvage RRP vs Two—Cycle Salvage Cryosurgery

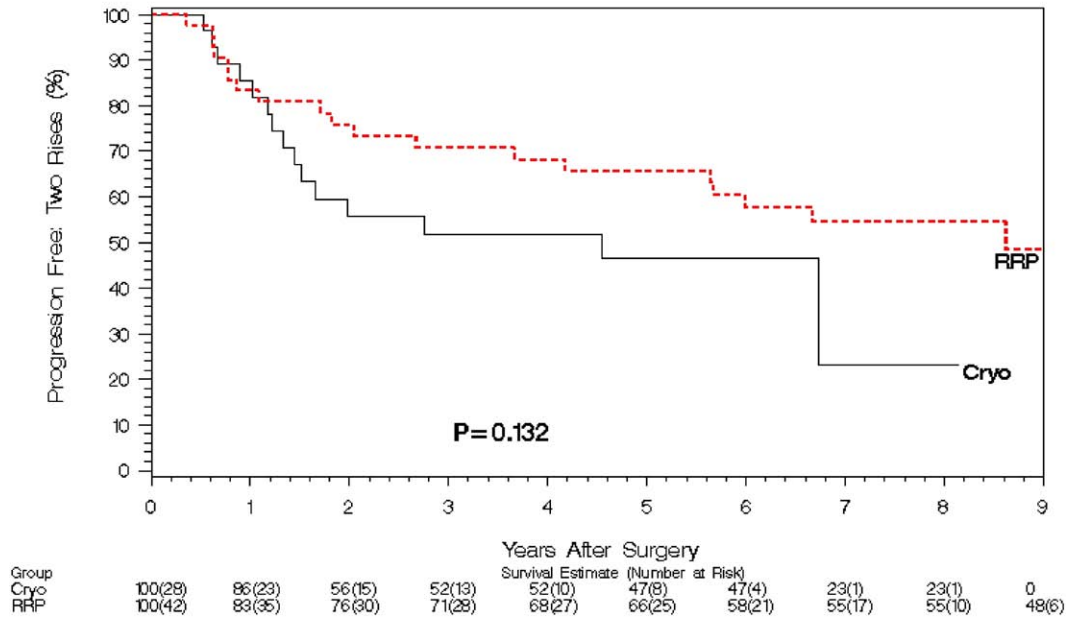


Figure 4. bDFS defined as 2 increases above nadir PSA in SRP group compared to patients undergoing double freeze-thaw cycle SCT

The SRP data set at M. D. Anderson has approximately 70 cases but does not have the length of followup or a sufficient number of patients by our

study criteria to facilitate a long-term comparison of salvage treatment outcomes. SRP was the preferred mode of salvage local therapy at the Mayo Clinic

Comparison of Salvage RRP to Salvage Cryosurgery

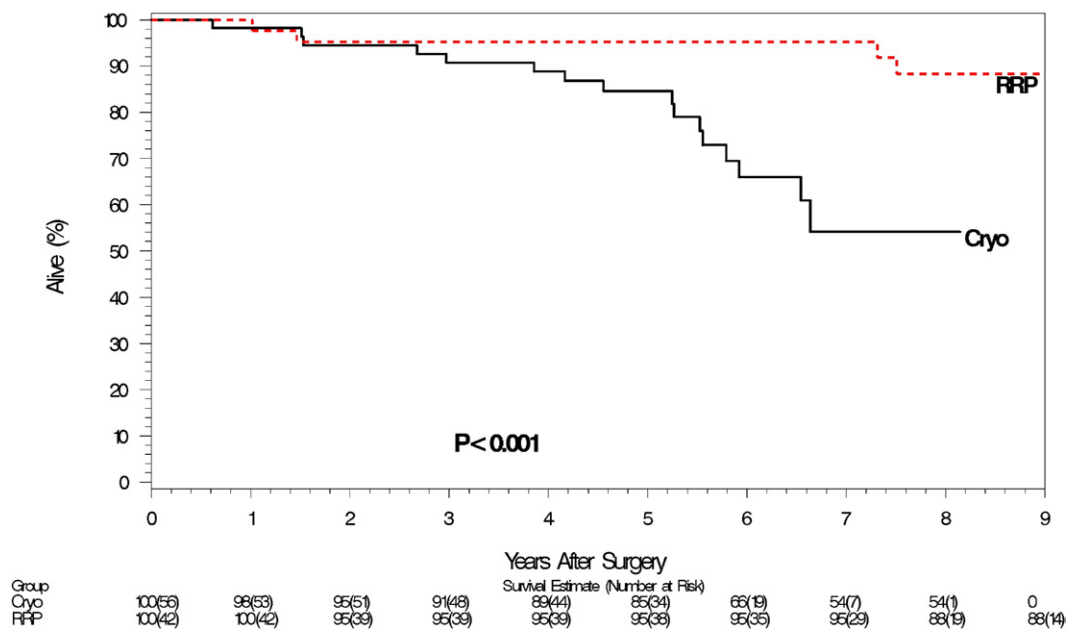


Figure 5. OS in patients undergoing salvage local therapy

Comparison of Salvage RRP to Salvage Cryosurgery

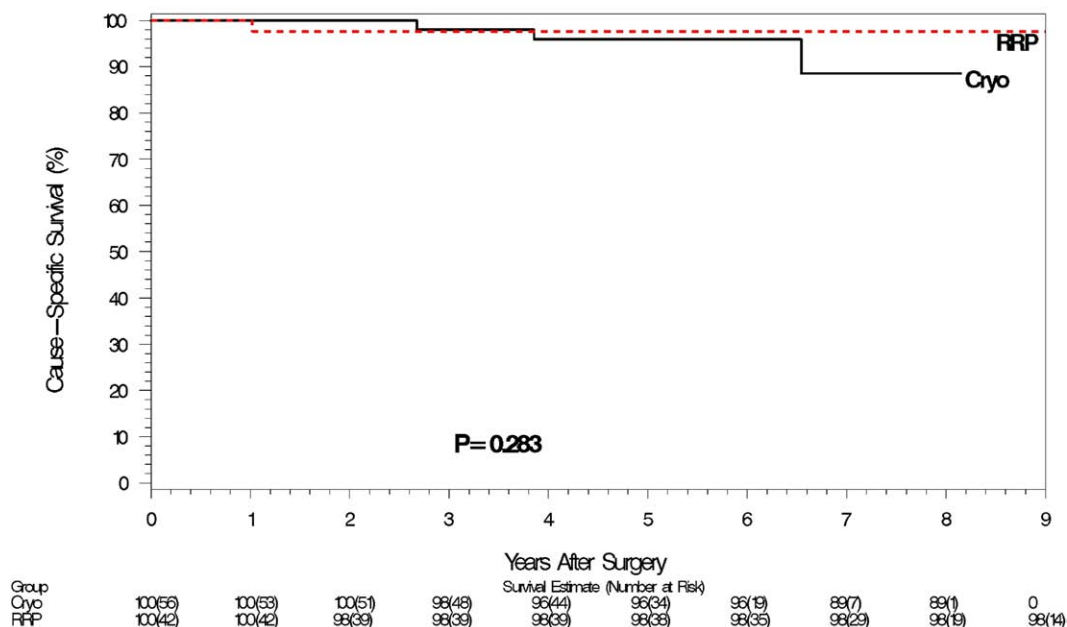


Figure 6. DSS in patients undergoing salvage local therapy

between 1990 and 1999 such that the Mayo salvage prostatectomy data set has enough patients by our study criteria. Therefore, we compared SCT at M. D. Anderson to SRP at the Mayo Clinic using our study criteria to reduce patient heterogeneity which is a significant problem in salvage patient populations. Furthermore, we had a single study pathologist review as many biopsies as possible to reduce the risk of institutional bias in assigning Gleason scores to post-radiation biopsies. Therefore, we do not believe

that institutional treatment bias explains our results.

Our study was not intended to determine the mechanism of treatment failure for either treatment modality. However, differences in the extent and completeness of treatment offer a potential explanation for our observations. In SRP the prostate gland, periprostatic tissues including the neurovascular bundles, and the seminal vesicles are completely removed. By comparison it is currently not possible

Table 2. Cox model hazard ratio estimates

Event	Univariate Cox Model			Multivariate Cox Model		
	Hazard Ratio	95% CI	p Value	Hazard Ratio	95% CI	p Value
Any PSA 0.4 ng/ml or greater:						
SRP vs SCT	0.252	0.150–0.425	<0.0001	0.237	0.132–0.424	<0.0001
Gleason	Not available			0.955	0.690–1.322	0.7813
PSA (\log_2)	Not available			1.178	0.895–1.551	0.2436
Two increasing PSAs:						
SRP vs SCT	0.409	0.229–0.732	0.0026	0.474	0.252–0.891	0.0205
Gleason	Not available			1.017	0.712–1.452	0.9260
PSA (\log_2)	Not available			1.148	0.857–1.538	0.3547
Overall survival:						
SRP vs SCT	0.152	0.047–0.492	0.0017	0.206	0.059–0.720	0.0134
Gleason	Not available			2.398	1.258–4.573	0.0079
PSA (\log_2)	Not available			1.050	0.647–1.705	0.8423
Disease specific survival:						
SRP vs SCT	0.298	0.029–3.046	0.3070	0.464	0.032–6.688	0.5728
Gleason	Not available			1.346	0.323–5.619	0.6834
PSA (\log_2)	Not available			1.115	0.316–3.942	0.8653

to destroy the entire prostate gland by freezing it. SCT must be performed with a urethral warming catheter to protect the urethra during the freezing process to prevent urethral complications such as tissue sloughing.⁷ The urethral warming catheter results in a ring of preserved viable periurethral tissue that may harbor cancer.¹¹ In a study of 350 patients who underwent radical prostatectomy Leibovich et al found that 17% had disease touching the urethra.¹² The distance between cancer and the urethra was less for patients with a higher pretreatment PSA or a Gleason score of 4 or 5 in the preoperative biopsy specimen. Having disease close to the urethra was more common in patients with locally advanced tumors. Many patients with post-radiation therapy recurrent cancer have locally advanced tumors and, therefore, are at risk for periurethral involvement. In addition to the ring of preserved tissue around the urethra, depending on the size, shape and contour of the prostate gland, there may be zones of incomplete prostate freezing between the cryotherapy probes or at the periphery of the coalesced ice ball resulting in foci of persistent viable prostate tissue and incomplete destruction of the prostate cancer. Izawa et al examined prostate biopsies from 113 patients who had undergone SCT, and found cancer cells in 23%, and benign or atypical glands in 56%.¹³ Although only those biopsies with cancer present predicted for subsequent bDFS, the high prevalence of benign and atypical glands in these biopsies supports the concept that foci of untreated glands exist. Thus, we theorize that SCT leaves small areas of untreated prostate glands that may harbor cancer, resulting in a lower bDFS than SRP.

Our study is limited by its retrospective design and that there are other prognostic factors not controlled for. Most patients in our report were initially diagnosed and received radiation therapy for prostate cancer in a community setting, and were referred to the Mayo Clinic or M. D. Anderson when the recurrent cancer was discovered. Therefore, we stratified the 2 treatment groups by parameters that were fairly objective and for which we had first-hand source information. We were not able to match the study population for every prognostic variable, particularly those related to the initial diagnosis of prostate cancer for which we lacked reliable source information in many patients. In particular we were not able to control for dose and type of initial radiation, initial clinical stage, grade at diagnosis, PSA at presentation before radiation and PSA doubling time before therapy because this information was not available in many cases.

It is important to note that SCR in our series was performed using ultrasound guided free-hand placed liquid nitrogen probes (second generation tech-

nique), which has been replaced by thin argon based probes, often placed using a perineal grid (third generation technique). Although argon based cryotherapy has less morbidity (probably related to smaller probes and judicious use of thermocouples), there are no data to our knowledge to show that liquid nitrogen based cryotherapy is less effective than argon. Although argon and liquid nitrogen achieve adequate freezing temperatures, supercooled liquid nitrogen actually has a lower temperature (-209°C) than argon (-187°C).¹⁴ Although most cryotherapists currently use a perineal grid for probe placement, there are no data to show that free-hand cryotherapy has a worse outcome than grid based cryotherapy. Most published series of SCR have few patients treated with argon with more than 5 years of followup. For instance the recent report on salvage cryotherapy outcomes from the Cryo On-Line Data registry included 279 patients treated with argon or nitrogen systems, of which only 47 had a minimum of 5-year followup (most of whom were treated with nitrogen).¹⁵ Of the 279 patients in this report 142 (51%) received hormonal therapy and 5-year bDFS using a nadir plus 2 ng/ml definition was 54.5%. Ng et al reported on 187 patients, 176 of whom were treated with argon and 71% of whom had neoadjuvant hormonal therapy.¹⁶ Using a nadir plus 2 ng/ml definition they reported 5-year bDFS of 56% in patients with pre-salvage PSA less than 4 ng/ml and 29% in those with pre-salvage PSA between 4 and 10 ng/ml. Our study differs significantly from these reports in that none of our patients received hormonal therapy and we used more stringent definitions of biochemical failure. When these important differences are considered the 5-year bDFS in our double freeze-thaw population compares favorably to these reports (24% by the PSA 0.4 ng/ml or greater definition and 47% by the 2 increase definition). Thus, there is no evidence that the efficacy of cryotherapy in our series is artificially low or worse than that of other long-term reports. Until data from argon treated hormone naïve patients mature, facilitating another comparison, SRP should be regarded as having superior bDFS and being the best option for younger patients.

Our study is the first to our knowledge to compare treatment outcomes for patients undergoing salvage therapy for recurrent prostate cancer after radiation stratified by extent of therapy, pre-salvage PSA and tumor grade. Our study convincingly demonstrates superior bDFS for SRP compared to SCT. Physicians should consider patient age, comorbidity, anticipated life expectancy and operative risk in determining which salvage therapy to recommend. We believe that young, healthy patients with recurrent prostate cancer should consider SRP as the option most likely to cure the cancer. Although the number

of patients cured with SCT is lower than that for SRP, older patients, those with significant comorbidity and those unwilling to consider salvage radical prostatectomy may consider SCT as an option that may help control PSA for a period and potentially delay the need for hormonal therapy. We believe that these treatment options are appropriate in different populations of patients with recurrent prostate cancer.

CONCLUSIONS

We conducted a retrospective comparison of SRP compared to SCT stratified by extent of therapy, pre-salvage PSA and tumor grade. Our study demonstrates that SRP results in superior bDFS compared to SCT. SRP is more appropriate for young, healthy patients, whereas SCT may be more appropriate for older patients and those unwilling to undergo SRP.

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EDITORIAL COMMENTS

The authors from 2 centers retrospectively combined data on local salvage therapies for prostate cancer. To address the issue of disparity in data sets strict inclusion criteria were used, resulting in a relatively small number of eligible subjects. Patients who were less robust, and at higher risk for perioperative and postoperative complications with major surgery likely self-selected for salvage cryoablation, partly accounting for the higher noncancer death rate and lower overall survival in this group. The authors provided a plausible explanation for the difference in biochemical disease-free survival based on the mechanism of action of cryoablation. The absence of disease specific survival difference likely was due to a low event rate (prostate cancer related death) to date and the small sample size.

While this report deals with biochemical and survival outcomes, perioperative and postoperative complications as well as quality of life issues (published previously by these authors) need to be considered when discussing salvage treatment modalities. This report should not be viewed as an indictment against salvage cryoablation. It confirms the usefulness of salvage prostatectomy and strengthens the case for individualized salvage therapy for radiation failure based on tumor parameters as well as patient age and comorbidities.

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This is a carefully attempted retrospective study comparing outcomes after 2 different post-radiation salvage methods (radical prostatectomy and cryotherapy) performed at different institutions. To date there have been few large studies directly comparing different salvage modalities. However, the study does have limitations. The authors adjusted for pre-salvage variables such as PSA, grade and stage but were unable to include PSA doubling time and clinical prognostic factors from the original diagnosis. These additional factors clearly influence the success of subsequent salvage attempts.¹ Definitions of biochemical failure are also controversial, particularly after cryotherapy. The differences seen between surgery and cryotherapy appeared to decrease when the now standard double-freeze technique was compared.

We are left to continue the debate regarding which approach is best for patients with recurrent disease after radiation. Other options include salvage brachytherapy² and more experimental approaches such as high intensity focused ultrasound.³ Given the long natural history of the disease observation remains an option for select older patients. Toxicities associated with salvage therapy can also be considerable and need to be carefully considered when counseling patients. These may represent a moving target since radiation dose escalation in the modern era may also increase the morbidity of current attempts at salvage.

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Despite the fact that radiorecurrent prostate cancer can be cured by radical salvage prostatectomy, many physicians rarely move patients beyond mere palliative androgen deprivation therapy which will ultimately result in locally progressive castration resistant disease and which is associated with a high frequency of treatment associated side effects.^{1,2} Although only SRP has been shown to achieve long-term cure rates, few patients have been considered candidates for SRP in the past due to the morbidity reported in earlier series.³ However, morbidity has decreased significantly with modern SRP so that second line radical prostate cancer surgery for apparently organ confined radiorecurrent prostate cancer should be offered SRP by skilled and experienced surgeons.^{4,5}

In this article the benefit of SRP in terms of local cancer control and overall survival becomes evident. The authors compared the oncological efficacy of the 2 established salvage procedures, SRP and salvage cryosurgery, in a cohort of 42 and 56 men, respectively. In both arms of this retrospective study pa-

tients with locally advanced or poorly differentiated disease were excluded from study, pre-radiation and pre-salvage patient characteristics were comparable, and both procedures were performed by experienced surgeons according to modern treatment protocols. After a mean followup of 7.8 and 5.6 years for SRP and SCT, respectively, oncological outcome was significantly superior for SRP in terms of bDFS, as was overall survival with and without adjusting for post-radiation biopsy Gleason sum.

The data of this study emphasize that SRP should be considered the preferred second line local treatment for radiorecurrent PCA in men with organ confined relapse and long life expectancy. The percentage of post-radiation biopsies involved with cancer, PSA doubling time before SRP and the pre-radiation characteristics should be considered when counseling patients for second line local therapy.⁵

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REPLY BY AUTHORS

We agree with the need to individualize salvage therapies and believe that it is best if patients with recurrent prostate cancer after radiation are seen at centers that offer salvage prostatectomy and salvage cryotherapy. Physicians should consider patient age, comorbidity and tumor characteristics, including stage at diagnosis, grade, number of positive biopsy cores, presence or absence of seminal vesicle invasion, pre-salvage PSA and PSA doubling time. Patients need to be well informed of the potential complications of salvage therapy and the differences in efficacy. Although our study suggests that SCT is less effective than SRP, SCT is less invasive and has a shorter convalescence. Our article is not intended as an indictment of salvage cryotherapy. We believe that there is a definite role for SCT as it is best suited for older patients, patients with comorbidity or those who decline surgery.

In terms of long-term efficacy, there are more data to support the use of SRP and SCT than salvage brachytherapy or high intensity focused ultrasound. Although patients may consider brachytherapy or high intensity focused ultrasound, they should be informed that these treatments have less evidence to support their use. They should be re-

garded as experimental and only offered as part of a scientific protocol.

We share the frustration that many patients with locally recurrent prostate cancer following radiation therapy are not offered salvage local treatment. Agarwal et al recently used the CaPSURE® database to evaluate the frequency of salvage therapies in a large community and academic population in the United States.¹ Of 430 patients with disease relapse after radiation therapy 402 (93.5%) received salvage hormonal therapy, an approach that is known to be noncurative. Only 17 men received potentially curative therapy, including 4 (0.9%) who underwent SRP and 13 (3%) who underwent SCT.

Sadly the majority of patients who have disease relapse after initial radiation therapy are being offered noncurative therapies despite the finding that salvage prostatectomy and salvage cryotherapy are safe and effective. Our study suggests that SRP is the most effective salvage modality and less than 1% of patients in the study by Agarwal et al underwent salvage prostatectomy. What can be done to improve this situation? We need to redouble our efforts to educate patients and community physicians on the safety and potential benefits of salvage local therapies.

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