

# Salvage Intensity-Modulated Radiation Therapy for Locally Recurrent Prostate Cancer After Cryotherapy

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## Abstract

**Few data exist regarding irradiation for prostate adenocarcinoma after cryotherapy failure. In this study, we summarized our results of postcryotherapy high-dose intensity-modulated radiotherapy for biochemically recurrent prostate adenocarcinoma. Nine patients were treated to a median dose of 79.2 Gy (range, 72-81 Gy). At a median of 31 months of follow-up, 7 patients experienced biochemical control, and no patients experienced grade 3 or higher toxicities.**

**Background:** To summarize our results of intensity-modulated radiation therapy (IMRT) for prostate adenocarcinoma after cryotherapy failure. **Materials and Methods:** Patients underwent IMRT with curative intent for biochemically recurrent prostate cancer after cryotherapy. Radiation was delivered to a minimum dose of 72 Gy (range, 72-81 Gy). Acute and late treatment-related gastrointestinal and genitourinary effects were scored according to Common Toxicity Criteria version 3.0. Prostate-specific antigen failure was defined by Radiation Therapy Oncology Group-American Society for Therapeutic Radiology and Oncology 2006 consensus definition. **Results:** Nine patients were treated from 2008 to 2010. The median follow-up was 31 months (range, 15-40 months). The mean preradiotherapy prostate-specific antigen was 4.3 ng/mL (range, 1.07-15.6 ng/mL). The median elapsed time between cryotherapy and IMRT was 20.5 months (range, 8.5-56.5 months). Biochemical control was achieved in 7 patients. Two patients developed distant metastases shortly after completion of radiotherapy. No patients experienced grade 3 or higher toxicities. **Conclusions:** Our results suggest that high-dose IMRT after cryotherapy failure is well tolerated, without severe morbidity. The results also showed that IMRT can render a significant number of patients biochemically free of disease after initial cryotherapy. High-dose IMRT should be considered as a treatment option for these potentially salvageable cases.

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## Introduction

The introduction of serum prostate-specific antigen (PSA) as a marker for prostate cancer and its use since the late 1980s has led to

a dramatic increase in the number of newly diagnosed prostate cancers in the United States, with an estimated 217,730 new cases diagnosed in 2010, which account for 28% of new cancer cases in men.<sup>1</sup> The advent of the PSA era also has led to a stage migration toward diagnosis of clinically early-stage disease more likely to be confined to the prostate.<sup>2</sup> For example, the percentage of patients with low-risk disease has risen to 45.3% in 1999-2001 compared with 29.8% in 1989-1992 ( $P < .0001$ ).<sup>3</sup>

Cryotherapy is an option for the primary treatment of localized early-stage prostate adenocarcinoma. Biopsy-proven local recurrence and/or persistence can occur in >20% of patients and PSA failure in >30% at 18 months of follow-up.<sup>4</sup> The therapeutic options for the salvage of cryotherapy failure include repeated cryotherapy, radical prostatectomy, endocrine therapy, and external beam radiotherapy (RT). Repeated cryotherapy has been reported with high complica-

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tion rates.<sup>5</sup> Salvage prostatectomy after complete cryoablation is extremely difficult owing to tissue reaction and fibrosis.<sup>6</sup> Few data exist regarding salvage irradiation dose and its adverse effects.<sup>7-9</sup> We aim to summarize our results of high-dose intensity-modulated RT (IMRT) for prostate adenocarcinoma after cryotherapy failure.

## Materials and Methods

We retrospectively identified all the patients who underwent salvage radiation treatments after cryotherapy failure for prostate adenocarcinoma. All the patients were identified as developing an isolated local recurrence after cryotherapy by a rising PSA level and/or a positive biopsy, with a negative distant metastatic workup. Four patients had biopsy-confirmed local failure. All the patients treated with RT had undergone standard, whole-gland cryoablation as the primary treatment option for localized disease. The cryotherapy was accomplished by using a percutaneous transperineal approach under transrectal ultrasound guidance. Pelvic lymph node sampling for staging purposes was not done.

For radiation planning, computed tomographic simulation and a 3-dimensional (3D) treatment planning system were used to plan delivery of the prescribed dose with a conformal technique. Seven patients received 45 Gy (1.8 Gy per fraction), with 3D conformal radiation with a 4-field technique or IMRT to the prostate, seminal vesicles, and lymph nodes at risk, which was followed by an IMRT boost to a 0.7-cm margin around the prostate and seminal vesicles, to a minimum dose of 79.2 Gy. The median dose delivered with this technique was 79.2 Gy (range, 79.2-81 Gy). Two patients were treated with IMRT for the whole treatment to a total of 72 Gy to a 0.7-cm margin around the prostate and seminal vesicles alone. All the patients were treated under image guidance with weekly portals or, when available, daily cone-beam computed tomography by using implanted prostatic fiducial markers.

The patients were followed-up with routine evaluations, including history, physical examination, and PSA measurement. Risk-group stratification was based on stage, initial PSA value, and Gleason score according to D'Amico et al<sup>10</sup> PSA failure was defined by RTOG-ASTRO (Radiation Therapy Oncology Group–American Society for Radiation Oncology) 2006 consensus definition.<sup>11</sup> Acute and late therapy-related gastrointestinal (GI) and genitourinary (GU) effects were scored according to the Common Toxicity Criteria version 3.0.

## Results

A total of 9 patients were treated from 2008 to 2010. Cryotherapy for these patients was performed between 2005 and 2008. Patient characteristics are summarized in Table 1. The mean age at the time of initial diagnosis was 67 years (range, 49-76 years). The mean precryotherapy Gleason score was 7, and the mean precryotherapy PSA was 8.3 ng/mL (range, 4.6-18 ng/mL). Most patients were intermediate-to-high risk (1 low risk, 5 intermediate risk, and 3 high risk). The median interval between cryotherapy and the initiation of IMRT was 20.5 months (range, 8.5-56.5 months). Four patients had biopsy-confirmed local failure after cryotherapy. The treatment at first recurrence was IMRT in 6 patients and hormonal therapy with IMRT in 3 patients. In 1 patient, 2 cryotherapy procedures failed

**Table 1** Patient Characteristics. Mean ng/mL 4.3

<b>Age, Mean (Range), y</b>	65 (52-82)
<b>Clinical Stage, No. (%)</b>	
T1c	3 (33)
T2a-c	5 (56)
T3	0 (0)
NR	1 (11)
<b>Gleason Grade, No. (%)</b>	
6	3 (33)
7	3 (33)
8-10	3 (33)
<b>Precryotherapy PSA, No. (%)</b>	
<10.0 ng/mL	7 (78)
10.0-20.0 ng/mL	2 (22)
>20.0 ng/mL	0 (0)
<b>Risk Group, No. (%)</b>	
Low	1 (11)
Intermediate	5 (56)
High	3 (33)
<b>Pre-Irradiation PSA, No. (%)</b>	
0-2.5 ng/mL	6 (67)
2.6-5 ng/mL	2 (22)
5.1-10 ng/mL	0 (0)
10.1-20 ng/mL	1 (11)
>20 ng/mL	0 (0)
<b>Interval, Cryotherapy to XRT, Mean (Range), mo</b>	20.5 (8.5-56.5)
<b>ADT, No. (%)</b>	
No	6 (67)
Yes	3 (33)

Abbreviations: ADT = androgen deprivation therapy; NR = not reported; PSA = prostate-specific antigen; XRT = radiotherapy.

before salvage IMRT. The mean PSA value before irradiation was 4.3 ng/mL (range, 1.1-15.6 ng/mL). The median prescribed radiation dose for all the patients was 79.2 Gy.

Of the 3 patients at high risk, 2 had biopsy-confirmed local failure. Two patients received whole-pelvis RT without concurrent hormonal therapy as part of their salvage RT treatment. The third patient with high-risk disease received IMRT to the prostate and/or seminal vesicles without whole-pelvis RT; this was delivered with concurrent hormonal therapy.

The median follow-up was 31 months (range, 15-40 months). No patients experienced grade 3 or higher acute GI or GU symptoms. Most patients developed only mild-to-moderate acute dysuria and urinary frequency during RT. No patient developed significant sub-acute morbidity. No patient experienced grade 3 or higher late GI or GU symptoms. PSA control was achieved in 7 of the 9 patients at the last follow-up. Only 1 of 7 patients who received pelvic lymph node irradiation had biochemical recurrence after salvage RT vs. 1 of 2 patients who did not receive pelvic lymph node irradiation. One

**Table 2** Results From Salvage Radiotherapy, Review of the Literature, Comparison With Series Described in This Article

Study	No. Patients	Mean Precryotherapy PSA, ng/mL	Median Interval From Cryotherapy to RT, mo	Mean Pre-RT PSA, ng/mL	Median Prescribed Dose, Gy	Grade 3 or Higher Toxicity, %	Median Follow-Up, mo	Biochemical Control Rate, %
Burton et al <sup>7</sup>	49	15.7	NR	2.4	64.8	0	32	61
McDonough et al <sup>9</sup>	6	NR	36	2.3	66	1 <sup>a</sup>	34	66
Hepel et al <sup>8</sup>	16	8.7	50	6	73	0	33	75
Our Series	9	8.3	20.5	4.3	79.2	0	31	78

Abbreviations: NR = not reported; PSA = prostate-specific antigen; RT = radiotherapy.

<sup>a</sup>Proctitis, which required blood transfusion and cauterization.

patient who failed had high-risk disease without biopsy-confirmed local recurrence, had a pre-RT PSA of 2.1 ng/mL, and had received whole-pelvis RT as part of his salvage RT treatment without concurrent hormonal therapy. The second patient with failed treatment had intermediate-risk disease, without biopsy-confirmed local recurrence, had a pre-RT PSA of 15.6 ng/mL, and had received IMRT to the prostate and seminal vesicles only with concurrent hormonal therapy.

## Discussion

Cryotherapy is considered as one of the treatment options for patients with localized prostate cancer. The biochemical recurrence rate after primary cryotherapy has been reported at >30%.<sup>4,12</sup> There is controversy as to the best treatment for patients who experience biochemical failure after cryotherapy. The therapeutic options include external beam RT, radical prostatectomy, repeated cryotherapy, endocrine therapy, and watchful waiting, of which the first 3 can be considered curative. Salvage cryotherapy carries the disadvantages of limited efficacy and high morbidity. Koppie et al<sup>13</sup> reported that only 8 of 24 patients who underwent repeated cryotherapy had a favorable PSA outcome. Cox and Crawford<sup>5</sup> found a complication rate of 67% in patients who underwent repeated cryotherapy. Complications included urinary retention (29%), urinary incontinence (27%), and tissue sloughing (19%). Salvage prostatectomy after complete cryoablation is extremely difficult owing to tissue reaction and fibrosis.<sup>6</sup> Grampas et al<sup>14</sup> reported on 6 patients who underwent salvage prostatectomy for cryotherapy failure. Five of the 6 patients were considered to be without evidence of disease after surgery. However, the follow-up period was only 12 months and, therefore, too short to assess the complication or success rates.

We found that postcryotherapy high-dose IMRT is a feasible and safe treatment option. All the patients in our series were identified as developing an isolated local recurrence after cryotherapy. Seven of the 9 patients were biochemical recurrence-free, with a median follow-up of 31 months, which showed oncologic control to be comparable with other potentially curative salvage therapies. Many radiation oncologists are hesitant to recommend high-dose IMRT for cryotherapy failure because of concerns of high complication rates. In our series, there were no grade 3 or higher acute or late GI or GU toxicities. These complication rates are comparable, if not better, than complication rates seen with other salvage therapies.<sup>15-20</sup>

To our knowledge, there are only 3 publications that have reported their postcryotherapy external beam RT experience (see

Table 2).<sup>7-9</sup> Burton et al<sup>7</sup> evaluated 49 patients treated from 1990 to 1999 with salvage radiation after cryotherapy failure. A high proportion of patients were intermediate-to-high risk. The mean precryotherapy PSA value was 15.7 ng/mL. Twenty-five patients were stage T3 or higher. Eleven patients had a Gleason score of 7, and 9 patients had a Gleason score of 8 or higher. RT was delivered by using a 3D conformal technique. Four patients had whole-pelvis RT; 45 received prostate and seminal vesicle irradiation alone. The median prescribed dose was substantially lower than in our series, 64.8 Gy (range, 50.4-68.4 Gy). Biochemical control was achieved in 61% of patients at a median follow-up of 32 months. A dose-response was seen, with improved PSA control with higher radiation doses, 69% (>64 Gy) vs. (52% (<64 Gy) ( $P = .024$ ). No grade 3 or higher toxicities were seen.

McDonough et al<sup>9</sup> reported a series of 6 patients treated from 1993 to 1998. All the patients had biopsy-proven locally recurrent disease. Two patients had a Gleason score of 7, and 1 patient had a Gleason score of 8. RT was delivered by using a 3D conformal technique. All the patients received RT to the prostate and seminal vesicles alone. The median dose was 66 Gy (range, 60-70.2 Gy). Biochemical control was achieved in 66%, at a median follow-up of 34 months. One patient developed grade 3 rectal bleeding that required transfusion and cauterization.

Both of these series showed a low risk of late toxicity when moderate doses of radiation were used. To evaluate the feasibility of >70 Gy salvage irradiation after cryotherapy failure, Hepel et al<sup>8</sup> identified 16 patients treated from 1997 to 2007 with radiation after cryotherapy. Three patients were treated adjuvantly, and 13 patients were treated for local failure. The mean precryotherapy PSA value was 8.7 ng/mL. Eight patients had a Gleason score of 7, and 4 patients had a Gleason score of 8 or higher. RT was delivered by using 3D conformal and IMRT techniques. Most patients had whole-pelvis RT. The median dose was 73 Gy. Biochemical control was achieved in 75%, at a median follow-up of 33 months. No grade 3 or higher toxicities were seen.

In our series, we identified 9 patients treated with salvage radiation after cryotherapy failure. Patient characteristics were comparable with the previously reported series. The mean precryotherapy PSA value was 8.3 ng/mL. Three patients had a Gleason score of 7. Three patients had a Gleason score of 8 or higher. We used IMRT and daily image guidance to dose escalate to a median dose of 79.2 Gy (range, 72-81 Gy). Seven of 9 patients received whole-pelvis RT. Biochem-

ical control was achieved in 78%, and no acute or late toxicities were observed.

Several limitations of our study should be acknowledged. This study was a retrospective observation of a small study population with a short-term follow-up. To fully evaluate long-term GI and GU toxicity outcomes in this population, many more years of follow-up data will be needed. Whereas longer follow-up is necessary before more definite conclusions can be made, these data show that high-dose salvage radiation after cryotherapy failure is well tolerated and can render a significant number of patients biochemically free of disease. Studies such as this one are important to add to the body of literature regarding RT for biochemically recurrent prostate adenocarcinoma after cryotherapy.

## Conclusion

Our preliminary results suggest that high-dose IMRT after cryotherapy failure is well tolerated, without severe acute or late morbidity, and can render a significant number of patients biochemically free of disease after initial cryotherapy. Analysis of our data suggests that some patients with locally recurrence disease may be cured with high-dose IMRT. Pelvic lymph node irradiation was well tolerated and may improve salvage. On the basis of these preliminary results, future trials are needed to establish the long-term efficacy and tolerability of adjuvant high-dose RT for patients with recurrent prostate cancer after cryotherapy.

## Clinical Practice Points

- Biochemical recurrence of prostate adenocarcinoma after primary cryotherapy can occur in up to a third of patients, and therapeutic options for salvage of cryotherapy failure are limited.
- Few data exist regarding irradiation for prostate adenocarcinoma after cryotherapy failure; previous studies of postcryotherapy RT report modest rates of biochemical control at median doses of 64.8–73 Gy.
- In this study, we reported that high-dose postcryotherapy IMRT to a median dose of 79.2 Gy achieved biochemical control in 7 of 9 patients with minimal toxicity.
- Analysis of these preliminary data suggests that high-dose IMRT after cryotherapy failure is well tolerated and can render a significant number of patients biochemically free of disease.
- On the basis of these preliminary results, future trials are needed to establish the long-term efficacy and tolerability of

adjuvant high-dose RT for patients with recurrent prostate cancer after cryotherapy.

## Disclosure

The authors have stated that they have no conflicts of interest.

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