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Original Article

The biochemical efficacy of primary cryoablation combined with prolonged total androgen suppression compared with radiotherapy on high-risk prostate cancer: a 3-year pilot study

Young Hwii Ko[1], Seok Ho Kang[1], Young Je Park[2], Hong Seok Park[1], Du Geon Moon[1], Jeong Gu Lee[1], Duck Ki Yoon[1], Je Jong Kim[1], Jun Cheon[1]

[1]Department of Urology, MIS & Robotic Urologic Surgery Centre, Korea University School of Medicine, Seoul 136-705, Korea
[2]Department of Radiation Oncology, Korea University School of Medicine, Seoul 136-705, Korea

Abstract

To gain beneficial effects in the management of high-risk prostate cancer, an integrated approach that combines local therapy and androgen deprivation therapy (ADT) was used. We compared biochemical responses between primary cryosurgical ablation of the prostate (CSAP) combined with prolonged ADT and radiation combined with ADT, which is the established modality in high-risk disease. A total of 33 high-risk patients received CSAP combined with ADT for 3 months before and up to 24 months after treatment. This patient group was matched with another 33 patients who had undergone three-dimensional conformal radiation therapy (3D-CRT) with the same protocol for ADT. Biochemical recurrence (BCR) was assessed by the American Society for Therapeutic Radiation Oncology (ASTRO) definition, the Phoenix definition and a prostate-specific antigen (PSA) cutoff of 0.5 ng mL^{-1}. Median follow-up was 61.0 ± 11.9 months for the CSAP + ADT group and 86.0 ± 15.8 months for the 3D-CRT + ADT group. In the CSAP group, major complications including rectourethral fistula and incontinence were not noted. In the CSAP + ADT group, 57.0% had BCR using the ASTRO definition, 21.2% using the Phoenix definition and 54.5% using a PSA cutoff of 0.5 ng mL^{-1}. In the 3D-CRT + ADT group, 54.5%, 21.2% and 54.5% had BCR using the ASTRO, Phoenix and PSA definition, respectively. In the CSAP + ADT group, the BCR-free survival (BRFS) was 54 ± 10 months using the ASTRO definition, 65 ± 5 months using the Phoenix definition and 51 ± 4 months using a PSA cutoff of 0.5 ng mL^{-1}. In the 3D-CRT + ADT group, the BRFS was 68 ± 12, 93 ± 19 and 70 ± 18 months using the ASTRO, Phoenix and PSA definition, respectively. By the log-rank test, the BRFS values for each group were not statistically different. This intermediate-term result indicated that primary CSAP combined with prolonged ADT offers a parallel biochemical response compared with radiotherapy in high-risk prostate cancer.

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Keywords: androgen ablation therapy, cryoablation for the prostate, radiotherapy

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1 Introduction

High-risk, localized or locally advanced prostate cancer represents a complex and diverse disease with many available treatment modalities. Although prostatectomy

and radiation represent the two major therapeutic modalities for this patient group, single modality treatment with either surgery or radiation results in a progression-free survival of only about 50% [1]. Thus, an integrated approach that combines both local and various systemic therapies, including chemotherapeutic agents, immune boosters and androgen deprivation therapy (ADT), has been used in an attempt to gain beneficial effects in the management of high-risk prostate cancer [2]. Because the androgen-signalling pathway is integral in prostate cancer progression [3], ADT has been highlighted as an optimal systemic modality. Although the mechanism is not clearly understood, results from several randomized clinical trials for both localized and locally advanced diseases showed that the combination of radiotherapy and ADT consistently resulted in improved disease-free survival and decreased biochemical recurrence (BCR) rate in patients with high prostate-specific antigen (PSA) levels, a high Gleason score or high-volume disease [4–6].

Cryosurgical ablation of the prostate (CSAP), although still investigational, has emerged as a focal tool for the treatment of localized prostate cancer. Compared with conventional surgical removal, CSAP allows for decreased hospitalization time, reduced postoperative morbidity, decreased interval for return to daily activities and reduced overall treatment cost [7–9]. Thus, particularly for patients with advanced age or significant comorbidities who prefer a proactive approach but are not considered good candidates for conventional surgery, CSAP can be an attractive alternative method of treatment. In contrast to radiotherapy, exposure to radiation is not required, and the process is completed in a single session.

Cryosurgical ablation of the prostate with short-term ADT for 3–6 months had been utilized in several series, mainly for the purpose of comparison with radiotherapy [10–12]. However, in terms of ADT in a combination strategy, the method and duration has not been clearly established. As the extension of ADT duration for 24 months in combination with radiotherapy had been proven to result in significant improvement in biochemical response and disease-free survival compared with its short-term counterpart [4], prolonged ADT with CSAP may also lead to a synergistic effect, providing a wider therapeutic territory over which has been directly affected by cryoablation, especially for high-risk patients in whom systemic disease is likely. We present intermediate-term follow-up data comparing

biochemical response between primary CSAP combined with prolonged ADT and radiation with ADT, which is a currently established modality in localized or locally advanced high-risk disease in patients with poor operability. To the best of our knowledge, these data have the longest combination period between these two modalities.

2 Materials and methods

2.1 Patient enrollment and data collection

From December 2003 to December 2006, CSAP was performed on 83 patients with localized or locally advanced prostate cancer. Indications for CSAP were limited to patients over the age of 70 years or those who were at high risk for conventional radical prostatectomy at our institution. High operative risk was defined as an American Society of Anesthesiology (ASA) physical status score over three. Prostate adenocarcinoma was proven histologically through transrectal ultrasound (TRUS)-guided 12 core biopsy that was clinically staged as T1–T3 disease according to the 1992 TNM staging system, on the basis of digital rectal examination and/or TRUS findings. Patients were required to have no evidence of lymphatic or distant metastatic disease by bone scan, computer-assisted tomography or endorectal coil magnetic resonance imaging. Patients who had undergone previous hormone treatment, radiotherapy or any ablative technique were not considered candidates for CSAP.

On the basis of the preoperative Gleason score, serum PSA and clinical stage, patients with high-risk disease were defined by the D'Amico classification scheme (serum PSA over 20 ng mL^{-1}, Gleason score over 8 and/or clinical stage over T2c). The 33 patients who were defined as high risk received ADT as part of maximal androgen blockage; this therapy consisted of a combination of subcutaneous injection of gonadotropin-releasing hormone (GnRH) agonist (leuprolide acetate or goserelin) at an interval of 1 or 3 months and 50 mg of oral bicalutamide, which was administered for 3 months. After cryoablation, patients received adjuvant ADT for up to 24 months. For this patient group (the CSAP + ADT group), perioperative and follow-up data were collected prospectively after approval by the institutional review board.

This patient group was matched with another 33 patients from a preexisting database of the 102 patients who had undergone three-dimensional conformal

radiation therapy (3D-CRT) and ADT using the same protocol. The 3D-CRT has been conducted at our institution since April 2000. All patients who underwent 3D-CRT at our institution were registered in a specific database that included information such as age, clinical stage, Gleason score and serial PSA. A follow-up protocol for 3D-CRT was also constantly adapted to patients with CSAP by the same investigator (J.C.). These allowed us to match the parameters of the CSAP + ADT group against those of the 3D-CRT + ADT group. A match-paired analysis was performed with respect to age, patient ASA score, prostate volume, initial PSA, clinical stage and Gleason score to compare the two groups equally.

None of the patients in this series received a routine follow-up biopsy. Follow-up visits were conducted every 3 months for 2 years and at every 6 months for an additional 3 years, and then annually thereafter.

2.2 CSAP and 3D-CRT technique

The detailed procedure for CSAP was described in our previous reports on prostate cryoablation [8]. It is noteworthy that for TRUS guidance with 17-G cryonee-dles (1.47 mm in diameter; Galil Medical, Westbury, NY, USA), third-generation equipment was used in all patients. Urethral warming and thermosensor monitor-ing was routinely used, and the freezing and thawing cycle was repeated. With the aid of a brachytherapy template, the entire prostate was targeted during the ablation procedure, and focal cryoablation for improve-ment of potency was not attempted in this series. Pelvic lymph node dissection, as an independent staging procedure, was not conducted in any patient.

In 3D-CRT, patients were treated once daily and days per week using a high-energy megavoltage (MV) X-ray over 10 MV. The daily dose was 1.8 Gy for the initial 25 treatments, totaling 45 Gy for the whole pelvis, including the external iliac and obturator node, and 1.8 Gy for the final 9–12 treatments, totaling 16.2–21.6 Gy for the prostate as a boost. Therefore, patients received a total median dose of 65 Gy (range 61.6–66.6 Gy) to the prostate plus a 1.5-cm margin using a four-field 3D-CRT technique. The dose was increased to 70 Gy in 2007 in response to changing standards of practice and introduction of intensity-modulated radia-tion therapy at our institution [13].

2.3 Study end points and statistical analysis

Serum PSA for biochemical assessment and uri-nalysis for urinary tract infection were measured at each follow-up visit, and gastrointestinal, urinary and endocrinological toxicities were assessed. Because survival efficacy requires maturation of data and all pa-tients were followed up for a minimum of 3 years after initial treatment using each modality, the primary end point of this study to evaluate treatment response was BCR at 36 months. Owing to the varying definition of BCR and the lack of an established definition for CSAP, we assessed BCR using three different criteria. The first was the American Society for Therapeutic Radiation Oncology (ASTRO) criteria, which was defined as more than three consecutive increases in serum PSA following nadir. The second was the Phoenix criteria, which was defined as an increase of more than 2 ng mL^{-1} from the nadir level of PSA [14]. The third criterion was defined as an inability to achieve and maintain a PSA value of ≤ 0.5 ng mL^{-1}, which was suggested by Bahn *et al.* [7]. Initiation of other anti-tumor treatments, including the reinitiation of ADT, was considered recurrence, regard-less of PSA response.

All data were entered into the SPSS 12.0 (SPSS Inc., Chicago, IL, USA), and survival curves were estimated using Kaplan–Meier techniques. The Fisher exact test was used to compare the proportion of patients in each treatment arm. All *P*-values were two-sided and $P < 0.05$ were accepted as significant.

3 Results

The pretreatment characteristics of the two treatment groups are summarized in Table 1. The mean initial PSA before ADT was 22.5 ± 15.2 ng mL^{-1} for the CSAP + ADT group and 19.6 ± 16.1 ng mL^{-1} for the 3D-CRT + ADT group. There was no significant difference in age, prostate volume, initial PSA, Gleason score or clinical stage between the two treatment groups. Median follow-up (range) was 61.0 ± 11.9 months (36–73 months) for CSAP and 86.0 ± 15.8 months (59–116 months) for 3D-CRT ($P < 0.001$).

In the CSAP group, 22 patients (66.7%) were over 70 years old, and the mean ASA score was 2.6 ± 0.7 (1–4). A total of 21 patients (63.6%) had an ASA score over three. The mean operative time was 112.8 ± 25.1 min. No one needed a postoperative transfusion, and the mean duration of hospitalization was 3.3 ± 1.3 days (2–4). The peritreatment complications are sum-marized in Table 2. One patient experienced tran-sient urinary retention, and three patients had scrotal

Table 1. Pretreatment characteristics of patients (Mean ± SD).

Characteristics	CSAP + ADT group (n = 33)	3D-CRT + ADT group (n = 33)	*P*-value
Age (years)	69.2 ± 5.6 (60–79)	72.6 ± 5.9 (61–82)	0.10
Prostate volume (cm^3)	29.2 ± 14.0 (14–63)	28.6 ± 7.5 (18–41)	0.86
Initial PSA	22.5 ± 15.2 (5.6–49.3)	19.6 ± 16.1 (4.7–56.2)	0.33
Gleason score (n)			
2–6	8	7	
7	12	14	0.21
8–10	13	12	
Clinical stage (n)			
T2a–b	8	7	
T2c	10	13	0.18
T3a–c	15	13	
Follow-up (months)	61.0 ± 11.9 (36–73)	86.0 ± 15.8 (59–116)	< 0.001

Abbreviations: 3D-CRT, three-dimensional conformal radiation therapy; ADT, androgen deprivation therapy; CSAP, cryosurgical ablation of prostate; PSA, serum prostate-specific antigen.

Table 2. Morbidity and complications occurring in each treatment group.

Adverse events	CSAP + ADT group (%)	3D-CRT + ADT group (%)	*P*-value
Perioperative n (%)	5 (15.2)		—
Transfusion	—	—	
Scrotal swelling	3 (9.1)	—	
Perineal discomfort	2 (6.1)	—	
Urinary n (%)	13 (39.4)	22 (66.7)	0.048
Irritative voiding symptom	11 (33.3)	20 (60.6)	
Transient retention	1 (3.0)	1 (3.0)	
Urinary tract infection	1 (3.0)	2 (6.1)	
Incontinence	—	2 (6.1)	
Rectourethral fistula	—	—	
Gastrointestinal n (%)	11 (21.2)	23 (69.7)	0.006
Diarrhea	3 (9.1)	13 (39.4)	
Constipation	4 (12.1)	5 (15.2)	
Hematochezia	—	1 (3.0)	
Proctalgia	4 (12.1)	11 (33.3)	
Fecal incontinence	—	—	
Hormonal n (%)	5 (15.2)	5 (15.2)	—
Hot flushing	4 (12.1)	5 (15.2)	
Gynecomastia	2 (6.1)	1 (3.0)	

Abbreviations: CSAP, cryosurgical ablation of prostate; ADT, androgen deprivation therapy; 3D-CRT, three-dimensional conformal radiation therapy.

swelling. Most commonly, 11 patients had irritative voiding symptoms, but this usually subsided within a month. Major complications including rectourethral fistula and incontinence were not noted during follow-up. Owing to their old age or comorbidities, most patients (87%) experienced erectile dysfunction preop-

eratively. Induced by concurrent ADT, four patients experienced hot flushes and two patients had gynecomastia, but these were managed conservatively. In the 3D-CRT group, irritative voiding was the most commonly occurring symptom (60.6%). The incidence of urinary and gastrointestinal adverse events was significantly

higher in the 3D-CRT + ADT group (*P* = 0.048 and 0.006, respectively).

The BCR of each treatment group was quite similar (Table 3). A total of 19 patients (57.6%) in the CSAP + ADT group had BCR using the ASTRO definition, seven patients (21.2%) using the Phoenix definition and 18 patients (54.5%) using a PSA cutoff of 0.5 ng mL^{-1}. In the 3D-CRT + ADT group, 18 patients (54.5%), seven patients (21.2%) and 18 patients (54.5%) had BCR using each definition, respectively. At 36 months, although the BCR rate was significantly lower in the CSAP + ADT group using the ASTRO definition(9.1% *vs.* 36.6%, *P* = 0.008), BCR rates using other definitions were similar (*P* = 0.16 and 0.76, respectively).

The Kaplan–Meier survival curves also revealed similarity in BCR-free survival (BRFS). In the CSAP + ADT group, the BRFS was 54 ± 10 months using the ASTRO definition, 65 ± 5 months using the Phoenix definition and 51 ± 4 months using a PSA cutoff of 0.5 ng mL^{-1}. In the 3D-CRT + ADT group, the BRFS was 68 ± 12, 93 ± 19 and 70 ± 18 months, respectively. By log-rank test, the BRFS was not statistically different using each definition (Figure 1). The disease-specific survival and overall survival were also similar in each group.

4 Discussion

Improved screening for prostate cancer has led to a higher incidence of low-stage, low-volume disease in elderly patients with a long list of comorbidities [15]. This shift in demographics has prompted interest in less-aggressive approaches to treatment, including active surveillance and focal cancer ablation. Originally accepted primarily for salvage after local failure of radiation therapy, cryoablation is now used increasingly often as a primary treatment. Results from several large studies have showed that cryoablation of the prostate provides a long-term, durable response with regard to disease control [16]. Recent advances in technology for cryoablation have also produced significant decreases in associated complications and morbidity. Owing to its minimally invasive nature, with the theoretical advantage of being able to freeze beyond the anatomic prostate, the procedure has gained in popularity. However, similar to other monotherapeutic strategies, despite success in disease treatment, prostate cryoablation still yields low, yet significant recurrence rates that are greater for high-risk patients. From the recent largest multicentre study for 1 198 patients with a mean follow-up of 24.4 ± 25.9 months, the 5-year BCR-free rate was 91.1% for low-risk patients using the Phoenix definition. However, for high-risk patients, it was decreased to 62.2% [17].

Thus, to improve this decreased response rate in high-risk patients, we added total androgen ablation therapy to primary cryoablation in a neoadjuvant and adjuvant fashion. Owing to its action of inducing apoptotic cell

Table 3. Results regarding biochemical failure and survival.

	CSAP + ADT group (*n* = 33)	3D-CRT + ADT group (*n* = 33)	*P*-value
BCR rate (%)			
ASTRO definition	57.6	54.5	0.69
Phoenix definition	21.2	21.2	—
PSA (0.5 ng mL^{-1} cutoff)	54.5	54.5	—
BCR rate at 36 months (%)			
ASTRO definition	9.1	36.6	0.008
Phoenix definition	3.0	12.1	0.16
PSA (0.5 ng mL^{-1} cutoff)	33.3	36.6	0.76
BRFS (months) (Mean ± SD)			
ASTRO definition	54 ± 10	68 ± 12	0.79
Phoenix definition	65 ± 5	93 ± 19	0.95
PSA (0.5 ng mL^{-1} cutoff)	51 ± 4	70 ± 18	0.65
Disease-specific survival (%)	97	97	—
Overall survival (%)	88	91	—

Abbreviations: 3D-CRT, three-dimensional conformal radiation therapy; ADT, androgen deprivation therapy; ASTRO, American Society for Therapeutic Radiation Oncology; BCR, biochemical recurrence; BRFS, biochemical recurrence-free survival; CSAP, cryosurgical ablation of prostate; PSA, serum prostate-specific antigen.

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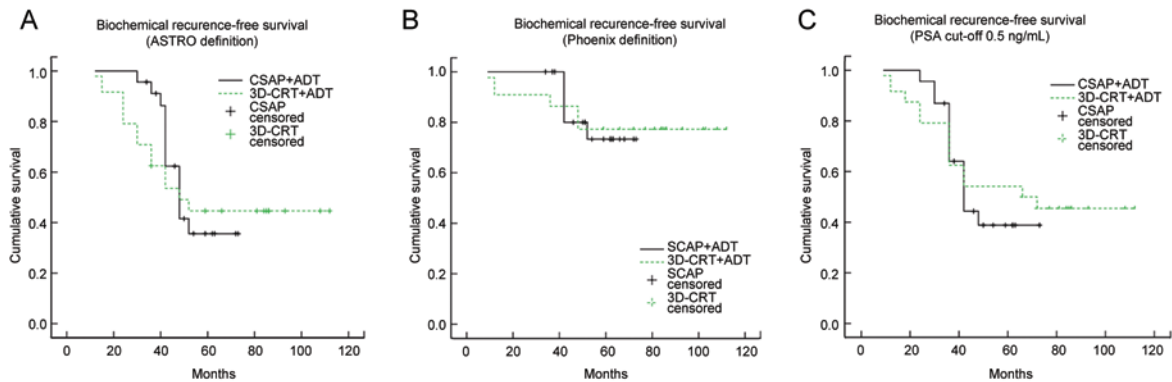Young Hwii Ko *et al*.

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Figure 1. Biochemical recurrence-free survival of cryoablation with hormone therapy versus radiotherapy with hormone therapy, using the American Society for Therapeutic Radiation Oncology (ASTRO) definition (A), Phoenix definition (B) and prostate-specific antigen (PSA) cutoff of 0.5 ng mL^{-1}(C).

death, ADT is a widely utilized therapeutic option for the treatment of prostate cancer [18]; its use as an adjuvant or neoadjuvant modality has already been attempted in many studies with prostatectomy and radiation [19]. In cryoablated lesions, in the central area in which a temperature of –40ºC was achieved, the lesion was rendered completely necrotic; however, in the peripheral lesion, in which the temperature was –5 ºC to –15 ºC, prostate cancer cells were resistant to mild freezing [20]. Inadequate control of the freeze-zone periphery might have a negative effect on tumor control, resulting in BCR. The cellular degradation pattern in this lesion was typically associated with late-stage apoptosis [21]; thus, to improve the efficacy of cryoablation in the peripheral area, it is necessary to enhance cell death. On the basis of these observations, we hypothesized that if apoptosis is initiated by neoadjuvant ADT, this could be enhanced by sub-zero temperatures and freezing. In addition, neoadjuvant ADT may downsize the disease before the ablation procedure, as already shown in combination with prostatectomy [22]. After cryoablation, cells that are resistant to freezing may be continuously affected by adjuvant ADT.

Our data present evidence that cryoablation combined with prolonged ADT can be utilized as a primary treatment tool for high-risk prostate cancer. In this series, because we focused on the high-risk patient group, including localized and locally advanced disease in which systemic disease is likely, all patients had received adjuvant ADT for 24 months after primary CSAP. The theory that these patients eventually fail because they already have local or distant micro-meta-

static disease at the time of diagnosis is the rationale for prolonged neoadjuvant or adjuvant hormone therapy in high-risk patients [12].

Despite short-term use only, this combination was tried in two recent randomized series. For localized disease with a median follow-up of 100 months, Donnelly *et al*. [10] compared cryoablation and radiotherapy, with 122 patients in each treatment arm. Between 62% and 69% of each treatment arm was classified as a high-risk group, which was defined as two or three of the following: PSA ≥ 10 ng mL^{-1}, Gleason score ≥ 7 and clinical stage ≥ T2b. In their series, all patients received neoadjuvant ADT using GnRH agonist monotherapy, with 160 patients monitored for three months and 71 patients for six months. The authors reported similar BCR using the Phoenix definition in both treatments measured at 36 months after initial therapy (17.1% for cryoablation and 13.2% for radiotherapy). Significantly fewer positive biopsies were documented after cryoablation than after radiation therapy (7.7% *vs*. 28.9%). For localized and locally advanced disease (T2c–T3b) with a mean follow-up of 37 months, Chin *et al*. [11] compared 33 patients who underwent cryoablation and 31 patients who received radiotherapy. All patients received three months of neoadjuvant and three months of adjuvant ADT using GnRH agonist monotherapy. In this trial, unlike the results from the trial with localized disease, the BCR rate was higher in the cryoablation group using the ASTRO definition (64% *vs*. 45%) with a short BRFS (28 *vs*. 41 months). However, the difference in these two trials in terms of patient number and enrollment criteria, definition of BCR and follow-up

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duration should be kept in mind. Moreover, as shown in our data, the BCR differed depending on the definition that was chosen, which makes it difficult to directly compare each study outcome.

We recognize that several limitations exist in the current study. For the assessment of primary end point, we used only BCR, and regular prostate biopsies were not performed. Although PSA is a major component of treatment outcome assessment for prostate cancer, biochemical response only represents a single component of treatment outcome, and this should be correlated with posttreatment biopsy status and metastasis-free survival, as well as cause-related death, for full elucidation of therapeutic outcomes. However, considering that progression is relatively slow compared with other solid organ tumors, survival efficacy of prostate cancer in our series requires maturation of data. Actually, in this series, although seven patients died during the follow-up, only two deaths were due to prostate cancer (one each from the CSAP and 3D-CRT arms) and five were due to unrelated causes. Thus, we adopted a surrogate end point of BCR instead of death from prostate cancer or metastatic progression. However, in terms of BCR, in contrast to surgical and radiation therapy, there is no established definition to evaluate efficacy of prostate cryoablation [14]. Although we assessed BCR using the ASTRO and Phoenix definitions, both criteria were originally suggested for the purpose of evaluating the response after radiation therapy. Indeed, even with a fixed point of 36 months, there are significant differences between each BCR definition in our series. Moreover, because this is the retrospective analysis of prospectively collected data from a small number of the patients, these results should be interpreted with care, and we do not conclude that the methods used in our study are superior to the conventional modality. Further studies to elucidate this will be required.

The other major limitation of this investigation is that all patients in both treatment arms had received the same fixed protocol of ADT. To validate the efficacy of prolonged ADT as a combination strategy with CSAP, direct comparison with a CSAP-only group or an ADT-only group would be necessary. However, all patients in this trial were classified as a high-risk group and we think that monotherapy, whether focal or systemic therapy alone, cannot be justified for these patients due to known limitations in response [23, 24]; therefore, we instead compared the efficacy of prolonged ADT with CSAP with radiotherapy with ADT. In addition,

although our results showed a comparable outcome to radiation combined with ADT, the question regarding the proper duration and method of ADT still remains unanswered. Finally, the radiation dose in this series is relatively lower than that which is currently suggested for high-risk prostate cancer. Because a dose–response relationship in the treatment of prostate cancer is now generally accepted, radiotherapy with higher doses may provide potential benefit over CSAP.

We do not think that our current data are sufficient to justify the use of CSAP as a first-line option in high-risk patient groups. However, it is noteworthy that our patient criteria for CSAP were limited to patients with an ASA physical status score over 3 or those over the age of 70 years, leaving cryoablation, rather than surgical resection, as the last surgical treatment option. It is also noteworthy that all procedures were conducted safely with a negligible complication rate for patients with poor operability. In this regard, prostate cryoablation combined with ADT can be perceived as a safer option in certain patient categories of high-risk groups.

The goal of CSAP is to ablate the cancerous portion of the prostate while minimizing damage to noncancerous tissue. Still, the application of cryoablation in prostate cancer is as yet an undeveloped technology; therefore, in both technological and clinical aspects, there is room for additional advancement. In this regard, our data indicate that compared with radiotherapy in high-risk prostate cancer, primary CSAP combined with prolonged ADT offers a parallel biochemical response. Longer studies and more data are needed to establish the durability of these responses.

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