Whole-gland ablation therapy versus active surveillance for low-risk prostate cancer: a prospective study

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Introduction The objective of this study is assess the outcomes of whole-gland ablation (high-intensity focused ultrasound (HIFU), cryotherapy and brachytherapy) and active surveillance (AS) in patients with low-risk prostate cancer (PCa).

Material and methods This prospective non-randomised study included 155 patients with low-risk PCa managed with either ablative therapy or AS. Follow-up included mpMRI, biopsies, prostate-specific antigen (PSA), quality of life and complications for up to 24 months. The primary endpoint was cancer progression. The secondary endpoint was the impact of each treatment on the quality of life.

Results Mean total preoperative PSA was 8.8 ±1.5 ng/ml. Of 155 patients, 125 received treatment: 45 – HIFU; 45 – cryoablation; 35 – brachytherapy. Thirty were under AS. Mean nadir PSA levels were 0.64 ±0.55 ng/ml for HIFU, 0.53 ±0.38 ng/ml for cryoablation and 0.48 ±0.34 ng/ml for brachytherapy. In the AS group, mean PSA was 9.9 ±3.8 ng/ml. Biochemical relapse-free survival rates at 24 months were 81.8% for HIFU, 85% for cryoablation, 93.9% for brachytherapy and 93.3% for AS. In only one HIFU patient relapse was not confirmed on biopsy. Increased anxiety was found in up to 6.7% after treatment and in 36.7% of patients undergoing AS. The Kaplan-Meier analysis revealed no statistical differences between the techniques.

Conclusions Whole-gland ablative therapy can be considered a viable treatment modality for carefully selected patients with low-risk PCa who are reluctant to select AS due to anxiety.
if the neoplasm shows signs of growth [5]. Current American Urological Association guidelines list active surveillance as a primary care option in patients with clinically localized low-risk prostate cancer. Among possible conditional care options are brachytherapy and cryoablation. High-intensity focused ultrasound (HIFU) is considered to be alternative treatment, since it lacks solid evidence of efficacy [6].

A large meta-analysis carried out by Ramsay et al. [7] showed that the oncological efficacy of techniques aimed at preserving the patient’s quality of life was 80–90%. Despite reports considering even minimally invasive surgery as overtreatment [8], there are patients who are dissatisfied with active surveillance. According to Marzouk et al., up to 29% of patients experience anxiety during surveillance, prompting some of them to seek active treatment [9].

The aim of our work was to assess the possible roles of alternative care modalities (cryoablation, brachytherapy, HIFU) in the era of active surveillance for low-risk localized prostate cancer in a single patient population.

**MATERIAL AND METHODS**

**Patient selection**

This prospective observational non-randomized trial included a consecutive cohort of 155 patients with prostate cancer who underwent cryoablation, brachytherapy, HIFU therapy or were under active surveillance. Inclusion criteria were low-risk prostate cancer according to the D’Amico classification (Gleason score $3 + 3 = 6$; PSA $< 10$ ng/ml; T1-T2a), two or less positive cores in one lobe and a prostate volume of $\leq 50$ cc. Exclusion criteria were any prior treatment of the prostate, urethral stricture, bladder neck sclerosis or LUTS (IPSS $<15$, Qmax $<15$).

Prior to making a decision on treatment modality, all of the patients were assessed by the International Prostate Symptom Score (IPSS) and International Index of Erectile Function Questionnaire (IIEF) questionnaires, underwent prostate multiparametric magnetic resonance imaging (mp-MRI) and combined transperineal systematic + MRI fusion biopsy.

**Follow-up and monitoring**

The patients underwent prostate-specific antigen (PSA) tests every 3 months after surgery/beginning of AS. MpMRI was repeated at 12 and 24 months. Repeat combined transperineal systematic + MRI fusion biopsy was employed in cases of biochemical recurrence as defined by Phoenix (nadir + 2 ng/ml) or in cases of lesion progression on prostate mpMRI.

In the AS group, biochemical progression was defined as a two-fold PSA increase from the initial level. All patients, regardless of disease progression, underwent repeat prostate biopsy at 12 and 24 months. Functional parameters (IPSS, IIEF-5) and PSA levels were evaluated at 3, 6, 12, 18 and 24 months after surgery or start of AS. Urinary incontinence rate was assessed with pad-test. At 12 and 24 months, all patients were assessed by the Hospital Anxiety and Depression Scale (HADS) with a threshold of 8 for borderline anxiety/depression and 11 for significant anxiety/depression.

**Decision on treatment modality**

The final decision regarding the optimal treatment option was based on the patient’s data (age, cancer location, prostate volume and whether the patient was interested in preserving potency), capabilities of available methods and tumor characteristics.

Cryoablation was selected for patients with low IIEF-5 not interested in postoperative erectile function. Brachytherapy was favored for apical prostate cancer. HIFU therapy was only considered for posterior prostate cancer. Elderly patients were mostly managed with active surveillance.

**Treatment**

HIFU was performed under US guidance with the Ablatherm HIFU device. All of the other procedures were done under transrectal US guidance (BK Medical FlexFocus 800). For cryoablation we used a third-generation SeedNet Gold system with IceSeed or 17 G IceRod cryoablation needles and a Gaymar warming catheter (for thermal protection of the urethra). For brachytherapy, I-125 Iso seeds with activity of 0.36–0.5 mCi were implanted. The total radiation dose was approx. 140 Gy. All surgeries were performed in accordance with standard protocols.

**Statistical analysis**

For statistical analysis we used IBM SPSS Statistics 23.0. Patient data were expressed as mean $\pm$ standard deviation (minimum, maximum). For comparison of the means, analysis of variance (ANOVA) was used. Confidence intervals of the means were calculated on the basis of Student’s criterion with $p = 0.05$. The significance of the frequency difference was determined using the chi-squared test. Kaplan–Meier survival curves and logrank test...
were employed for survival analysis. A p-value of 0.05 was chosen as a threshold for statistical significance.

**RESULTS**

From 2016 to 2017, 30 patients were managed with active surveillance and 125 patients underwent whole-gland treatment with HIFU (n = 45), cryoablation (n = 45) or brachytherapy (n = 35). Age difference was significant among the groups (p = 0.003), with older patients going for active surveillance. Mean total PSA prior to surgery was 8.8 ±1.5 (range, 4.5–9.8) ng/ml. Mean prostate volume was comparable among the groups – 40.5 ±10.4 (range, 25–50) cc (p >0.05). Voiding parameters (IPSS) and QoL were also similar (p >0.05). Patient data and mean preoperative IIEF-5, IPSS and QoL are given in Table 1.

Nadir PSA levels within 6 months were 0.64 ±0.55 for HIFU, 0.53 ±0.38 for cryoablation and 0.48 ±0.34 for brachytherapy. In the AS group, mean PSA was 9.9 ±3.8 ng/ml with a mean PSA increase of 1.8 ng/ml at 2 years. Biochemical relapse-free survival (bRFS) at 24 months after surgery was 81.8% for HIFU, 85.0% for cryoablation and 93.9% for brachytherapy. In two patients under AS, a two-fold PSA increase was found (6.7%) (Figure 1). The Kaplan-Meier test (Figure 1) revealed no statistically significant differences in survival rates between the groups (Table 2). Repeat combined MRI fusion and systematic biopsy found relapse in 7/45 (15.5%) after HIFU, 5/45 (15%) after cryoablation and 2/35 (6.1%) after brachytherapy; disease upstaging was detected in 2/30 (6.7%) AS patients.

HIFU and cryoablation resulted in a significant change in IPSS with brachytherapy yielding the least significant postoperative IPSS change. IIEF-5 scores decreased both after HIFU and brachytherapy (p <0.001), whereas severe erectile dys-

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**Table 1. Preoperative parameters**

|                      | HIFU (n = 45) | Cryoablation (n = 45) | Brachytherapy (n = 35) | Active surveillance (n = 30) | p      |
|----------------------|---------------|-----------------------|------------------------|-----------------------------|--------|
| Age, years           | 63.9 ±3.7 (48–72) | 64.4 ±3.8 (60–74) | 64.2 ±3.5 (56–70) | 66.2 ±4.0 (63–70) | 0.003* |
| Prostate volume, cc  | 41.6 ±9.1 (26–50) | 41.1 ±9.6 (25–50) | 39.0 ±9.8 (30–50) | 39.0 ±9.8 (27–50) | 0.659  |
| PSA, ng/ml           | 8.7 ±0.9 (5.7–9.8) | 8.6 ±1.2 (4.5–9.5) | 8.4 ±1.5 (4.4–9.8) | 8.8 ±0.8 (6.1–9.6) | 0.351  |
| IIEF-5, score        | 16.4 ±3.5 (9–23) | 11.7 ±3.5 (5–18) | 15.6 ±3.5 (9–23) | 16.6 ±3.9 (9–22) | p <0.001* |
| IPSS, score          | 9.9 ±3.5 (5–15) | 10.8 ±3.3 (4–15) | 9.8 ±3.6 (3–15) | 9.2 ±3.9 (3–14) | 0.311  |
| QoL, score           | 1.9 ±0.8 (1–3) | 2.0 ±0.9 (1–4) | 1.9 ±0.8 (1–3) | 1.9 ±0.7 (1–3) | 0.752  |

Data indicated as mean ±SD (range); *statistically significant difference; HIFU – high-intensity focused ultrasound; PSA – prostate-specific antigen; IIEF – Index of Erectile Function Questionnaire; IPSS – International Prostate Symptom Score; QoL – quality of life

**Table 2. Oncological outcomes**

|                      | HIFU (n = 45) | Cryoablation (n = 45) | Brachytherapy (n = 35) | Active surveillance (n = 30) | p      |
|----------------------|---------------|-----------------------|------------------------|-----------------------------|--------|
| PSA, nadir, ng/ml    | 0.64 ±0.55 (0.2–2.5) | 0.53 ±0.38 (0.1–1.8) | 0.48 ±0.34 (0.1–1.7) | 0.98 ±3.8 (4.5–25.9) | p <0.001* |
| Biochemical recurrence, N (%) | 8 (18.2) | 5 (15.0) | 2 (6.1) | 2 (6.7) | 0.086  |
| Relapse-free survival, N (%) | 7 (15.6) | 5 (15.0) | 2 (6.1) | 2 (6.7) | 0.140  |

*statistically significant difference; HIFU – high-intensity focused ultrasound; PSA – prostate-specific antigen; N (%) – number (percentage)
function was found in 36 (80.0%) patients after cryoablation, with a significant drop in IIEF-5 scores (p <0.001). As for AS, the IPSS score at the initial stage of the study was comparable with IPSS at 24 months of follow-up (p = 0.265), and the IIEF-5 score decreased in most of the patients (p = 0.010). Functional outcomes in all of the groups are given in Table 3. The majority of the patients after cryoablation, HIFU and brachytherapy had normal levels of anxiety according to HADS; only patients with relapses or severe complications reported increased anxiety, whereas in the AS group 11 (36.7%) patients had abnormal anxiety scoring over 8 on HADS (Table 3). At 12 months after surgery, de novo urinary incontinence was observed in 4 (8.9%) patients after brachytherapy, 3 (6.7%) patients after HIFU and 2 (4.4%) patients after cryoablation. One patient (2.2%) developed a rectourethral fistula after cryoablation. The patient complained of marked gross hematuria 3 days after catheter removal. A double-barrel sigmoidostomy was performed. However, subsequent conservative management was ineffective, and the patient underwent a York-Mason repair (parasacrococcygeal transsphteric approach). In 1 month, voiding recovered and the urethral catheter was removed. After this case, rectal irrigation with warm (37–38°C) saline was used during all subsequent cryoablation surgeries [10]. All of the other complications were classified as Clavien-Dindo Grade I (Table 4).

**DISCUSSION**

Our study found that AS and ablative methods yield similar RFS or progression free-survival rates (6.1–15.5% vs. 6.7%). However, AS avoids unnecessary complications which were found in the ablative treatment group (Clavien-Dindo II – 4.2–8.9%; Clavien-Dindo III – 2.2%), whilst leading to significantly higher anxiety levels (2.2–6.7 vs. 36.7%). All ablative techniques were comparable, with brachytherapy showing insignificantly better RFS complication rates.

The current study is one of many proving that AS and active treatment in patients with low-risk pros-

**Table 3. Comparison of functional outcomes at 24 months after surgery or start of AS**

|                      | HIFU (n = 45) | Cryoablation (n = 45) | Brachytherapy (n = 35) | Active surveillance (n = 30) | p      |
|----------------------|--------------|-----------------------|------------------------|-----------------------------|--------|
| Initial IPSS, score  | 9.9 ±3.5 (5–12) | 10.8 ±3.3 (4–12) | 9.8 ±3.6 (3–15) | 9.2 ±3.9 (3–13) | 0.311  |
| IPSS at 6 months, score | 11.7 ±3.3 (5–15) | 12.5 ±3.8 (3–16) | 11.9 ±3.3 (2–13) | 9.4 ±3.3 (3–13) | p <0.001* |
| IPSS at 12 months, score | 10.9 ±3.0 (5–13) | 11.5 ±3.2 (3–15) | 13.4 ±3.1 (2–17) | 9.9 ±3.0 (2–16) | p <0.001* |
| IPSS at 24 months, score | 11.0 ±3.5 (5–14) | 10.5 ±3.2 (3–16) | 11.4 ±3.9 (2–16) | 10.4 ±3.6 (2–18) | p <0.001* |
| p                    | p <0.001*    | p <0.001*            | p <0.001*             | 0.265          |
| Initial IIEF-5, score | 16.4 ±3.5 (9–23) | 11.7 ±3.5 (5–18) | 15.6 ±3.5 (9–23) | 16.6 ±3.9 (9–22) | p <0.001* |
| IIEF-5 at 6 months, score | 8.4 ±3.1 (2–13) | 2.8 ±2.6 (1–6) | 6.6 ±3.4 (6–10) | 15.6 ±3.0 (9–22) | p <0.001* |
| IIEF-5 at 12 months, score | 9.9 ±4.1 (6–15) | 4.1 ±3.1 (1–10) | 9.6 ±3.3 (3–11) | 16.1 ±3.3 (8–20) | p <0.001* |
| IIEF-5 at 24 months, score | 10.4 ±3.1 (6–18) | 4.8 ±2.6 (1–8) | 11.6 ±3.4 (6–15) | 14.2 ±3.7 (8–22) | p <0.001* |
| p (initial vs. 24-mo) | p <0.001*    | p <0.001*            | p <0.001*             | 0.010*         |

Data indicated as mean ±SD (range); *statistically significant difference; HIFU – high-intensity focused ultrasound; IPSS – International Prostate Symptom Score; IIEF – Index of Erectile Function Questionnaire

**Table 4. Postoperative complications**

|                      | HIFU (n = 45) | Cryoablation (n = 45) | Brachytherapy (n = 35) | Active surveillance (n = 30) | p      |
|----------------------|--------------|-----------------------|------------------------|-----------------------------|--------|
| PSA, nadir, ng/ml    | 0.64 ±0.55 (0.2–2.5) | 0.53 ±0.38 (0.1–1.8) | 0.48 ±0.34 (0.1–1.7) | 9.8 ±3.8 (4.5–25.9) | p <0.001 |
| Anxiety (HADS), N (%) | 3 (6.7) | 1 (2.2) | 2 (6.7) | 11 (36.7) | p <0.05* |
| Scrotal edema, N (%) | 12 (21.1%) | 28 (62.2%) | – | – | p <0.001* |
| Stress urinary incontinence, N (%) | 3 (6.7%) | 2 (4.4%) | 4 (8.9%) | – | 0.360 |
| Radiation cystitis, N (%) | – | – | 1 (4.2%) | – | 0.437 |
| Radiation proctitis, N (%) | – | – | 1 (4.2%) | – | 0.437 |
| Rectourethral fistula, N (%) | – | 1 (2.2%) | – | – | 0.562 |

*statistically significant difference; HIFU – high-intensity focused ultrasound; PSA – prostate-specific antigen; HADS – Hospital Anxiety and Depression Scale; N (%) – number (percentage)
tate cancer is likely to have similar progression and relapse rates [11, 12]. And the minimal progression rates of low-risk disease that have led to a shift from radical treatment to active surveillance [13]. However, in most of the trials, AS is compared to radical prostatectomy or radiotherapy, focusing on higher complications rates after surgery [14]. A possible trade-off between radical prostatectomy and AS is ablative therapy, which allows for 80–90% long-term RFS rates and minimum levels of urinary and sexual toxicity [7]. We believe it should be a viable option for anxious patients and those who are unable to undergo AS or may not adhere to all of the required follow-up steps. However, ablative techniques are rather heterogeneous and even have different recommendation grades. Our findings show that all ablative surgeries and AS have similar short-term oncological (bRFS, 81.8–93.9%) and functional outcomes and safety.

We also observed low urinary and sexual toxicity: de novo urinary incontinence was only found in 6.7% of patients in the HIFU group. Published data indicates a rate of 10%. However, with focal HIFU gaining popularity this rate could drop significantly [7]. Cryoablation also proved its safety in terms of urinary toxicity with only 4.4% of patients experiencing de novo incontinence. Similar rates were observed in previous studies – Chiang et al. found that out of 114 patients who underwent cryoablation, 98.4% did not have urinary incontinence at 3 months after surgery [15]. However, sexual toxicity is a well-known side effect of cryoablation [16]. In our study, we only recommended cryoablation for those patients who had already had erectile disorders or were not interested in maintaining potency. According to Bostwick et al., this is the main reason why the majority of surgeons (74.7%) select cryoablation for elderly patients with poor erectile function (IIIEF-5 <12) [17]. Unsurprisingly, we found erectile dysfunction in 86.6% of patients after cryoablation. However, only half of them were potent before the surgery. Brachytherapy led to de novo incontinence in 8.9% of patients, yet it allowed for only minor changes in IIIEF-5 (15.6 prior to ablation vs. 11.6 at 24 months).

The most severe complication was a rectourethral fistula after cryoablation (Clavien-Dindo IIIb). Its reported frequency usually varies from 0% to 0.6% [18] with some authors noting a rate of 6% [19]. In our study, it was observed in one patient (2.2%). It necessitated two additional hospitalizations and extensive rectal wall reconstruction (York-Mason technique).

However, active surveillance is not without its drawbacks. Annual biopsies may trigger increased anxiety and lead to adverse events [20]. According to Marzouk et al., of those patients who will not have any complications, 29% may have increased anxiety and up to 8% might eventually shift to surgery [9]. In fact, Dall’Era et al. faced the same problem while working on their meta-analysis [21]. In 7–13% of cases, patients stop active surveillance and opt for active treatment. These patients with low-risk PCa unwilling to be actively monitored are ideal candidates for minimally invasive prostate cancer treatment [22].

It should be noted that the management strategies differ a lot in terms of the anxiety that they elicit. In our study as many as 36.7% of patients on AS had increased anxiety, while in the ablative group, one patient with a rectourethral fistula after cryoablation reported anxiety at 24 months, and moderate anxiety was found in some of those who experienced de novo urinary incontinence [a total of 8 (6.4%) out of 125 patients]. We did observe a statistically significant difference between these two groups (p <0.001). Patients on AS had high anxiety levels, comparable to those of the patients who had severe surgical complications.

Among other possible advantages, ablative therapies may be considered for intermediate-risk cancer. Musunuru et al. previously showed that patients under active surveillance may have a significantly increased risk of distant metastases [23]. Therefore, recent guidelines of urological associations do not recommend active surveillance as an option for intermediate-risk patients. Oishi et al. in their latest work showed that the RFS rate for intermediate-risk patients undergoing whole-gland cryoablation was 84% at 5 years [24]. A comparative trial on cryoablation and brachytherapy by Gestaut et al. showed 51.4% and 89.7% RFS rates respectively [25]. These facts offer additional proof of ablative surgery potentially becoming a treatment option for intermediate-risk patients. However, in our trial we did not aim at assessing ablation efficacy in patients with different risks. Our goal was to compare the results of AS and ablation.

**Limitations**

This study has several limitations. It is a non-randomized study with a short follow-up and a small number of patients in each group. Given the latest data on efficacy of active surveillance and minimally invasive techniques, as well as differences in survival rates, a follow-up period of 3–5 years would be most adequate. As for group sizes, current preliminary data did not allow us to estimate differences using Kaplan-Meier curves. Further research may
shed some light on potential differences between the treatment options. However, we were aiming to show that whole-gland ablative techniques can be considered a feasible alternative for patients who decline AS. Finally, the choice of ablative modality depended on the patient’s condition and tumor characteristics.

CONCLUSIONS

Whole-gland ablative therapy is an effective treatment option with a low risk of side effects. It could be considered a reasonable choice for carefully selected patients with low-risk localized prostate cancer, reluctant to be under active surveillance. One of the advantages of ablative therapy over AS is lower anxiety among treated patients. However, while disease progression rates after minimally invasive treatment and under active surveillance were comparable at 2 years of follow-up, longer follow-up is needed to draw more reliable conclusions.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

References

1. Tillmann HL, Kaiser T, Fox Z, et al. Impact of coinfection with HIV-1 and GB virus C in patients receiving a ritonavir-boosted HAART regimen: a substudy to the MaxCmin1 trial. Journal of acquired immune deficiency syndromes. 2005; 40: 378-380.
2. Kaprin AD, Starinski VV, Petrova GV. Zlokachestvennyye novoobrazovaniya v Rossi v 2015 godu (zabolovae-most i smertnost). Malignant neoplasms in Russia in 2015 (incidence and mortality). PA Hertsen Moscow Oncology Research Center. 2017; p. 4.
3. Schroder FH, Hugosson J, Roobol MJ, et al. Screening and prostate cancer mortality: results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow-up. Lancet. 2014; 384: 2027-2035.
4. Lu-Yao GL, Albertsen PC, Moore DF, Lin Y, DiPaola RS, Yao SL. Fifteen-year Outcomes Following Conservative Management Among Men Aged 65 Years or Older with Localized Prostate Cancer. Eur Urol. 2015; 68: 805-811.
5. Albertsen PC. Observational studies and the natural history of screen-detected prostate cancer. Curr Opin Urol. 2015; 25: 232-237.
6. Sanda MG, Cadeddu JA, Kirby E, et al. Clinically Localized Prostate Cancer: AUA/ASTRO/SUO Guideline. Part I: Risk Stratification, Shared Decision Making, and Care Options. J Urol. 2018; 199: 683-690.
7. Ramsay CR, Adewuyi TE, Gray J, et al. Ablative therapy for people with localised prostate cancer: a systematic review and economic evaluation. Health Technol Assess. 2015; 19: 1-490.
8. Hamdy FC, Donovan JL, Lane JA, et al. 10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer. N Engl J Med. 2016; 375: 1415-1424.
9. Marzouk K, Assel M, Ehdaihe B, Vickers A. Long-Term Cancer Specific Anxiety in Men Undergoing Active Surveillance of Prostate Cancer: Findings from a Large Prospective Cohort. J Urol. 2018; 200: 1250-1255.
10. Cytron S, Paz A, Kravchick S, Shumalinski D, Moore J. Active rectal wall protection using direct transperineal cryo-needles for histologically proven prostate adenocarcinomas. Eur Urol. 2003; 44: 15-20.
11. Klotz L, Vesprini D, Sethukavalan P, et al. Long-term follow-up of a large active surveillance cohort of patients with prostate cancer. J Clin Oncol. 2015; 33: 272-277.
12. Bokhorst LP, Valdagni R, Rannikko A, et al. A Decade of Active Surveillance in the PRIAS Study: An Update and Evaluation of the Criteria Used to Recommend a Switch to Active Treatment. Eur Urol. 2016; 70: 954-960.
13. Pierorazio PM, Walsh PC, Partin AW, Epstein JI. Prognostic Gleason grade grouping: data based on the modified Gleason scoring system. BJU Int. 2013; 111: 753-760.
14. Sharma V, Wymer KM, Borah BJ, et al. Cost-Effectiveness of Active Surveillance, Radical Prostatectomy and External Beam Radiotherapy for Localized Prostate Cancer: An Analysis of the Protect Trial. J Urol. 2019; 202: 964-972.
15. Chiang PH, Liu YY. Comparisons of oncological and functional outcomes among radical retropubic prostatectomy, high dose rate brachytherapy, cryoablation and high-intensity focused ultrasound for localized prostate cancer. Springerplus. 2016; 5: 1905.
16. Babaian RJ, Donnelly B, Bahn D, et al. Best practice statement on cryosurgery for the treatment of localized prostate cancer. J Urol. 2008; 180: 1993-2004.
17. Bostwick DG, Waters DJ, Farley ER, et al. Group consensus reports from the Consensus Conference on Focal Treatment of Prostatic Carcinoma, Celebration, Florida, February 24, 2006. Urology. 2007; 70 (6 Suppl): 42-44.
18. Bahn DK, Lee F, Badalament R, Kumar A, Greski J, Chernick M. Targeted cryoablation of the prostate: 7-year outcomes in the primary treatment of prostate cancer. Urology. 2002; 60 (2 Suppl 1): 3-11.
19. Mack D, Jungwirth A, Adam U, et al. Long-term follow-up after open perineal cryotherapy in patients with locally confined prostate cancer. Eur Urol. 1997; 32: 129-132.
20. Wade J, Rosario DJ, Macefield RC, et al. Psychological impact of prostate biopsy: physical symptoms, anxiety, and depression. J Clin Oncol. 2013; 31: 4235-4241.
21. Dall’Era MA, Albertsen PC, Bangma C, et al. Active surveillance for prostate cancer: a systematic review of the literature. Eur Urol. 2012; 62: 976-983.
22. Tay KJ, Polascik TJ, Elshafei A, Tsvian E, Jones JS. Propensity Score-Matched
Comparison of Partial to Whole-Gland Cryotherapy for Intermediate-Risk Prostate Cancer: An Analysis of the Cryo On-Line Data Registry Data. J Endourol. 2017; 31: 564-571.

23. Musunuru HB, Yamamoto T, Klotz L, et al. Active Surveillance for Intermediate Risk Prostate Cancer: Survival Outcomes in the Sunnybrook Experience. J Urol. 2016; 196: 1651-1658.

24. Oishi M, Gill IS, Ashrafi AN, et al. Primary Whole-gland Cryoablation for Prostate Cancer: Biochemical Failure and Clinical Recurrence at 5.6 Years of Follow-up. Eur Urol. 2019; 75: 208-214.

25. Gestaut MM, Cai W, Vyas S, et al. Low-Dose-Rate Brachytherapy Versus Cryotherapy in Low- and Intermediate-Risk Prostate Cancer. Int J Radiat Oncol Biol. 2017; 98: 101-107.