MONOGRAPHIC ISSUE: FOCAL THERAPY IN PROSTATE CANCER
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FOCAL CRYOTHERAPY FOR LOCALIZED PROSTATE CANCER

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Summary.- *OBJECTIVE: To systematically review the oncological and functional outcomes of contemporary primary prostate focal cryotherapy for localized prostate cancer in the context of current developments in prostate focal therapy.*

METHODS: We performed a systematic search of the Pubmed, Cochrane and Embase databases to identify studies where primary prostate focal cryotherapy was performed to treat prostate cancer. These included reports on focal/ lesion/ sector ablation, hemi-ablation and partial prostate ablation. We excluded salvage focal therapy studies. Where multiple reports were published over time from a single cohort, the latest one was used.

RESULTS: Our search yielded 290 publications, including 17 primary reports on eight single-center cohort studies and one multi-center registry report. Of 1,595 men identified, mean age was 60.5-69.5 years and mean PSA 5.1-7.8 ng/ml. When stratified by D'Amico risk criteria, 52% of the aggregate total number of men were low-risk, 38% intermediate-risk and 10% high-risk. Besides 12-core TRUS biopsy, 3 cohorts reported using TTMB and one included mpMRI to select men for focal treatment. Median follow-up ranged from 13-63 months. BPFS ranged from 71-98%. The overall post-treatment positive biopsy rate was 8-25%. Among 5 cohorts with a mandatory 6-12 month post-treatment biopsy, 216 of 272 men (79%) did undergo biopsy, with 47 positive (21.8%). Of these, 15 were infield, 26 outfield, 2 bilateral and 4 undeclared. Ten upgraded to Gleason≥7. Overall, two men had metastatic disease and none died of prostate cancer. Post-treatment continence rates were 96-100% and rates of erectile dysfunction ranged from 0-42%. The rate of post-treatment urinary retention ranged from 0-15%. The rate of recto-urethral fistula was 0-0.1%.

CONCLUSION: Focal cryotherapy for localized prostate cancer is a safe and provides good preservation of sexual and urinary function. Accurate cancer localization and risk stratification is key to patient selection. In highly selected patients, focal therapy has good short to medium term oncological efficacy.

Keywords: *Prostate focal therapy. Multiparametric MRI. Ablation. Prostatectomy. Radiation. Biopsy.*

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Resumen.- *OBJETIVO: Revisión sistemática de los resultados oncológicos y funcionales de la crioterapia focal primaria de la próstata contemporánea en el contexto de los desarrollos actuales en terapia focal prostática.*

MÉTODOS: Realizamos una búsqueda sistemática de las bases de datos PubMed, Cochrane y Embase para identificar estudios donde se realizara crioterapia focal primaria prostática para el tratamiento del cáncer de próstata. Éstos incluían comunicaciones de ablación focal/lesional/sectorial, hemiablación y ablación prostática parcial. Excluimos los estudios de terapia focal

de salvamento. En los casos en que había múltiples artículos de una única cohorte publicados en el tiempo se utilizó el último.

RESULTADOS: Nuestra búsqueda obtuvo 290 publicaciones, incluyendo 17 comunicaciones primarias de ocho estudios de cohortes de un único centro y una comunicación de un registro multicéntrico. De 1595 hombres identificados, la edad media era 60,5-69,5años y el PSA medio 5,1-7,8 ng/ml. Estratificando por los criterios de riesgo de D`Amico, el 52% del numero total agregado de hombres eran de bajo riesgo, el 38% de riesgo intermedio y el 10% de alto riesgo.

Aparte de la biopsia transrectal de 12 muestras, 3 cohortes comunicaban la utilización de la biopsia por mapeo transperineal con plantilla y una incluía la RMN multiparamétrica para seleccionar casos para terapia focal. La mediana de seguimiento tenía un rango entre 13-63 meses. La supervivencia libre de progresión bioquímica estaba en un rango del 71 al 98%. La tasa global de biopsia positiva después de tratamiento era del 8-25%. Entre 5 cohortes con una biopsia obligatoria a los 6-12 meses post-tratamiento, 216 de 272 hombres (79%) fueron sometidos a biopsia, con 47 biopsias positivas (21,8%). De éstos, 15 estaban dentro del campo, 26 fuera, 2 bilaterales y 4 no declaradas. 10 casos ascendieron a Gleason≥7. Globalmente, dos hombres tuvieron enfermedad metastática y ninguno murió del cáncer de próstata. Las tasas de continencia post-tratamiento fueron del 96-100% y las de disfunción eréctil en el rango entre 0-42%. Las tasa de retención urinaria post tratamiento estaban en el rango entre 0-15%. La tasa de fístula recto-uretral fue de 0-0,1%.

CONCLUSIÓN: La crioterapia focal para el cáncer de próstata localizado es segura y ofrece una buena preservación de las funciones urinaria y sexual. La localización precisa del cáncer y la estratificación por riesgos son esenciales para la selección del paciente. En pacientes altamente seleccionados la terapia focal tiene una buena eficacia oncológica a corto y medio plazo.

Palabras clave: *Terapia focal prostática. RMN multiparamétrica. Ablación. Prostatectomía. Radiación. Biopsia.*

INTRODUCTION

Localized prostate cancer has traditionally been treated using surgical extirpation or whole-gland irradiation. While both these techniques offer excellent cancer control, post-treatment quality of life is not uncommonly marred by urinary and/or sexual dysfunction because of collateral damage to bowel, the urinary sphincter and/or erectile nerves (1, 2).

At the same time, there is increasing evidence that not all prostate cancer needs to be treated. A randomized trial of radical prostatectomy versus active surveillance showed no overall advantage with radical intervention (the Prostate Intervention Versus Observation Trial, PIVOT) (3). Several large prostate cancer active surveillance series are now ongoing, with the two longest-running cohorts showing a very low rate of metastasis and death from prostate cancer with avoidance of intervention in up to 50 to 60% of men at 10 to 15 years (4, 5).

The interests in maintaining quality of life and the reduction of prostate cancer overtreatment have led to investigators evaluating focal therapy as a tool in the gland-sparing approach to treating prostate cancer (6). The goal of focal therapy for localized prostate cancer is to ablate a specific focus of cancer within the prostate gland while minimizing damage to surrounding structures. In carefully selected men, this may provide the opportunity to eradicate clinically significant prostate cancer while preserving urinary and sexual function. When paired with close monitoring, men with clinically significant disease treated with focal therapy may even be "downgraded" back to the active surveillance pool (7).

Improvements in ablative devices together with advances in prostate imaging allowing for improved diagnosis, accurate image-guided biopsy and image-guided treatment now provide grounds to translate the theoretical concept of focal therapy into reality. Cryotherapy causes cellular death primarily by the formation of lethal intra-cellular ice during the freeze-phase and secondarily, through an inflammatory cascade resulting in cell necrosis during the thaw-phase (8). Third generation cryotherapy probes utilizing argon and helium gas generate ice balls of predictable size and temperature thus allowing the precision required for focal ablation. However, as with other ablative devices now available for treatment of prostate cancer, evidence regarding oncological efficacy and functional outcome remain anecdotal. We aim to systematically review the outcomes of focal prostate cryotherapy in the literature and discuss their results in the context of current developments in focal therapy.

METHODS

We performed a systematic search of the Pubmed, Cochrane and Embase databases to identify studies where primary prostate focal cryotherapy was performed to treat prostate cancer, using combinations of the search terms 'cryotherapy' OR 'cryoablation' OR 'cryosurgical' OR 'partial ablation' OR 'targeted

ablation' OR 'image guided therapy' AND 'prostate'. We excluded salvage focal therapy studies and selected the latest report when multiple reports were published over time from a single cohort. When a full text version of the latest report was available, this was favored over an abstract.

RESULTS

Our search yielded a total of 290 publications, of which 17 primary reports were identified for detailed review. Further analysis identified 8 single-center cohort studies and 1 multi-center registry report from the Cryo On-Line Data (COLD) registry (Ward et al.) on primary focal cryotherapy for in-depth analysis (9-17).

Inclusion Criteria

Of the eight cohorts and one registry, two cohorts were prospectively designed. Both required patients to be re-staged to determine the local extent of disease prior to focal ablation. The Universite Paris-Descartes group (Durand et al.) required all men to have confirmed unilateral Gleason 6 cancer with a minimum 12-core staging TRUS biopsy demonstrating less than a third of cores positive and maximum core involvement less than 50% as well as an mpMRI demonstrating no extra-prostatic extension (11). The University of Colorado group (Barqawi et al.) required men to undergo a staging transperineal template mapping biopsy, enrolling only those with disease less than a maximum clinical stage T2b, Gleason 3+4, maximum 20% total prostate

Table I. Inclusion, selection and follow-up protocols.

Study	Inclusion criteria	Pre-intervention Diagnostic Work-up	Follow-up protocol
Lian et al. 2016	Unilateral cancer PSA<20 1-2 cores <50% involvment Gleason 6-7 cT2b or less	Minimum 12 core biopsy	3 mo 1st yr then 6 mo PSA 12-core TRUS biopsy at 6-12 mo then yearly/ triggered
Durand et al. 2014	PSA <10 Positive cores <33% %core <50 Unilateral Gleason 6 or less	12 core staging TRUS biopsy + mpMRI	3 mo 1st yr then 6 mo PSA 12 core TRUS mandatory at 12 mo
Barqawi et al. 2014	40-85 yrs cT1-T2b Gleason 3+4 or less Less than 50% positive core After TTMB, <20% total prostate, index lesion <5cc, 4 or less zones involved	TTMB	PSA at 3, 6, 12, 18, 24 mo 12 mo mandatory 12 core TRUS biopsy
Hale et al. 2013	Low – intermediate risk	Staging TTMB	3 mo PSA for 2 years then 6 mo Triggered TRUS bx if PSA/DRE abn
Bahn et al. 2012	Unilateral, Gleason 7 or less	TRUS biopsy	3-6 mo PSA 6-12 mo TRUS then yearly
Ward et al. 2011	NR	NR	NR
Truesdale et al. 2010	Unilateral cancer	TRUS biopsy	3, 6 mo serum PSA and every 6 mo after. 12-core TRUS if BCR (Phoenix)/ positive DRE
Onik et al. 2008	Unilateral cancer	TRUS biopsy, restaging TTMB after 2001	3 mo PSA for 2 years then 6 mo Routine biopsy at 1 yr
Ellis et al. 2007	Unilateral, clinical stages T1-T3	NR	3 mo for 1st year then 6 mo PSA Biopsy criteria not defined

TTMB: Trans-perineal Template Mapping Biopsy; NR: Not Reported; TRUS: Trans-rectal ultrasound; mo: month; DRE: digital rectal examination; BCR: Biochemical Recurrence.

involvement, maximum 4 biopsy sector involvement and an index lesion of less than 5 cc (10). In this cohort, investigators specifically wanted to apply focal ablation to the affected sectors rather than hemi-ablation. The rest of the cohorts were of retrospective design and generally included patients with low to intermediate risk disease confined unilaterally, with the aim of treating the cancer with hemi-ablation (Table I). The COLD registry study measured trends in focal cryotherapy adoption and did not define an inclusion criteria with regards to cancer extent (17).

Focal Technique

In six of the eight cohorts, the focal technique applied was transrectal ultrasound guided hemi-ablation. In one cohort (Ellis et al.), a posterior hockey stick technique was used (12). In the last cohort (Barqawi et al.), targeted sectoral ablation of the index lesion was performed, using the assistance of gold fiduciary markers placed at the time of biopsy (10). The COLD registry study reported on all patients undergoing partial prostate ablation and the proportion receiving hemi-ablation or more extensive ablations was not specified (17).

All the cohort reports described the deployment of third generation cryo-ablation techniques, using argon and helium gas-based systems with the standard two freeze-thaw cycles. Onik et al. described the use of three freeze-thaw cycles to a nadir of -20 degrees Celsius where lesions were peri-urethral (15). Seven of the eight cohorts reported the use of thermal probes for temperature monitoring during ablation and six reported the use of urethral warming catheters. The COLD registry study did not report details on the technique of focal cryotherapy (17).

Follow-up Protocol

All eight cohort studies reported follow-up with 3-6 monthly history, physical examination and serum PSA measurements (Table I). Five of the eight cohorts, included a mandatory prostate biopsy at 6-12 months after treatment (9-11, 14, 15). The other three reported that prostate biopsy would be offered in the event of biochemical recurrence. The COLD registry study did not report a detailed follow-up protocol (17).

Table II. Demographics.

Study	N	Mean Age (years)	D'Amico Risk Group	PSA
Lian et al. 2016	41	67	Low risk – 23 (56%) Int. risk – 18 (44%)	Median 7.1
Durand et al. 2014	48	67	All low risk	Mean 6.1
Barqawi et al. 2014	62	60.5	All low risk	Mean 5.1
Hale et al. 2013	26	Median 65	Low risk – 23 (88.5%) Int. risk – 3 (11.5%)	PSA <10 – 24 men PSA 10-20 – 2 men
Bahn et al. 2012	73	Median 64	Low risk 24 (33%) Int. risk 49 (67%)	Median 5.4
Ward et al. 2011	1160	67.8	Low risk 541 (47%) Int. risk 473 (41%) High risk 143 (12%)	NR
Truesdale et al. 2010	77	69.5	Low risk – 44 (57%) Int. risk – 31 (40.3%) High risk – 2 (2.6%)	Median 6.54
Onik et al. 2008	48	NR	Low risk – 23 (48%) Int. risk – 18 (38%) High risk – 7 (14%)	Mean 7.8
Ellis et al. 2007	60	69	Low risk – 40 (66.7%) Int. risk – 14 (23.3%) High risk – 6 (10%)	Mean 7.2

Int.: intermediate; PSA: prostate specific antigen; NR: Not Reported.

Patient Populations

The eight single center cohorts included a total of 435 men. Including the COLD registry report, this amounted to an overall total of 1,595 men undergoing primary focal cryotherapy (Table II). The mean age of the men undergoing treatment ranged from 60.5 to 69.5 years. The mean/median serum PSA ranged from 5.1 to 7.8ng/ml. The mean/ median prostate volumes ranged from 33 to 44.8 ml. When stratified by D'Amico risk criteria, 52% of the aggregate total number of men treated were low-risk, 38% intermediate-risk and 10% high-risk.

Oncological Outcomes

Median follow-up ranged from 13 to 63 months. Biochemical failure using serum PSA was a measured outcome in eight of the nine studies. Of these, three used the ASTRO criteria, three used the Phoenix criteria, one used an increase in serum PSA greater than 0.5 ng/ml over nadir, and another an increase in serum PSA above pre-treatment levels as definitions of biochemical failure. The reported biochemical progression free survival rate ranged from 71 - 98% (Table III).

Repeat prostate biopsy was a measured outcome in all of the nine studies. The overall positive biopsy rate was between 8% and 25%. Among the 5 cohorts with a mandatory 6-12 month TRUS biopsy, 216 of 272 men eventually underwent biopsy, with a positive biopsy rate of 21.8%. Of 47 positive biopsies, 15 were ipsilateral (within the ablative field), 26 contralateral (outside of the ablative field), 2 bilateral and 4 undeclared. Of the 47 positive biopsies, ten upgraded the disease to Gleason 7 or more.

There were no deaths from prostate cancer reported. Two men were presumed to have metastatic disease based on PSA progression with negative prostate biopsy.

Table III. Oncological Outcome.

Study	N	Median follow-up (months)	Biochemical progression definition	BPFS	Biopsy Trigger	Total number biopsied	Biopsy Outcome	Mets.	Death
Lian et al. 2016	41	63	Phoenix	95%	Mandatory	32	7 positive – 2 ipsi. (1 Gl. 7), 5 contra. (2 Gl. 7)	0	0
Durand et al. 2014	48	13.2	Phoenix	98%	Mandatory	46	12 positive - 5 ipsi. (2 Gl. 7), 6 contra (all Gl 6), 1 bilat. (Gl 7)	0	0
Barqawi et al. 2014	62	28	Increase above pre-operative level	71%	Mandatory	62	12 positive - 7 ipsi, 4 contra, 1 bilat. (all Gleason 6) 2 positive – both	NR	NR
Hale et al. 2013	26	19.1	0.5 over nadir	88%	PSA triggered	2	Gl. 6 12 positive - 1 ipsi.	0	0
Bahn et al. 2012	73	44.4	NR	NR 75.7%	Mandatory	48	(Gl. 8), 11 contra. (3 Gl. 7)	0	0
Ward et al. 2011	1160	NR	ASTRO	at 2yr 72.7%	NR	164	43 positive	NR	NR
Truesdale et al. 2010	77	24	Phoenix	92% at 1 yr	PSA triggered	22	10 positive – 2 ipsi, 7 contra, 1 bilat.	NR	0
Onik et al. 2008	48	54	ASTRO	85% absolute	Mandatory	28	4 positive – all contra.	2 (presumed)	0
Ellis et al. 2007	60	15.2	ASTRO	80.4%	PSA triggered	35	14 positive. (13 contra, 1 ipsi)	NR	NR

BPFS: biochemical progression free survival; Mets.:metastasis; ipsi.: ipsilateral; contra.: contralateral; bilat.: bilateral; NR: Not Reported.

Functional Outcomes and Complications

Post-treatment continence rates were reported at 96-100% using various definitions (Table IV). The rates of erectile dysfunction ranged from 0-42% using various definitions. The rate of post-treatment urinary retention ranged from 0 to 15%. The rate of recto-urethral fistula was 0-0.1%.

DISCUSSION

The aim of focal therapy is to reduce the morbidity of prostate cancer treatment while maintaining oncological efficacy. The results of our review suggest that focal cryotherapy is well-tolerated, with a low complication rate and favorable sexual and urinary functional outcomes. In a comprehensive review of prostatectomy outcomes, De Carlo et al. reported a weighted mean 12-month continence rate of 83%, 71% and 93% after open, laparoscopic and robotic radical prostatectomy respectively, using no pads or no leak as an aggregate definition of continence (2). In the same review, the reported rates of erection sufficient for intercourse after open and robotic radical prostatectomy at 12 months were 56% and 61% respectively. After radiation, men are less likely to suffer from incontinence and immediate

Table IV. Complications/Functional Outcomes.

Study	Complication	Definition of Continence	Continence	Definition of Potency	Potency
Lian et al. 2016	Retention 3.4%	No pad	97.6% at 6 weeks (mild incontinence) 100% at 1 year	Ability to have intercourse	76.9% of those previously potent
Durand et al. 2014	Retention 15% Recto-urethral fistula 2% Cavernous corpus necrosis 2% Urethral stenosis 2%	No pad	100%	IIEF	Mild reduction in IIEF at 3 months then back to baseline at 6 months
Barqawi et al. 2014	NR	Not defined AUA SS	100% 1.5 point decrease in AUA SS at 24 mo	IIEF	No change at 24 mo
Hale et al. 2013	4% (1 retention needing TURP), 1 UTI 4% Rash 4% (1)	No pad	100%	Need for assistance/ IIEF	73% needed assistance No impotence
Bahn et al. 2012	Rectal injury - 0%	No pad	100%	Ability to penetrate	74% at 1 yr and 86% in 2.4 yr
Ward et al. 2011	Recto-urethral fistula 0.1%, retention 1.2%	No leak	98.6%	Ability to have intercourse	58.1%
Truesdale et al. 2010	NR	AUA SS	2.5 point decrease in AUA SS at 12 mo	IIEF	1.9 point decrease in IIEF at 12 mo
Onik et al. 2008	NR	No pad	100%	Ability to penetrate	90% of those previously potent
Ellis et al. 2007	Recto-urethral Fistula 0	No leak	96.4%	Ability to have intercourse	61% at 6 mo and 70.6% at 12 mo of those previously potent

IIEF: International Index of Erectile Function; AUA SS: American Urological Association Symptom Score; mo: month; RU: rectal-urethral; NR: Not Reported; TURP: transurethral resection of prostate.

erectile dysfunction than those undergoing radical prostatectomy. However, results from the Prostate Cancer Outcomes Study suggest that these differences are greatest at 2 years and disappear at 5 years of follow-up (18).

Compared to these reported outcomes in the literature, the overall continence rate among the focal cryotherapy studies we reviewed was 96-100%. In five of the single-center cohorts where continence was defined as no use of pads, 100% continence was reported at 12 months. In one single center cohort (Ellis et al.) and the COLD registry report where continence was defined as no leak at all, continence was 96.4% and 98.6% respectively. In the two single-center cohorts where the AUA symptom score was used to define urinary outcomes, a decrease in symptom score of 1.5 to 2.5 points was noted at one year after focal therapy. Among the eight single-center series, erectile function appeared to be related to the extent of gland ablation. Among the six cohorts where hemi-ablation was employed, rates of erectile dysfunction, generally defined as erection insufficient for intercourse, ranged from 0% to 14%. In the cohort (Barqawi et al.) where a sector ablation was performed, no change in post-procedure IIEF was reported. In the cohort (Ellis et al.) where a posterior hockey stick approach was taken with greater potential compromise to both neurovascular bundles, the erectile dysfunction rate was 39% at 6 months and decreased to less than 30% at 12 months. The COLD registry report including all partial prostate ablations reported an erectile dysfunction rate of 41.9%.

Due to the long natural history of prostate cancer, the optimal timing to assess oncological efficacy should be at a minimum of 10 to 15 years follow-up. The longest median follow-up among the 8 single-center cohorts and 1 registry study for primary focal cryotherapy was 63 months. Using serum PSA as a surrogate marker, the overall early to intermediate term oncological control appears acceptable with biochemical progression free rates of 71-98%. However, this is confounded by the extent of gland ablation versus the volume of normal residual PSA-secreting prostate tissue, as well as the definition for biochemical recurrence. The interpretation of oncological outcomes as a whole is hampered by heterogeneity of patient selection resulting from accuracy of initial risk stratification, treatment extent and follow-up protocols.

The cause of oncological failure may be due to ablation failure, whereby cancer recurs within the treated zone, or selection failure, whereby clinically significant cancer exists outside the treated zone but was not detected at the time that focal therapy was chosen as the treatment of choice. Within the subgroup of five studies where mandatory re-biopsy at 6 to 12 months was stipulated, the cumulative positive biopsy rate was 21.8% and more than half of these occurred in the contralateral, untreated, gland. Nearly a quarter of these recurrences were Gleason 7 or greater. This may be considered reasonable given that a third of the cohort in the mandatory re-biopsy subgroup consisted of D'Amico intermediate to high risk patients prior to therapy. One important question that arises in this context is the adequacy of risk stratification and disease localization prior to the use of focal therapy. Among the five studies with mandatory re-biopsy, 12-core TRUS biopsy was used to select men for focal therapy prior to treatment. Traditional 12-core TRUS biopsy is prone to sampling error compared to more thorough transperineal mapping biopsies (19, 20). In men determined to be low-risk by 12-core TRUS biopsy going on active surveillance, up to 28% upgrade at the first 12-18 month re-biopsy (21).

In men thought to have low-risk cancer on TRUS biopsy undergoing radical prostatectomy, the incidence of cancer upgrade was up to 44% (22). Among the five studies with mandatory post-treatment re-biopsy protocols, only one (Barqawi et al.) used staging transperineal template mapping biopsy prior to treatment to select low-volume, single focus low-risk disease. Here, all positive re-biopsies were Gleason 3+3 cancer. It is of no surprise that the more thorough the pre-treatment evaluation when selecting candidates, the less likely one is to find clinically significant prostate cancer in the untreated zone post focal therapy.

The best means of risk stratification remains debatable (23). While it is clear that increasing the number of biopsy cores improves risk stratification, TTMB is usually performed under general anesthesia and is not without risks such as urinary retention (24). Multiparametric MRI (mpMRI) preferentially localizes higher-grade, larger volume disease, and detects extra-prostatic extension (25-27). MRI-TRUS fusion biopsy may be used to better risk stratify a man for focal therapy in the clinic setting (28). At the same time, the use of a targeted approach potentially reduces the number of biopsy cores required to achieve high accuracy in disease characterization. However, high quality mpMRI is highly equipment-dependent and the accuracy of the read may vary with the experience of the radiologist (29, 30). MRI-TRUS fusion biopsy also comprises many moving parts and takes time and experience to master (31). One international consensus group (Donaldson et al., 2015) agreed that a standard 12-core TRUS biopsy with concurring mpMRI findings constituted an adequate pre-intervention diagnostic workup (32). Where

mpMRI is not available, however, the group agreed that a template mapping biopsy should be performed for cancer localization.

Biochemical progression using serum PSA level is well established in the follow-up of prostate cancer after whole gland treatments (33, 34). After radical prostatectomy for localized prostate cancer, serum PSA should be undetectable and recurrence is defined as a PSA>0.2 ng/ ml (35). After radiation, biochemical recurrence was initially defined by the ASTRO criteria of 3 consecutive rises above nadir PSA, and later by the Phoenix criteria of nadir+2ng/ ml (36, 37). In whole gland cryotherapy, biochemical progression using the Phoenix criteria has been established as a valid endpoint (38).

PSA interpretation after focal therapy, however, is confounded by the volume of viable prostate parenchyma that is still PSA producing. The uncertainty regarding a normal post-treatment PSA reading was reflected in authors adopting various standards for biochemical recurrence, including the Phoenix, ASTRO or other self-defined criteria that precludes aggregate interpretation of biochemical progression-free survival outcomes. The heterogeneous extent of ablation among the nine reports further limits meaningful interpretation of biochemical disease-free survival. Unfortunately, even among the five studies with planned mandatory follow-up biopsy, only 79% of men eventually received one.

The findings of our review indicate that primary focal cryotherapy for localized prostate cancer appears to achieve its goals of low morbidity and functional preservation. Within the limits of follow-up, no man died of prostate cancer and the rate of metastatic disease was less than 0.5%. Men who had recurrent disease were not precluded from repeat focal or whole gland treatments including radical prostatectomy. A number of men with residual low-risk disease subsequently went on active surveillance, which highlights the potential role of focal therapy as an "extender" to men who might just fall outside the traditional boundaries of what is acceptable for active surveillance. A randomized trial comparing a hybrid strategy of focal therapy and active surveillance versus intervention would be ideal. However, given the long natural history of prostate cancer, it is unclear whether this will be feasible in the near future.

Ongoing work in defining lethal and metastatic clones as well as better elucidation of molecular risk factors may further enhance patient and lesion selection for focal therapy, as well as inform imaging and biopsy follow-up strategies.

CONCLUSION

Focal cryotherapy is a safe procedure for localized prostate cancer and provides good preservation of sexual and urinary function. Accurate cancer localization and risk stratification is key to patient selection. In highly selected patients, focal therapy has good short to medium term oncological efficacy.

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REFERENCES AND RECOMMENDED READINGS (*of special interest, **of outstanding interest)

1. Ataman F, Zurlo A, Artignan X, van Tienhoven G, Blank LE, Warde P, et al. Late toxicity following conventional radiotherapy for prostate cancer: analysis of the EORTC trial 22863. European Journal of Cancer. 2004;40(11):1674-81.
2. De Carlo F, Celestino F, Verri C, Masedu F, Liberati E, Di Stasi SM. Retropubic, laparoscopic, and robot-assisted radical prostatectomy: surgical, oncological, and functional outcomes: a systematic review. Urol Int. 2014;93(4):373-83.
*3. Wilt TJ, Brawer MK, Jones KM, Barry MJ, Aronson WJ, Fox S, et al. Radical prostatectomy versus observation for localized prostate cancer. N Engl J Med. 2012;367(3):203-13.
*4. Klotz L, Vesprini D, Sethukavalan P, Jethava V, Zhang L, Jain S, et al. Long-term follow-up of a large active surveillance cohort of patients with prostate cancer. J Clin Oncol. 2015;33(3):272-7.
5. Tosoian JJ, Mamawala M, Epstein JI, Landis P, Wolf S, Trock BJ, et al. Intermediate and Longer-Term Outcomes From a Prospective Active-Surveillance Program for Favorable-Risk Prostate Cancer. Journal of Clinical Oncology. 2015;33(30):3379-85.
6. Mouraviev V, Johansen TE, Polascik TJ. Contemporary results of focal therapy for prostate cancer using cryoablation. J Endourol. 2010;24(5):827-34.

7. Tay KJ, Mendez M, Moul JW, Polascik TJ. Active surveillance for prostate cancer: can we modernize contemporary protocols to improve patient selection and outcomes in the focal therapy era? Curr Opin Urol. 2015;25(3):185-90.
**8. Baust JG, Gage AA, Bjerklund Johansen TE, Baust JM. Mechanisms of cryoablation: clinical consequences on malignant tumors. Cryobiology. 2014;68(1):1-11.
*9. Bahn D, de Castro Abreu AL, Gill IS, Hung AJ, Silverman P, Gross ME, et al. Focal cryotherapy for clinically unilateral, low-intermediate risk prostate cancer in 73 men with a median follow-up of 3.7 years. European urology. 2012;62(1):55-63.
*10. Barqawi AB, Stoimenova D, Krughoff K, Eid K, O'Donnell C, Phillips JM, et al. Targeted focal therapy for the management of organ confined prostate cancer. The Journal of urology. 2014;192(3):749-53.
*11. Durand M, Barret E, Galiano M, Rozet F, Sanchez-Salas R, Ahallal Y, et al. Focal cryoablation: a treatment option for unilateral low-risk prostate cancer. BJU international. 2014;113(1):56-64.
*12. Ellis DS, Manny TB, Jr., Rewcastle JC. Focal cryosurgery followed by penile rehabilitation as primary treatment for localized prostate cancer: initial results. European journal of cancer care. 2007;70(6 Suppl):9-15.
*13. Hale Z, Miyake M, Palacios DA, Rosser CJ. Focal cryosurgical ablation of the prostate: a single institute's perspective. BMC urology. 2013;13:2.
*14. Lian H, Zhuang J, Yang R, Qu F, Wang W, Lin T, et al. Focal cryoablation for unilateral low-intermediate-risk prostate cancer: 63-month mean follow-up results of 41 patients. International urology and nephrology. 2015.
*15. Onik G, Vaughan D, Lotenfoe R, Dineen M, Brady J. The "male lumpectomy": focal therapy for prostate cancer using cryoablation results in 48 patients with at least 2-year follow-up. Urologic oncology. 2008;26(5):500-5.
*16. Truesdale MD, Cheetham PJ, Hruby GW, Wenske S, Conforto AK, Cooper AB, et al. An evaluation of patient selection criteria on predicting progression-free survival after primary focal unilateral nerve-sparing cryoablation for prostate cancer: recommendations for follow up. Cancer journal (Sudbury, Mass). 2010;16(5):544-9.
*17. Ward JF, Jones JS. Focal cryotherapy for localized prostate cancer: a report from the national Cryo On-Line Database (COLD) Registry. BJU international. 2012;109(11):1648-54.
18. Resnick MJ, Koyama T, Fan KH, Albertsen PC, Goodman M, Hamilton AS, et al. Long-term functional outcomes after treatment for localized prostate cancer. N Engl J Med. 2013;368(5):436-45.
19. Barzell WE, Melamed MR. Appropriate patient selection in the focal treatment of prostate cancer: the role of transperineal 3-dimensional pathologic mapping of the prostate--a 4-year experience. Urology. 2007;70(6 Suppl):27-35.
20. Tsivian M, Kimura M, Sun L, Mouraviev V, Mayes JM, Polascik TJ. Predicting unilateral prostate cancer on routine diagnostic biopsy: sextant vs extended. BJU international. 2010;105(8):1089-92.
21. Dall'Era MA, Albertsen PC, Bangma C, Carroll PR, Carter HB, Cooperberg MR, et al. Active surveillance for prostate cancer: a systematic review of the literature. Eur Urol. 2012;62(6):976-83.
22. Fu Q, Moul JW, Banez LL, Sun L, Mouraviev V, Xie D, et al. Association between percentage of tumor involvement and Gleason score upgrading in low-risk prostate cancer. Med Oncol. 2012;29(5):3339-44.
23. Tsivian M, Hruza M, Mouraviev V, Rassweiler J, Polascik TJ. Prostate biopsy in selecting candidates for hemiablative focal therapy. Journal of endourology / Endourological Society. 2010;24(5):849-53.
24. Tsivian M, Abern MR, Qi P, Polascik TJ. Short-term functional outcomes and complications associated with transperineal template prostate mapping biopsy. Urology. 2013;82(1):166-70.
25. Arumainayagam N, Ahmed HU, Moore CM, Freeman A, Allen C, Sohaib SA, et al. Multiparametric MR imaging for detection of clinically significant prostate cancer: a validation cohort study with transperineal template prostate mapping as the reference standard. Radiology. 2013;268(3):761-9.
26. Rosenkrantz AB, Mendrinos S, Babb JS, Taneja SS. Prostate cancer foci detected on multiparametric magnetic resonance imaging are histologically distinct from those not detected. J Urol. 2012;187(6):2032-8.
27. Gupta RT, Faridi KF, Singh AA, Passoni NM, Garcia-Reyes K, Madden JF, et al. Comparing 3-T multiparametric MRI and the Partin tables to predict organ-confined prostate cancer after radical prostatectomy. Urol Oncol. 2014;32(8):1292-9.
**28. Siddiqui MM, Rais-Bahrami S, Turkbey B, George AK, Rothwax J, Shakir N, et al. Comparison of MR/ultrasound fusion-guided biopsy with ultrasound-guided biopsy for the diagnosis of prostate cancer. Jama. 2015;313(4):390-7.
**29. Tay KJ, Gupta RT, Brown AF, Silverman RK, Polascik TJ. Defining the Incremental Utility of Prostate Multiparametric Magnetic Resonance Imaging at Standard and Specialized Read in Predicting Extracapsular Extension of Prostate Cancer. Eur Urol. 2015.
30. Garcia-Reyes K, Passoni NM, Palmeri ML, Kauffman CR, Choudhury KR, Polascik TJ, et al. Detection of prostate cancer with multiparame-

tric MRI (mpMRI): effect of dedicated reader education on accuracy and confidence of index and anterior cancer diagnosis. Abdom Imaging. 2015;40(1):134-42.
31. Tay KJ, Gupta RT, Rastinehad AR, Tsivian E, Freedland SJ, Moul JW, et al. Navigating MRI-TRUS fusion biopsy: optimizing the process and avoiding technical pitfalls. Expert Rev Anticancer Ther. 2015.
32. Donaldson IA, Alonzi R, Barratt D, Barret E, Berge V, Bott S, et al. Focal therapy: patients, interventions, and outcomes--a report from a consensus meeting. Eur Urol. 2015;67(4):771-7.
33. Pound CR, Partin AW, Eisenberger MA, Chan DW, Pearson JD, Walsh PC. Natural history of progression after PSA elevation following radical prostatectomy. Jama. 1999;281(17):1591-7.
34. Zumsteg ZS, Spratt DE, Romesser PB, Pei X, Zhang Z, Polkinghorn W, et al. The Natural History and Predictors of Outcome Following Biochemical Relapse in the Dose Escalation Era for Prostate Cancer Patients Undergoing Definitive External Beam Radiotherapy. Eur Urol. 2014.
35. Partin AW, Pound CR, Clemens JQ, Epstein JI, Walsh PC. Serum PSA after anatomic radical prostatectomy. The Johns Hopkins experience after 10 years. Urol Clin North Am. 1993;20(4):713-25.
36. Consensus statement: guidelines for PSA following radiation therapy. American Society for Therapeutic Radiology and Oncology Consensus Panel. Int J Radiat Oncol Biol Phys. 1997;37(5):1035-41.
37. Roach Iii M, Hanks G, Thames Jr H, Schellhammer P, Shipley WU, Sokol GH, et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: Recommendations of the RTOG-ASTRO Phoenix Consensus Conference. International Journal of Radiation Oncology Biology Physics. 2006;65(4):965-74.
38. Levy DA, Ross AE, ElShafei A, Krishnan N, Hatem A, Jones JS. Definition of Biochemical Success Following Primary Whole Gland Prostate Cryoablation. The Journal of Urology. 2014;192(5):1380-4.