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Review

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Magnetic Resonance Imaging-Guided Transurethral Ultrasound Ablation of Prostate Cancer: A Systematic Review

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Abstract

Purpose: MRI-guided transurethral ultrasound ablation (TULSA) uses real-time MR thermometry feedback to target prostate disease. We systematically review the literature to synthesize efficacy, functional, and safety outcomes and assess the influence of planned ablation fraction on outcome.
Materials and Methods: PubMed, Embase, and the Cochrane Library were searched from inception to June 2021 following Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. Studies reporting at least one efficacy, functional, or safety outcome after a single TULSA treatment were included. The relationship of freedom from salvage treatment and potency preservation with planned ablation volume was modeled.
Results: Two hundred twenty-four patients were treated in 10 studies with up to a 5-year follow-up, mainly for primary localized prostate cancer (PCa) plus smaller cohorts with recurrent PCa, and locally advanced PCa (LAPC). The prostate-specific antigen decline from baseline up to 2 years, including focal to whole-gland ablation plans, was 54% to 97%. The rate of salvage treatment after one TULSA treatment for primary PCa was 7% to 17%. Continence and potency preservation were from 92% to 100% and from 75% to 98%. Urinary symptoms were stable in men with good voiding function at baseline, and 85% of men with concurrent PCa and lower urinary tract symptoms met the criteria for improvement. Symptom relief in a small cohort of men with LAPC was observed. Grade III adverse events were incurred by 13/224 men (6%), with no rectal injury/fistula or Grade IV complication. The planned ablation fraction was linearly related to salvage-free survival. The relationship between potency preservation and planned ablation fraction followed a sigmoid curve.
Conclusions: As an alternative to conventional treatments, TULSA is safe and effective for prostate tissue ablation in men with primary PCa. There is also evidence that TULSA delivers effective relief of urinary symptoms while treating PCa in a single, low-morbidity procedure. The likelihood of freedom from additional treatment or potency preservation is associated with the planned ablation fraction.

Keywords: prostate cancer, minimally invasive therapy, MRI-guided therapy, transurethral MRI-guided ultrasound ablation, systematic review

Background

Prostate cancer (PCa) treatment has gone through three distinct phases in the past 30 years. Before adoption of prostate-specific antigen (PSA) screening, men presented with higher stage disease and were managed in a palliative manner with androgen deprivation therapy and surgery or radiotherapy to minimize local morbidity from urethral and ureteral obstruction. Widespread early detection efforts with PSA screening caused a marked increase in the incidence of PCa and a stage migration to organ-confined disease. This second phase was characterized by early radical therapy and,

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in retrospect, overtreatment of clinically insignificant disease. The current phase of PCa treatment attempts to strike a balance between curing or even temporizing significant PCa while minimizing exposure to radical therapy and the associated sexual and urinary morbidity.

Although conventional treatments for PCa including radical prostatectomy (RP) and external beam radiation therapy (EBRT) are effective, many men suffer long-term complications affecting sexual, urinary, and bowel function.[1,2] Salvage treatment options are limited by the incremental toxicity of repeat EBRT and the risks associated with salvage RP.[3] Prostate thermal ablation is therefore emerging as a treatment option that intends to minimize side effects and can be accomplished with a range of energies.[4] One such technique is magnetic resonance imaging-guided transurethral ultrasound ablation (TULSA) (TULSA-PRO®; Profound Medical, Inc., Mississauga, Canada).

The entire TULSA procedure takes place in the MR bore. First, an actively cooled ultrasound applicator (UA) comprising 10 transducer elements is inserted into the urethra. An endorectal device, also actively cooled, is inserted into the rectum to protect the anterior rectal wall. The physician plans and delivers the entire treatment using real-time MR images via the treatment delivery console. The UA is robotically advanced to the physician-prescribed position and the precise target volume is manually contoured on the MR images. The target volume can be drawn to accommodate disease characteristics and patient preferences. Such accommodations may include the choice of focal or whole-gland treatment plans and sparing of functionally important structures such as the neurovascular bundles and urinary sphincter.

Once treatment is initiated, the UA emits planar ultrasound to achieve coagulative necrosis to the capsule. MR thermometry images are acquired and updated every 6 seconds to provide real-time visualization of temperature. Through closed-loop feedback, the rotational motion of the UA and the ultrasound power and frequency emitted independently by the 10 transducer elements are automatically adjusted to match the prescribed treatment plan. Data from the registration study filed by the manufacturer indicate median ultrasound treatment delivery time of 51 minutes for a median of 40 cc target volume. A median of 97.6% of the prescribed prostate volume was heated to an ablative thermal dose with spatial ablation precision of ± 1.4 mm measured on MRI thermometry during treatment.[5]

Our objective is to perform a systematic review of studies investigating TULSA for the treatment of PCa. We identify the PCa disease states or indications that have been treated with TULSA and assess the reported efficacy, functional, and safety outcomes. It is well known that the amount of prostate tissue treated may impact these outcomes. Moreover, the real-time MRI guidance facilitates measurement of the proportion of the gland targeted for ablation as a continuous measure. We therefore also model the impact of the planned ablation fraction (the proportion of the gland targeted for ablation) on efficacy and functional outcomes.

Methods

We performed the review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement,[6] and searched the Embase, PubMed, and Cochrane Library databases with the string: ''transurethral ultrasound'' AND (''MRI'' OR ''magnetic resonance imaging'') AND (''therapy'' OR ''treatment'' OR ''ablation'' OR ''coagulation''). All searches retrieved results from inception up to June 29, 2021. Only studies in English-language journals were included. Review articles, opinion pieces, case reports, technical development, and preclinical studies were excluded.

To generate a pool of studies with homogeneous follow-up times, both initial and follow-up reports were included. If multiple studies on overlapping cohorts reported identical outcomes and follow-up time, we selected the study with the largest sample size. Conference abstracts (and presentations retrieved from conference websites) were included if the cohort, outcomes, and follow-up time were not duplicated in a published article or another conference presentation. Authors were contacted as needed for additional clarification.

The population, intervention, comparator, and outcome elements used to define study eligibility are as follows. The included population is men with PCa. The intervention is the TULSA procedure, without restriction on planned ablation fraction or ablation plan. Studies with or without a comparator arm, and that report at least one efficacy, functional, or safety outcome were included. The risk of bias for each included study was assessed with a modified Delphi quality appraisal tool.[7] This validated tool applied 18 checklist items to each study, grouped into the following categories: objective, population, intervention, cointervention, analysis and outcome measures, results, conclusions, and disclosures.

To describe the study characteristics, the following data were extracted: sample size, design, indication, and follow-up time. The study populations were described at baseline by age, PSA, Grade group, prostate volume, stage, and risk stratification. The following procedural characteristics were extracted for each study: the planned ablation fraction and treatment time. All efficacy, functional, and safety outcomes were extracted after a single TULSA treatment.

Efficacy outcomes were as follows: PSA decline at follow-up relative to baseline to provide a metric for ablation efficacy that may be comparable across PCa indications; the proportion of men receiving salvage treatment, defined as any additional treatment for PCa, including a second TULSA procedure; rates of clinically significant disease on biopsy; rates of positive multiparametric MRI (mpMRI); rates of biochemical recurrence (BCR). Men lost to follow-up or who declined the event (e.g., biopsy) were not included. Biopsy outcome was extracted only for studies with planned biopsy for all patients. For completeness, the efficacy outcomes in any studies without intent-to-treat were extracted, but were not included in the synthesis of results, given a nononcologic treatment plan that is not relevant to clinical practice.

Functional outcomes were the rates of potency and urinary continence preservation and the stability of lower urinary tract symptoms (LUTS) as defined by the International Prostate Symptom Score (IPSS). For potency and continence preservation, defined as preservation of baseline function according to study-specific thresholds, men without function at baseline or who were lost to follow-up were excluded. For cohorts or subgroups with urinary symptoms, the proportion of men meeting the study-specific criterion for urinary symptom improvement was also extracted.

To synthesize safety outcomes for TULSA, the following data were extracted: the frequency of adverse events by grade, the rate of any complications that were reported in more than one study, and the rate of any Grade III or higher complication or rectal injury or fistula. Finally, the duration of catheterization and the proportion of men discharged within the first postoperative day were extracted.

For men treated for primary PCa, we assessed the relationship between planned ablation fraction and both efficacy and functional outcomes. Planned ablation fraction was defined as the proportion of the overall prostate volume targeted for treatment, which could range on a continuous scale from lesion-targeted to whole-gland treatment. Regression analysis was used to develop a model for each of the following outcomes as a function of the planned ablation fraction: salvage-free survival (SFS) or the proportion of patients free from salvage treatment including a second TULSA, and the rate of potency preservation according to study-specific thresholds.

Only studies with intent-to-treat were included in the model for SFS. Confidence intervals were determined using the Clopper–Pearson method. Any planned ablation fraction given as a range was represented by a median value. The relationships between each of SFS and the rate of potency preservation *vs* ablation fraction were also assessed when the ablation fraction was dichotomized as whole-gland or subtotal, by applying a two-proportion z-test (test of equal proportions). Subtotal ablation was defined as the application of any ablation fraction excluding whole-gland. All calculations were performed in R (Version 4.0.3; R Foundation for Statistical Computing, Vienna, Austria) and Microsoft Excel (Version 2110; Microsoft Corporation, Redmond, CA).

Evidence Synthesis and Results

The PRISMA flowchart is shown in Figure 1. A total of 95 unique records were retrieved. After excluding technical development (24), preclinical abstracts (8), case reports (0), review articles or opinion pieces (6), and abstracts that were not relevant (3), 54 full-text articles or conference abstracts were assessed for eligibility. From this subset, 44 articles or abstracts were excluded for the following reasons:

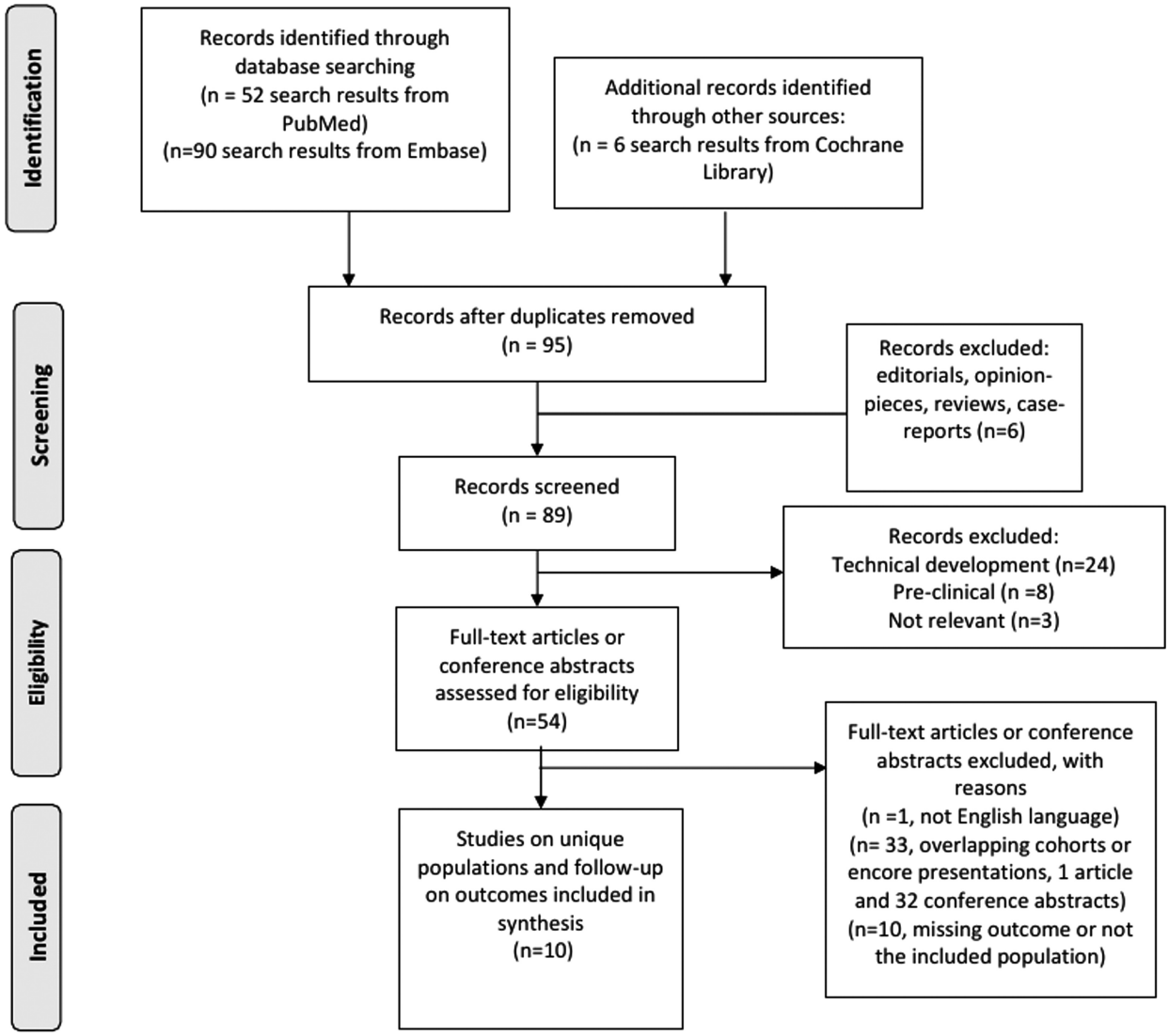

FIG. 1. PRISMA flow diagram. Overview of study selection to meet the inclusion criteria. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

overlapping cohorts with duplicate outcomes and time-to-follow-up or encore presentations (33); missing outcome (e.g., treat-and-resect studies with no clinical outcome) or not the included population (men without cancer) (10); and not English language (1). Ultimately 8 full-text articles and 2 conference abstracts and presentations were included, enrolling 224 unique patients in 7 cohorts across three indications (Table 1).

After applying the risk-of-bias assessment tool, most studies were found to meet the quality statements (Supplementary Table S1). The greatest sources of potential bias were of single-center study design, with patients treated at more than one center in 6/10 studies. For 12/18 questionnaire items, the response for all 10 studies was ''yes.'' Overall, the risk of bias in the 10 included studies was low.

Indications and study characteristics

The following three indications for TULSA were identified: primary localized PCa (198 patients, 4 unique cohorts,),[8–14] salvage treatment for recurrent PCa (16 patients, 2 cohorts),[10,15] and palliation for locally advanced PCa (LAPC) (10 patients, 1 cohort) (Table 1).[16] The LAPC cohort comprised men requiring palliative surgical treatment for urinary retention and gross hematuria. A subgroup of men with primary or recurrent PCa concurrent with LUTS was also identified (2 cohorts, 33 patients).[10,17] Men were followed for relief of LUTS after TULSA treatment for PCa if baseline IPSS ≥12 in one study, and if patients reported LUTS and full work-up confirmed a benign prostatic hyperplasia diagnosis in the other (Table 1).[10,17] In total, 224 men were treated with TULSA.

Study characteristics are detailed in Table 1. Efficacy, functional, and safety outcomes were available for all but one cohort at a median of 12- to 16-month follow-up (interquartile range [IQR] for 16 months: 12–22). One hundred forty-five men were enrolled in studies collecting extended follow-up (2–5 years), with 3- and 5-year follow-up available for 22 and 16 men. Of the 198 men treated for primary PCa, the risk stratification was as follows: 35% ($n=69$) low, 60% ($n=118$) intermediate, 5.6% ($n=11$) high risk. Median age in the LAPC cohort was 76.5 (range: 60–81), and in all other cohorts, the mean or median age was 66 to 71. At baseline, the men in the LAPC study suffered gross hematuria (9/10) and urinary retention requiring continuous catheterization (10/10) due to bladder outlet obstruction.

Thirty-three men with primary or recurrent PCa also had LUTS. Ablation fractions ranged from focal (12% ablation fraction) to whole-gland (98%), and the median ablation time ranged from 17 minutes (focal) to 51 minutes (whole-gland). Median (IQR) overall in-bore time was 117 (82–115) minutes for focal ablation and 243 (201–281) minutes for whole-gland ablation (MRI to recovery). The mean or median prostate volume treated for primary PCa was 37 to 60 mL (Table 1). All 10 studies reported outcomes after a single TULSA treatment, with 9/10 studies reporting on prospective cohorts.

Efficacy outcomes

Efficacy outcomes following one TULSA treatment are summarized in Table 2. The PSA decline from baseline to 1 to 2 years for all included studies with the PSA supplied at follow-up and including all ablation fractions was from 54% to 97% (Table 2). At a 5-year follow-up, the PSA decline was 89%,[13] while the early decline in PSA at 3 weeks after treatment was 34%.[14]

The proportion of men receiving salvage treatment by median of 16 to 24 months after a single TULSA treatment for primary PCa ranged from 7% to 17%.[8–10] The lower bound of the range was derived from whole-gland ablation plans at 24-month follow-up. There were two intent-to-treat cohorts including men with primary PCa: a prospective pivotal study with a 2-year follow-up ($n=115$),[8,9] and a retrospective clinical service report ($n=47$), with follow-up at a median (IQR) of 16 (12–22) months.[10]

Feasibility was also assessed in a prospective Phase I study ($n=30$)[11] with up to 5-year follow-up.[12,13] However, a non-oncologic treatment plan was applied and the intent of the study was to assess the feasibility and not to achieve definitive treatment. Therefore, the rates of salvage treatment, clinically significant disease, MRI recurrence, and BCR from the Phase I study were not included in the present synthesis. An additional six men were treated for primary PCa in a treat-and-resect study, which yielded only functional and safety outcomes at 3 weeks post-TULSA.[14]

For primary PCa, only the pivotal study incorporated an oncologic treatment plan and per-protocol biopsy. A 21% rate of clinically significant disease was reported on a 1-year, 10-core systematic, transrectal ultrasound-guided biopsy, with 7% of men proceeding to salvage treatment by 2 years.[8,9] In the clinical service report, men received biopsy as clinically indicated. Overall, 14/52 men (27%) in that report had a positive finding on MRI at follow-up, and 9/52 (17%) were biopsied. A systematic 10-core biopsy including 1 to 2 cores for any MRI-visible targets was performed in-bore. All 9 biopsies were positive, and of the 47 men treated for primary PCa, 8 (17%) went on to receive salvage treatment.[10]

The result from the regression analysis for SFS is shown in Figure 2A. After a single TULSA treatment for primary PCa, the variation in SFS over planned ablation fraction was explained by a weighted linear regression model with $R^2=0.92$. The difference in SFS between men treated with whole-gland *vs* subtotal ablation was significant ($p=0.02$).

Sixteen men received TULSA for recurrent PCa, between a prospective cohort of 11 men with radiorecurrent disease[15] and a retrospective cohort of 5 men with recurrence after high-intensity focused ultrasound (HIFU) (2), laser and HIFU (1), EBRT (1), and hyperthermia (1) (Table 2).[10] At a median of 12- to 16-month follow-up, 2/16 (12%) men experienced BCR and 3/16 (19%) had a positive mpMRI. Two of these three men, and another two men with negative BCR and mpMRI findings but whose recurrence was detected only on per-protocol PSMA-PET imaging, received salvage treatment after TULSA resulting in a 4/16 (25%) pooled rate of salvage treatment after one TULSA procedure for recurrent PCa.

Functional outcomes

Functional outcomes as defined in Table 3 were assessed with validated questionnaires, or by the surgeon in one report. Continence and potency preservation were assessed for 192 men treated for primary PCa at a median of 12 to 16 months (Table 3).[8,10,11] At baseline, 153/192 (80%) and 189/192

Table 1. Summary of the 10 Included Studies with Baseline Characteristics, Indication, and Treatment Parameters (Planned Ablation Fraction and Treatment Time)

Study (N)	*Design*	*Indication*	*FU (months)*	*Age (years)*	*BL PSA (ng/mL)*	*BL ISUP Grade Group (GG)*	*BL prostate volume (mL or cm^3)*	*Stage*[a]	*Risk stratification*	*Planned ablation fraction and treatment time (minutes)*[b]
Klotz[8] (*N*=115)	Pivotal study, prospective multicenter	Primary, localized PCa	12	65.9 (59–69)	6.3 (4.6–7.9)	GG1: Low-vol: 17/115 (15%) GG1: High-vol: 26/115 (23%) GG2: 69/115 (60%) GG3: 3/115 (2.6%)	37 (27–48) Max: 125	T1c: 89/115 (77%) T2a: 20/115 (17%) T2b: 1/115 (0.9%) T2: 5/115 (4.3%)	(NCCN) Low: 33% (38/115) Int: 67% (77/115)	Whole-gland, 98% of prostate sparing urethra and 3 mm at apex 51 (39–66). Range: 21–112
Eggener[9]	Pivotal study 2-year FU[c]		24							
Lumiani[10] (*N*=52)	Clinical service report, retrospective single-center	Primary, localized PCa: (47/52) Recurrent PCa: (5/52)	16 (12–22) Median (IQR)	Primary: 68 (63–76) Recurrent: 71 (67–75)	Primary: 8.3 (5.0–12) Recurrent: 7.0 (6.1–8.0)	Primary: GG1: 10/47 (21%) GG2: 27/47 (57%) GG3: 4/47 (8.5%) GG4: 2/47 (4.3%) GG5: 4/47 (8.5%) Recurrent: GG2: 2/5 (40%) GG3: 1/5 (20%) GG4: 1/5 (20%) GG5: 1/5 (20%)	40 (30–59)	Primary: T2a: 14/47 (30%) T2b: 18/47 (38%) T2c: 14/47 (30%) T2cN1: 1/47 (2.1%) Recurrent: T2b: 1/5 (20%) T2c: 3/5 (60%) T3a: 1/5 (20%)	(D′ Amico) Primary: Low: 15% (7/47) Int: 68% (32/47) High: 17% (8/47) Recurrent: Low: 0% (0/5) Int:60% (3/5) High: 40% (2/5)	Primary: <50% of gland: 17/47 (36%) >50 and <75%: 12/47 (26%) >75% and <100%:9/47 (19%) Whole-gland: 9/47 (19%) Recurrent: <50% of gland: 0/5 (0%) >50% and <75%: 3/5 (60%) >75% and <100%: 0/5 (0%) Whole-gland: 2/5 (40%)
		PCa and BPH subgroup: (24/52)		69.8 ± 8.4 Mean ± SD	8.4 (5.3–15)	N/A	57 ± 24 Mean ± SD Range: 23–122[d]	N/A	N/A	Treat PCa and debulk TZ and/or treat obstruction in bladder neck
Chin[11] (*N*=30)	Phase I safety and feasibility, prospective multicenter	Primary, localized PCa, without intent-to-treat	12	69 (67–71)	5.8 (3.8–8.0)	GG1: 24/30 (80%) GG2: 6/30 (20%)	44 (38–48)[d] 48 (21–95) Mean (range)	T1c: 30/30 (100%)	(D′ Amico) Low: 80% (24/30) Int: 20% (6/30)	Conservative whole-gland ablation with 3 mm safety margin from the outer prostate boundary corresponding to 90% of prostate 36 (26–44)
Nair[12] (*N*=22)	Phase I 3-year FU		36							
Nair[13] (*N*=16)	Phase I 5-year FU[c]		60							
Elterman[17] (*N*=9)	Phase I retrospective analysis of subgroup with BPH	PCa and BPH subgroup (IPSS≥12)	12	70 ± 2.9 Mean ± SD	5.9 ± 2.2 Mean ± SD	N/A	54.0 ± 23.2 Mean ± SD Max: 96.7 Range: 26.9–96.7[d]	N/A	N/A	

(*continued*)

Table 1. (Continued)

Study (N)	*Design*	*Indication*	*FU (months)*	*Age (years)*	*BL PSA (ng/mL)*	*BL ISUP Grade Group (GG)*	*BL prostate volume (mL or cm^3)*	*Stage*[a]	*Risk stratification*	*Planned ablation fraction and treatment time (minutes)*[b]
Anttinen[14] (*N* = 6)	Treat-and-resect, prospective single-center feasibility study	Primary, localized PCa	3 weeks	70 (67–70) Range: (42–84)	8.9 (7.6–12)	GG1: 1/6 (17%) GG2: 2/6 (33%) GG3: 2/6 (33%) GG4: 1/6 (17%)	60 (52–65) Range: (42–82)	T2: 4/6 (67%) T3: 2/6 (33%)	(EAU) Int: 3/6 High: 3/6	Focal plus 5 mm margin, and 3 mm margin near NVB. 12%–34% 17 (13–22). Range: 11–52
Anttinen[15] (*N* = 11)	Prospective single-center safety and efficacy study	Radiorecurrent PCa	12	69 (68–74)	7.6 (4.9–10)	GG2: 0/10 (0%) GG3: 5/10 (50%) GG4: 2/10 (20%) GG5: 3/10 (30%)	21 (18–24)	T2a: 1/11 (9.1%) T2b: 4/11 (36%) T2c: 5/11 (45%) N/A: 1/11 (9.1%)	N/A	25% of gland: 1/11 (9.1%) 50%: 4/11 (36%) 75%: 3/11 (27%) Whole-gland: 3/11 (27%) 49 (39–50)
Anttinen[16] (*N* = 10)	Prospective, single-center safety and efficacy study	Locally advanced PCa, palliative intent	12 (10–12) Median (IQR)	76.5 (60–81) Median (range)	18.5 (0.23–140) Median (range)	N/A	35 (12–213) Median (range)	T3: 5/10 (50%) T4: 5/10 (50%) Bladder invasion: 4/10 Metastases: 8/10	N/A	Target tumor compressing and/or invading prostatic urethra, tissue obstructing bladder neck; debulking 37 (16–58) mean (range)

The median and IQR are listed for age, BL PSA, BL prostate volume, and treatment time unless otherwise specified.

[a]Pivotal and Phase I studies report clinical stage, while the radiologic stage is listed for the other studies.

[b]For Lumiani et al.,[10] the treatment time is 36 (26–49) minutes for all 52 men. For Anttinen et al.,[14] the ablation fraction was computed for each patient from the published data as: target volume on treatment planning/prostate volume on BL MRI × 100%.

[c]Conference presentation plus additional updates from authors.

[d]Additional data supplied by authors.

BL = baseline; BPH = benign prostatic hyperplasia; EAU = European Association of Urology; FU = follow-up; IPSS = International Prostate Symptom Score; IQR = interquartile range; ISUP = International Society of Urological Pathology; NCCN = National Comprehensive Cancer Network; NVB = neurovascular bundles; PCa = prostate cancer; PSA = prostate-specific antigen; SD = standard deviation; TZ = transition zone.

Table 2. Summary of Efficacy Outcomes After a Single Transurethral Ultrasound Ablation Procedure

Study	*Prior PCa treatment(s)*	*FU at (months)*	*Salvage treatment for PCa*	*Clinically significant PCa on biopsy*	*Clinically significant PCa definition*	*MRI recurrence*	*Biochemical recurrence (Phoenix)*	*PSA decline from BL*
Klotz[8]	None (115/115)	12	8/115 (7.0%)	23/111 (21%)	High-volume GG1 (≥3 positive cores or ≥50% per core), or any GG2	31/104 (30%) PI-RADS v2 ≥ 3	3/115 (2.6%)	BL = 6.3 (4.6–7.9) FU = 0.5 (0.3–1.2) Δ = 92%
Eggener[9,c]		24	8/115 (7.0%)	N/A		N/A	N/A	BL = 6.3 (4.6–7.9) FU = 0.7 Δ = 89%
Lumiani[10]	Primary PCa (47/52): None		8/47 (17%)	N/A		12/47 (26%)	8/46 (17%)	BL = 8.3 (5.0–12)
	Recurrent PCa (5/52): 3/5 HIFU[b] 1/5 laser 1/5 EBRT 1/5 hyperthermia	16 (12–22) Median (IQR)	2/5 (40%)	N/A		2/5 (40%) "positive mpMRI"	1/5 (20%)	FU = 1.8 (1.0–3.1)[a] Δ = 78% BL = 7.0 (6.1–8.0) FU = 3.2 (0.5–4.0)[a] Δ = 54%
Chin[11]	None (30/30)	12	2/30 (6.7%)	9/29 (31%) (no intent-to-treat)	GG1 > 10 mm, GG2 > 3 mm, any GG3+ or increased total core length from BL biopsy	N/A	1/30 (3.3%)	BL = 5.8 (3.8–8.0) FU = 0.8 (0.6–1.1) Δ = 86%
Nair 2020[12]		36	9/30 (30%)	2/19 (10%): 1/19 *de novo*, 1/19 persistent (no intent-to-treat)			8/30 (27%)	BL = 5.8 (3.8–8.0) FU = 0.8 (0.4–1.6) Δ = 86%
Nair 2020[c,13]		60	10/30 (33%)	N/A	N/A		10/30 (33%)	BL = 5.8 (3.8–8.0) FU = 0.6 (0.4–1.2) Δ = 89%
Elterman[17]	None (9/9)	12	N/A	N/A	N/A	N/A	N/A	BL = 5.9 ± 2.2 FU = 1.0 ± 0.6 Δ = 84%
Anttinen[14]	None	3 weeks	N/A	N/A	N/A	N/A	N/A	BL = 8.9 FU = 5.8 Δ = 34%
Anttinen[15]	10/11 EBRT 1/11 HDR brachy 4/11 ADT		2/11 (18%)	3/10 (30%)	GG1 > 4 mm or GG ≥2	1/11 (9.1%) Likert 5	1/11 (9.1%)	BL = 7.6 (4.9–10) FU = 0.2 (0.2–0.9) Δ = 97%
Anttinen[16]	6/10 EBRT and 2–3 years ADT 4/10 ADT 3/10 pTURP	12 (10–12) Median (IQR)	N/A	N/A	N/A	N/A	N/A	BL = 18.5 (0.23–140) (range) FU = N/A

Δ is defined as the percentage change in PSA at FU relative to BL reporting the median (IQR) for the latter two quantities unless otherwise noted.

[a]Additional data supplied by authors.

[b]One patient received laser and HIFU before the TULSA procedure.

[c]Conference presentation.

ADT = androgen deprivation therapy; BL = baseline; EBRT = external beam radiation therapy; GG = Grade Group; HDR brachy = high dose-rate brachytherapy; HIFU = high-intensity focused ultrasound; mpMRI = multiparametric magnetic resonance imaging; PI-RADS v2 = Prostate Imaging Reporting and Data System Version; pTURP = palliative transurethral resection of the prostate; TULSA = transurethral ultrasound ablation.

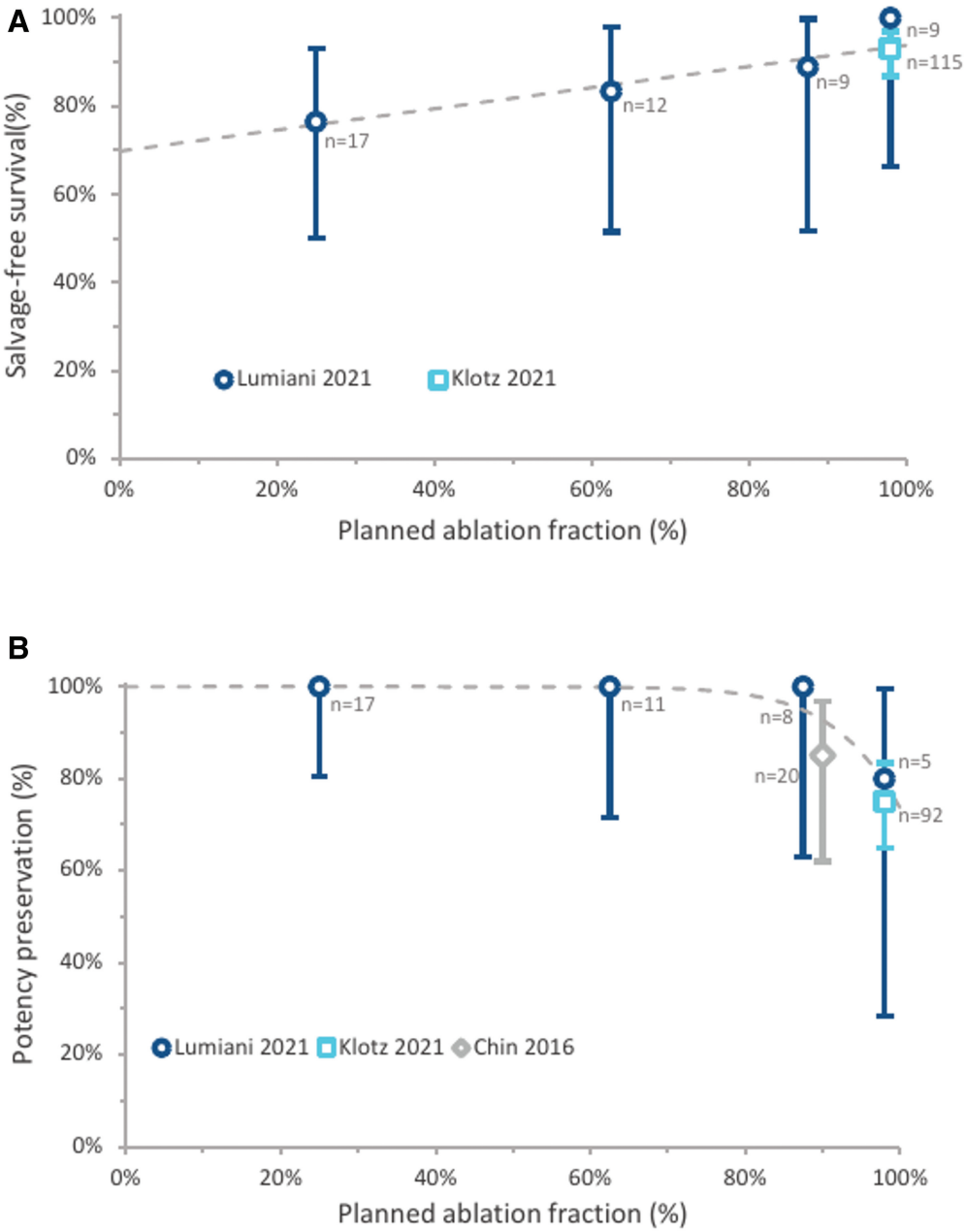

FIG. 2. Relationship between planned ablation fraction and: **(A)** salvage-free survival, or freedom from additional or salvage treatment by up to 2 years after a single TULSA procedure, and **(B)** the rate of potency preservation. Only studies with intent-to-treat were included in **(A)**, only men who were potent at baseline were included in **(B)**, and both **(A, B)** include only men treated for primary prostate cancer. Error bars indicate the 95% confidence intervals, and the legend indicates the study from which each data point was derived. The number of patients included at each data point is shown. Color images are available online.

(98%) men were potent and continent. At follow-up, potency and continence preservation ranged from 75% to 98% and from 92% to 100%. Potency preservation at 3 and 5 years was also available for the Phase I cohort. For the 22 men with a complete 3-year follow-up, 13/22 and 11/22 had erections sufficient for penetration at baseline and follow-up.[12] For the 16 men with a complete 5-year follow-up, 9/16 and 7/16 had erections sufficient for penetration at baseline and follow-up.[13]

For the additional six men treated for primary PCa with TULSA before RP, all preserved baseline potency and continence at the 3-week follow-up before surgery.[14] The change in rate of potency preservation with the planned ablation fraction was illustrated with a weighted, nonlinear least-squares model and fit to a sigmoidal dose/response relationship with a residual standard error of 0.012 (Fig. 2B). The difference in the proportions of men preserving potency between those treated with whole-gland *vs* subtotal ablation was significant ($p = 0.002$). All included studies that assessed erectile function allowed the use of erectile aid medications before and/or after treatment.

Among men treated for recurrent PCa, only four were potent before TULSA (all four preserved potency after

Table 3. Summary of Functional Outcomes After a Single Transurethral Ultrasound Ablation Procedure: Preservation of Potency and Continence, and Stability of Urinary Symptoms

Study	*Prior PCa treatment*	*FU at (months)*	*BL potency preserved*[a]	*BL continence preserved*	*Change in urinary symptoms*	*Definition for change in urinary symptoms*
Klotz[8]	None (115/115)	12	75% (69/92) IIEF Q2 ≥ 2	92% (103/112) EPIC pad-free	Δ = 14% BL: 7 (3–10) FU: 6 (3–9)	Change in IPSS
Eggener[9,b]		24	83.3% IIEF Q2 ≥ 2	93% EPIC pad-free	Δ = 28% BL = 7 (3–10) FU = 5	
Lumiani[10]	Primary PCa (47/52): None Recurrent PCa (5/52): 3/5 HIFU[a] 1/5 laser 1/5 EBRT 1/5 hyperthermia	16 (12–22) Median (IQR)	98% (40/41) 100% (4/4) Surgeon-assessed partial or full potency	98% (46/47) 100% (5/5) Pad-free	92% (47/52) 83% (20/24)	Proportion of men with no deterioration in urinary function (surgeon-assessed reduced nocturia, incomplete bladder emptying; discontinuation of either permanent catheterization or BPH medication) (PCa and LUTS subgroup, 24/52): Proportion of men with improvement in urinary function (surgeon-assessed reduced nocturia, incomplete bladder emptying; discontinuation of either permanent catheterization or BPH medication)
Chin[11]	None (30/30)	12	85% (17/20) IIEF Q2 ≥ 2	100% (30/30) EPIC leak-free and pad-free	Δ = 38% BL = 8 (5–13) FU = 5 (4–7)	Change in IPSS
Nair 2020[12]		36	BL = 13/22 FU = 11/22 IIEF Q2 ≥ 2	100% (22/22) EPIC leak-free and pad-free	Δ = 0% BL = 6 (5–13) FU = 6 (4–10)	Change in IPSS, for men continuing per-protocol FU at 3 years.
Nair 2020[b,13]		60	BL = 9/16 FU = 7/16 IIEF Q2 ≥ 2	100% (16/16) EPIC leak-free and pad-free	Δ = 25% BL = 8 (5–13) FU = 6 (6–9)	Change in IPSS, for men continuing per-protocol FU at 5 years.
Elterman[17]		12	Δ = 7% BL = 15 ± 9 FU = 16 ± 9 IIEF-15	N/A	Δ = 62% BL = 16 ± 4 FU = 6 ± 5 89% (8/9)	Change in IPSS Proportion of men with decrease in IPSS ≥6 points from BL
Anttinen[14]	None (6/6)	3 weeks	100% (3/3) IIEF Q2 ≥ 2	100 (6/6) EPIC urinary incontinence	Δ = 20% BL = 5 (4–6) FU = 4 (3–8)	Change in IPSS

(*continued*)

TABLE 3. (CONTINUED)

Study	Prior PCa treatment	FU at (months)	BL potency preserved[a]	BL continence preserved	Change in urinary symptoms	Definition for change in urinary symptoms
Anttinen[15]	10/11 EBRT 1/11 HDR brachy 4/11 ADT	12	N/A (11/11 men had severe ED at BL)	BL = 100 (100–100) FU = 96 (46–100) EPIC urinary incontinence	Δ = 12% BL = 8 (4–10) FU = 7 (5–18)	Change in IPSS
Anttinen[16]	6/10 EBRT and 2–3-year ADT 4/10 ADT	12	N/A	N/A	Δ = 100% (9/9) Δ = 100% (10/10)	Freedom from gross hematuria (1/10 men free from gross hematuria at BL) Freedom from permanent catheterization (0/10 men free at BL)

For the subgroups of men with cancer who also had benign prostatic hyperplasia at BL, improvement in urinary symptoms is also reported. Delta (Δ) is defined as the difference between BL and FU, normalized to BL and expressed as a percentage. Convention: a positive Δ denotes improvement. Median (IQR) is reported for IPSS and EPIC, and mean ± standard deviation for IIEF-15.

[a]Erectile aid medications were allowed at BL and/or FU in all studies that evaluated erectile function.

[b]Conference presentation.

BL = baseline; EPIC = Expanded Prostate Cancer Index; FU = follow-up; IIEF = International Index of Erectile Function; LUTS = lower urinary tract symptoms.

treatment). Within the prospective cohort of men with radiorecurrent disease, all 11 men had severe erectile dysfunction at baseline.[14] The median (IQR) Expanded Prostate Cancer Index Composite urinary incontinence domain score for this cohort decreased overall from 100 (100–100) at baseline to 96 (46–100) at 12 months. All five men in the retrospective cohort preserved pad-free continence.[10] Due to the poor health of the men treated for LAPC, functional questionnaires were omitted from the follow-up and potency and continence were therefore not assessed.[16]

Urinary symptoms were stable or improved with median IPSS decreasing from 0 to 3 points from baseline to the 12-month follow-up for all studies in which the questionnaire was administered (Table 3). Two studies also evaluated relief of symptoms after TULSA in men with PCa concurrent with LUTS (Table 3).[10,17] One study incorporated a targeted treatment plan, directed specifically to the transition zone and/or extension or obstruction in the bladder neck while also targeting PCa.[10] The other study assessed incidental symptom relief in a subgroup of men from the PCa Phase I study after subtotal ablation of the inner 90% of the prostate.[17] Overall 33 men with LUTS were treated and the rate of symptom improvement, notwithstanding variable definitions, was from 83% to 89% at a median of 12-to 16-month follow-up (Table 3).

Relief of urinary symptoms in men with LAPC was assessed in one study.[16] All subjects ($n = 10$) were continuously catheterized at baseline due to urinary retention, and 9/10 men suffered gross hematuria. At the last follow-up (up to 1 year), 100% were free from gross hematuria, 70% were free from catheterization, and 10% had intermittent catheterization (Table 3).

Safety outcomes

Adverse events across all 10 included studies are summarized in Table 4. There was no rectal injury or fistula, and no life-threatening or fatal adverse event of Clavien–Dindo (C-D) Grade IV or Common Terminology Criteria for Adverse Events (CTCAE) Grade IV or higher. A CTCAE Grade III or C-D Grade III adverse event was incurred by 13 men (6%).[8,10,11,14] These included three urinary tract infections (UTIs) and three occurrences of epididymitis. Definitive treatments for epididymitis were typically hospitalization with intravenous antibiotics. The most common Grade II or higher adverse events among the 198 men treated for primary PCa were UTI ($n = 53$ occurrences, 0%–33%) and retention ($n = 16$), followed by urinary incontinence (pad use) and epididymitis ($n = 10$, 9).

For LAPC, 80% of men were diagnosed with UTI at baseline, and 20% at follow-up. Retention was resolved by catheterization, medication, and in one case transurethral resection of the prostate. At 12 months, pad use persisted in 3 men.[8,11] No new serious or severe (Grade III) adverse event was reported at extended follow-up (2–5 years). Discharge took place on treatment day, within 24 hours of treatment, or on the first postoperative day for 166/224 (74%) men.[8,10,11,14–16]

Among the men treated with TULSA for recurrent PCa or for LAPC ($n = 26$), there was one Grade III event: retention treated with suprapubic catheter and Double-J stents after treatment of radiorecurrent disease. The most common event in these populations was UTI ($n = 10$ occurrences, all C-D I or II), followed by retention ($n = 3$).

Table 4. Adverse Events Reported for Unique Cohorts of Men Treated with Transurethral Ultrasound Ablation

Cancer indication	*Primary prostate cancer*				*Recurrent prostate cancer*		*Locally advanced PCa*
Study (N)	*Chin*[11] *(30)* (N = *30*)[a]	*Klotz*[8] (N = *115*)[a]	*Anttinen*[14] (N = *6*)[b]	*Lumiani*[10] (N = *47*)[b] *(subgroup)*	*Lumiani*[10] (N = *5*)[b] *(subgroup)*	*Anttinen*[15] (N = *11*)[b]	*Anttinen*[16] (N = *10*)[b]
Urinary tract infection	10 (33%) G2	40 (25%) G2 3 (3%) G3		1 (2.1%) C-D I	1 (20%) C-D I	4 (36%)	3 (30%) C-D I 2 (20%) C-D II
Epididymitis	1 (3.3%) G3	6 (5%) G2 2 (1%) G3		1 (2.1%) C-D I			
Urethral stricture/ bladder outlet obstruction	1 (3.3%) G1 1 (3.3%) G2	1 (1%) G1 2 (2%) G3		1 (2.1%) C-D IIIa, TURP for BOO from persistent BPH			
Urinary retention	3 (10%) G1 5 (17%) G2	9 (7%) G2 2 (2%) G3		6 (13%) C-D I		2 (18%) C-D II 1 (9.1%) C-D III, SPC and Double-J stents	
Urinary incontinence	1 (3.3%) G1 3 (10%) G2 At 12 months: 1/30 (3.3%) G1 (no pads)	21 (17%) G1 7 (6.0%) G2 At 12 months: 3 (2.6%) G2					
Hematuria	13 (43%) G1 2 (6.7%) G2	43 (35%) G1 2 (2%) G2		1 (2.1%) C-D I			
Nocturia				1 (2.1%) C-D IIIa, cystoscopy to evaluate residual prostate tissue, self-resolved after 3 months			
Pain/discomfort (bladder, urinary tract)		4 (3%) G1 4 (3%) G2 1 (1%) G3					
Urethral calculus		1 (1%) G3					
Urinoma		1 (1%) G3					
Rectal injury or fistula	0	0	0	0		0	0
Classification	G3: 1 (3.3%) G4: 0	G3: 9 men (7.8%) G4: 0	Nil.	C-D IIIa: 2 (4.2%) C-D IIIb: 0 C-D IV: 0	C-D III: 0 C-D IV: 0	C-D III: 1 (9.1%)	C-D III: 0 C-D IV: 0
Length of catheterization median (IQR), and type	2.2 (2.0–3.3) weeks, SPC	17 (11–24) days, SPC	2–3 days, Foley	2 weeks, for 48/52 (88%) of men, SPC		7 days (1–14) median (IQR). Foley: 9/11 SPC: 2/11	N/A

Complications of any grade that are reported in more than one study, and all Grade III complications are listed. The number of events is reported for all studies except Chin et al.[11] 2016 (no. of men). Percentages are the proportion of men incurring ≥1 adverse event relative to the number of men enrolled in the study. In the FU reports, no new serious or severe adverse events were reported up to 5 years. Adverse events for the subgroup analysis in Elterman et al.[17] 2021 study are included in Chin et al.[11] 2016, and Lumiani et al.[10] 2021 includes adverse events for the subgroup of men treated for PCa concurrent with LUTS.

[a]Common Terminology Criteria for Adverse Events classification system.

[b]Clavien–Dindo classification system.

BOO = bladder outlet obstruction; C-D = Clavien–Dindo; G = grade; GA = general anesthesia; SPC = suprapubic catheter; TURP = transurethral resection of the prostate.

Discussion

Ablative therapies for PCa aim to deliver equivalent oncologic and superior functional outcomes relative to gold standard treatments. TULSA is an emerging technology that received FDA clearance in 2019 for the ablation of prostate tissue, and this review found positive early and midterm oncologic and functional outcomes from single-arm studies. In 224 patients across 10 studies, TULSA demonstrated effective ablation of prostate tissue with a PSA decline of 54% to 97% over all indications and ablation plans.

For primary PCa, the proportion of men who went on to receive salvage treatment by up to 2 years after one TULSA procedure with intent to treat was 10% (16/162), falling in line with clinically acceptable rates set by an ablative therapy consensus panel and similar to the reported outcome after RP.[18,19] The feasibility of a variety of salvage treatments has been demonstrated: a second TULSA (7), RP (5), EBRT (3), and brachytherapy (1).[9,10,20] A report assessing the technical feasibility and safety of salvage RP after TULSA in four men concludes that the operative difficulty and perioperative morbidity were negligible when using an open approach to facilitate access to the perineum and rectum.[20]

Only 16 men were treated for recurrent PCa in the included studies, and outcomes are interpreted with caution. Of the 4/16 (25%) men who had salvage treatment, 3 of these treatments were directed by out-of-field recurrence.[10,15] One of the out-of-field recurrences (plus an in-field failure that was managed expectantly) was seen only on per-protocol PSMA-PET.[15] Both men had negative mpMRI and no biochemical failure. After TULSA for recurrent PCa, the additional treatments were as follows: repeat TULSA (3) and androgen deprivation therapy (1).

Failure analysis revealed the following reasons for recurrence after TULSA for primary or recurrent PCa: insufficient thermal coverage or margins around the target, calcifications disrupting the beam path, out-of-field recurrence, and tumor falling outside of device specifications.[8,10] The proportion of men with effective eradication of Grade Group 2 disease at baseline with clinical benefit at the 1-year biopsy increased from 79% to 85% when patients with calcifications at screening were excluded from the analysis.[8] Such failures highlight the sensitivity of TULSA to in-field prostate calcifications, a potential disadvantage of the approach.

A strength of the largest study included in this review is per-protocol biopsy with exceptionally high uptake and sampling density.[8] The rates of clinically significant disease and any disease were 23/111 (21%) and 39/111 (35%), similar to the rates of positive biopsy after modern EBRT including stereotactic body radiation therapy.[8,21] In contrast, the rate of MRI-visible lesions after TULSA was 30% including equivocal findings (Table 2).[8]

By 2 years, BCR occurred in 2.6% of men applying the Phoenix definition, which, although widely adopted, has not been validated for ablative therapies.[8,22] The discrepancies between BCR and biopsy or MRI outcomes, as seen in Table 2, highlight the need for more sensitive PSA or biomarker-based predictors of recurrence, and standardized reporting of postablation MRI findings. However, tissue-based sampling remains the gold standard for determining the postablation oncologic outcome.

Results indicate favorable preservation of potency and continence with stability of urinary symptoms, and promising symptom relief for men with PCa concurrent with LUTS seeking a single minimally invasive treatment. Of 153 men who were potent before treatment, 126 remained so at 12 months yielding an 18% loss of baseline potency. Most of the men who were potent at baseline (76%) received whole-gland ablation. The loss of baseline potency reported in the Prostate Cancer Outcomes Study was 72% and 43% 2 years after RP and EBRT.[23,24] Pad-free continence was preserved in 179/189 men (95%), durable to 5 years (Table 2).[13] Favorable IPSSs were maintained in men with good baseline function, while 83% to 89% of men with LUTS in addition to PCa met the criteria for symptom improvement (Table 3).[10,17]

Treatment plans targeting PCa ranged from focal to whole-gland, with optional neurovascular bundle and/or urethral sphincter sparing. Combination treatments targeted PCa along with obstructive tissue in the transition zone or median lobe (Table 1). The fraction of prostate tissue included in the ablation plan had a predictable impact on efficacy and safety (Fig. 2). The likelihood that a patient would be free from additional treatment increased linearly with planned ablation fraction from 76% for focal lesion-targeted ablation to 94% for whole-gland ablation, while the proportion of men preserving baseline potency ranged from 100% when targeting less than three-quarters of the prostate to 75% in whole-gland treatments.

Similarly, the ablation fraction dichotomized as focal *vs* whole-gland has been shown to be the most important factor related to preservation of function after HIFU or cryotherapy.[25] These models may help weigh risks and benefits to inform individualized treatment planning.

Although the sample size is small, the highest rate of Grade III adverse events was incurred in TULSA treatment of radiorecurrent disease (Table 4). The most common adverse event overall was UTI (64/224 = 29%), but the majority of these were reported in two regulatory clearance studies where rates included asymptomatic positive culture at the 1-month urine analysis.[8,11]

The authors of these studies also postulated that high infection rates could be a result of the suprapubic catheter being placed with cystoscopy guidance in the MRI control area instead of a traditional surgical suite or as a result of prolonged post-treatment suprapubic catheterization. While it is plausible that shifting practice toward urethral catheterization and reduced duration may decrease the rate of UTI requiring intervention, the data in Table 4 are insufficient to support any definitive conclusion.

There are notable promising niche areas for TULSA. Favorable outcomes have been reported after TULSA treatment of larger volumes and large prostates. For men with primary PCa, the upper quartile for baseline prostate volume was ≥48 to 65 mL representing a typical upper range, and the largest prostate treated with whole-gland ablation was 125 mL (Table 1). The transurethral delivery is amenable to treating anterior lesions, which may lie beyond the reach of transrectal approaches, and bilateral or diffuse disease. Finally, men may safely continue anticoagulant therapy during TULSA treatment. Forty percent of the men with LAPC treated with TULSA were receiving anticoagulant therapy at baseline and during treatment.[16] In contrast, men who cannot safely discontinue anticoagulant therapy may be excluded from other therapies.

A key limitation of this review is the small sample size for recurrent PCa and LAPC. Multicenter studies are few and

Level 1 evidence awaits results from a randomized-controlled trial comparing TULSA with RP (NCT 05027477). There was variability in the definitions and thresholds for functional outcomes, which were surgeon-assessed in one report. Finally, we report the rate of salvage treatment for primary PCa at 16 to 24 months as a surrogate for oncologic outcome, which awaits longer follow-up.

However, the present review is the first to our knowledge reporting Level 2a evidence of TULSA treatment for PCa, with the goal of supporting clinical decision-making by synthesizing key outcomes for this emerging technology which promises to meet a broad set of clinical needs. The outcomes for recurrent PCa and LAPC, although qualified, provide promising early evidence supporting the potential for TULSA to meet a multiplicity of clinical needs when treatment options may be limited.

Conclusion

TULSA is a safe and effective modality for prostate tissue ablation, demonstrating PSA reduction across PCa indications and functional preservation. Early oncologic outcomes following TULSA treatment of primary PCa are favorable, and LUTS may be simultaneously improved. The TULSA procedure has also effectively treated recurrent PCa and relieved symptoms associated with locally advanced PCa. There is potential for prediction of potency preservation and SFS from the fraction of the gland targeted for ablation represented as a continuous variable.

Authors' Contributions

All authors have made substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND drafting the work or revising it critically for important intellectual content; AND final approval of the version to be published; AND agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary Material

Supplementary Table S1

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Abbreviations Used

ADT = androgen deprivation therapy
BCR = biochemical recurrence
BL = baseline
BOO = bladder outlet obstruction
BPH = benign prostatic hyperplasia
C-D = Clavien–Dindo
CTCAE = Common Terminology Criteria for Adverse Events
EAU = European Association of Urology
EBRT = external beam radiation therapy
EPIC = Expanded Prostate Cancer Index
FU = follow-up
G = grade
GA = general anesthesia
GG = Grade Group
HDR brachy = high dose-rate brachytherapy
HIFU = high-intensity focused ultrasound
IIEF = International Index of Erectile Function
IPSS = International Prostate Symptom Score
IQR = interquartile range
LAPC = locally advanced prostate cancer
ISUP = International Society of Urological Pathology
LUTS = lower urinary tract symptoms
MRI/MR/mpMRI = magnetic resonance imaging/magnetic resonance/multiparametric MRI
NCCN = National Comprehensive Cancer Network
NVB = neurovascular bundles
PCa = prostate cancer
PI-RADS v2 = Prostate Imaging Reporting and Data System Version
PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analyses
PSA = prostate-specific antigen
PSMA-PET = prostate-specific membrane antigen-positron emission tomography
pTURP = palliative transurethral resection of the prostate
RP = radical prostatectomy
SD = standard deviation
SFS = salvage-free survival
SPC = suprapubic catheter
TACT = Pivotal Study of MRI-guided Transurethral Ultrasound Ablation in Patients with Localized Prostate Cancer
TULSA = transurethral ultrasound ablation
TZ = transition zone
UA = ultrasound applicator
UTI = urinary tract infection