Primary Whole-gland Ablation for the Treatment of Clinically Localized Prostate Cancer: A Focal Therapy Society Best Practice Statement

Sriram Deivasigamani [a] [†], Srinath Kotamarti [a] [†], Ardeshir R. Rastinehad [b], Rafael Sanchez Salas [c], J.J.M.C.H. de la Rosette [d], Herbert Lepor [e], Peter Pinto [f], Hashim U. Ahmed [g], Inderbir Gill [h], Laurence Klotz [i], Samir S. Taneja [e], Mark Emberton [j], Nathan Lawrentschuk [k], James Wysock [e], John F. Feller [l], Sebastien Crouzet [m], Praveen Kumar M. [n], Denis Seguier [a] [o], Eric S. Adams [a], Zoe Michael [a], Andre Abreu [h], Kae Jack Tay [p], John F. Ward [q], Katsuto Shinohara [r], Aaron E. Katz [e], Arnauld Villers [o], Joseph L. Chin [s], Phillip D. Stricker [t], Eduard Baco [u], Petr Macek [v], Ardalan E. Ahmad [w], Peter K.F. Chiu [x], E. David Crawford [y], Craig G. Rogers [z], Jurgen J. Futterer [aa], Soroush Rais-Bahrami [bb], Cary N. Robertson [a], Boris Hadaschik [cc], Giancarlo Marra [dd], Massimo Valerio [ee], Kian Tai Chong [ff], Veeru Kasivisvanathan [j], Wei Phin Tan [e], Derek Lomas [gg], Jochen Walz [hh], Gustavo Cardoso Guimaraes [ii], Nikos I. Mertziotis [jj], Ezequiel Becher [kk], Antonio Finelli [i], Ali Kasraeian [ll], Amir H. Lebastchi [h], Anup Vora [mm], Mark A. Rosen [nn], Baris Bakir [oo], Rohit Arcot [a] [pp], Samuel Yee [x], Christopher Netsch [qq], Xiaosong Meng [rr], Theo M. de Reijke [ss], Yu Guang Tan [p], Stefano Regusci [tt], Tavya G.R. Benjamin [b], Ruben Olivares [uu], Mohamed Noureldin [vv], Fernando J. Bianco [ww], Arjun Sivaraman [xx], Fernando J. Kim [yy], Robert W. Given [zz], Shawn Dason [aaa], Tyler J. Sheetz [aaa], Sunao Shoji [bbb], Ariel Schulman [ccc], Peter Royce [ddd], Taimur T. Shah [g], Stephen Scionti [eee], Georg Salomon [fff], Pilar Laguna [d], Rafael Tourinho-Barbosa [ggg], Alireza Aminsharifi [hhh], Xavier Cathelineau [v], Paolo Gontero [dd], Armando Stabile [ii], Jeremy Grummet [ddd], Leila Ledbetter [a], Margaret Graton [a], J. Stephen Jones [jjj], Thomas J. Polascik [a] on behalf of the Focal Therapy Society

[a] Duke Cancer Institute and Duke University Medical Centre, Durham, NC, USA

[b] Smith Institute for Urology at Lenox Hill, New York, NY, USA

[c] Division of Urology, McGill University, Montreal, Quebec, Canada

[d] Department of Urology, Istanbul Medipol Mega University Hospital, Istanbul, Turkey

[e] Department of Urology, NYU School of Medicine, NYU Langone Health, New York, NY, USA

[f] Urologic Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA

[g] Division of Urology, Imperial College London & Imperial College Healthcare NHS Trust, London, UK

[h] Institute of Urology, Keck Medicine of USC, University of Southern California, Los Angeles, CA, USA

i

Division of Urology, University of Toronto, Toronto, Ontario, Canada

j

Division of Surgery, University College London, London, UK

k

Department of Urology, Royal Melbourne Hospital, Melbourne, Victoria, Australia

l

Halo Diagnostics, Indian Wells, CA, USA

m

Department of Urology, University Hospital of Lyon, Lyon, France

n

Department of Pharmacology, PGIMER, Chandigarh, India

o

Department of Urology, University Lille Nord de France, Lille, France

p

Department of Urology, Singapore General Hospital, Singapore

q

Department of Urology, MD Anderson Cancer Center, Houston, TX, USA

r

Department of Urology, University of California San Francisco, San Francisco, CA, USA

s

Department of Urology, University of Western Ontario, London, Ontario, Canada

t

Department of Urology, University of New South Wales, Sydney, Australia

u

Department of Urology, Oslo University Hospital, Oslo, Norway

v

Department of Urology, Institute Mutualiste Montsouris, Paris, France

w

Department of Urology, University of Manitoba, Winnipeg, Manitoba, Canada

x

Department of Surgery, SH Ho Urology Centre, The Chinese University of Hong Kong, Hong Kong

y

Department of Urology, University of California San Diego, San Diego, CA, USA

z

Vattikuti Urology Institute, Henry Ford Health, Detroit, MI, USA

aa

Department of Radiology, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands

bb

Department of Urology, University of Alabama at Birmingham, Birmingham, AL, USA

cc

Department of Urology, University Hospital Essen, Essen, Germany

dd

Department of Urology, The University Hospital of Turin, Turin, Italy

ee

Service of Urology, University Hospital of Lausanne, Lausanne, Switzerland
ff

Surgi-TEN Specialists, Farrer Park Hospital, Singapore
gg

Department of Urology, Mayo Clinic, Rochester, MN, USA
hh

Department of Urology, Paoli-Calmettes Institute Cancer Center, Marseille, France
ii

BP- A Beneficencia Portuguesa de São Paulo, São Paulo, Brazil
jj

Department of Urology, Metropolitan General Hospital, Athens, Greece
kk

Centro de Urología - CDU, Buenos Aires, Argentina
ll

Kasraeian Urology, Jacksonville, FL, USA
mm

Chesapeake Urology, Silver Spring, MD, USA
nn

Department of Urology, Sutter Health, Sacramento, CA, USA
oo

Department of Radiology, Istanbul University, Istanbul, Turkey
pp

Department of Urology, Ochsner Clinic Foundation, New Orleans, LA, USA
qq

Department of Urology, ASKLEPOIS Clinic Barmbek, Hamburg, Germany
rr

Department of Urology, UT Southwestern Medical Center, Dallas, TX, USA
ss

Department of Urology, Amsterdam Medical Center, Amsterdam, The Netherlands
tt

Department of Interventional Oncology, Swiss International Prostate Centelenor, Geneva, Switzerland
uu

Department of Urology, Cleveland Clinic, Cleveland, OH, USA
vv

Urology, Hampshire Hospitals NHS Foundation Trust, UK
ww

Urological Research Network, Urologist Specialist Group, Miami Lakes, FL, USA
xx

Division of Urology, Washington University School of Medicine, St Louis, MO, USA
yy

Division of Urology, Denver Health Medical Center and University of Colorado Hospital, Denver, CO, USA
zz

Urology of Virginia, Virginia Beach, VA, USA
aaa

Department of Urology, The Ohio State University, Columbus, OH, USA

bbb

Department of Urology, Tokai University School of Medicine, Tokyo, Japan

ccc

Department of Urology, Maimonides Health Medical Center, New York, NY, USA

ddd

Division of Urology, Monash University, Melbourne, Australia

eee

Vituro Health, Sarasota, FL, USA

fff

Martini-Clinic Prostate Cancer Center, University Clinic Eppendorf, Hamburg, Germany

ggg

Department of Urology, Faculdade de Medicina do ABC, Salvador, Brazil

hhh

Department of Urology, Penn State Health Milton S. Hershey Medical Center, Hershey, PA, USA

iii

Unit of Urology/Division of Urology, IRCCS Ospedale San Raffaele, Milan, Italy

jjj

Department of Urology, Inova Health, Falls Church, VA, USA

Abstract

Context

Whole-gland ablation is a feasible and effective minimally invasive treatment for localized prostate cancer (PCa). Previous systematic reviews supported evidence for favorable functional outcomes, but oncological outcomes were inconclusive owing to limited follow-up.

Objective

To evaluate the real-world data on the mid- to long-term oncological and functional outcomes of whole-gland cryoablation and high-intensity focused ultrasound (HIFU) in patients with clinically localized PCa, and to provide expert recommendations and commentary on these findings.

Evidence acquisition

We performed a systematic review of PubMed, Embase, and Cochrane Library publications through February 2022 according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement. As endpoints, baseline clinical characteristics, and oncological and functional outcomes were assessed. To estimate the pooled prevalence of oncological, functional, and toxicity outcomes, and to quantify and explain the heterogeneity, random-effect meta-analyses and meta-regression analyses were performed.

Evidence synthesis

Twenty-nine studies were identified, including 14 on cryoablation and 15 on HIFU with a median follow-up of 72 mo. Most of the studies were retrospective (n = 23), with IDEAL (idea, development, exploration, assessment, and long-term study) stage 2b (n = 20) being most common. Biochemical recurrence–free survival, cancer-specific survival, overall survival, recurrence-free survival, and metastasis-free survival rates at 10 yr were 58%, 96%, 63%, 71–79%, and 84%, respectively. Erectile function was preserved in 37% of cases, and overall pad-free continence was achieved in 96% of cases, with a 1-yr rate of 97.4–98.8%. The rates of stricture, urinary retention, urinary tract infection, rectourethral fistula, and sepsis were observed to be 11%, 9.5%, 8%, 0.7%, and 0.8%, respectively.

Conclusions

The mid- to long-term real-world data, and the safety profiles of cryoablation and HIFU are sound to support and be offered as primary treatment for appropriate patients with localized PCa. When compared with other existing treatment modalities for PCa, these ablative therapies provide nearly equivalent intermediate- to long-term oncological and toxicity outcomes, as well as excellent pad-free continence rates in the primary setting. This real-world clinical evidence provides long-term oncological and functional outcomes that enhance shared decision-making when balancing risks and expected outcomes that reflect patient preferences and values.

Patient summary

Cryoablation and high-intensity focused ultrasound are minimally invasive treatments available to selectively treat localized prostate cancer, considering their nearly comparable intermediate- to long term cancer control and preservation of urinary continence to other radical treatments in the primary setting. However, a well-informed decision should be made based on one's values and preferences.

Introduction

Prostate cancer (PCa) remains the most frequent solid organ malignancy, and is the second and fifth leading cause of cancer-related death in men in the USA and worldwide, respectively [1], [2]. Owing to its prolonged natural history, there are opportunities for periodic, staged intervention to cure/control the disease, as evidenced by the use of active surveillance (AS) as a management option [3]. Historically, PCa treatment has been centered around radical prostatectomy (RP) or radiation therapy (RT). While effective, not all patient preferences and associated comorbidities, as well as contraindications to any single therapy, will allow them to be optimal candidates for RP or RT, necessitating the need for an alternative option, for example, ablation [4], [5], [6].

Contrary to radical therapy, AS has been embraced because it fundamentally avoids treatment-related sequelae. It is now the cornerstone of management for low-grade disease, and AS criteria have expanded [7], [8]. Further, efforts to preserve functional outcomes, optimize oncological results, and maintain overall positive quality of life/well-being have spurred the development of alternative therapies such as ablation [9]. Initially developed for poor surgical candidates, technological advancements in energy delivery and real-time image monitoring have reduced morbidity and expanded the use of ablation in PCa management.

Although prostate cryoablation (CRYO) emerged in the 1960s, it took three decades to improve the technology to deliver safer freezing/thawing processes and advance clinical adoption [10]. The 1990s witnessed the introduction of high-intensity focused ultrasound (HIFU); together with CRYO, these are the most prevalent and well-tested PCa ablative techniques. CRYO involves ice ball formation and freezing/thawing of intended tissues, inducing coagulative necrosis and cell death via mechanical and biochemical means [11]. Conversely, HIFU exacts coagulative necrosis through mechanical disruption and heating with ultrasound energy [11]. Covering either end of the temperature spectrum, the energy delivery for both approaches can be controlled precisely to conform delivery to specific gland areas/patterns depending upon clinical need. This allows for both whole-gland (WG) and partial-gland treatments.

According to current guideline recommendations, patients with clinically significant, organ-confined intermediate-risk PCa may be ablation candidates if they receive standard counseling addressing the side effects, recurrence risk, necessity for follow-up, and possibly additional therapy [12]. However, there is a paucity of long-term outcomes, comparative studies, and randomized controlled trials (RCTs) governing its use. Herein, we provide intermediate- to long-term real-world evidence via a comprehensive systematic review of WG CRYO and HIFU for localized PCa, and provide best practice recommendations for clinical utilization.

2. Evidence acquisition

The population, intervention, control, outcome, study design (PICOS) approach was used to provide a framework for the initial literature search (Supplementary Table 1) [13]. We conducted a full systematic review and meta-analysis using the *Cochrane Handbook for Systematic Reviews of Interventions* following the Preferred Reporting Item for Systematic Reviews and Meta-analyses (PRISMA) 2020 statement [14], [15]. The study was registered in the PROSPERO database (CRD42022384922).

2.1. Search strategy

The search was developed "a priori" and conducted by two professional medical librarians in consultation with the author team. It included keywords and subject headings exhaustively representing PCa and ablation, with the full search terms and criteria contained in Supplementary Table 2. Databases searched included MEDLINE (PubMed), Embase (Elsevier), Cochrane Library online, and Scopus (Elsevier).

Search hedges or database filters were used to remove publication types such as editorials, letters, case reports, comments, and animal-only studies, as appropriate. To maximize the yield of eligible articles not limited to a certain timeframe, we considered all articles published from inception through February 9, 2022. We searched for additional articles by reviewing the references of the selected articles and looking at the articles listed by the citation tracking feature of Web of Science and Scopus. The full text of the final selected articles was read for further screening.

2.2. Eligibility criteria

Included studies assessed the oncological and/or functional outcomes of WG CRYO or HIFU utilized as a primary treatment for localized PCa. We included RCTs, cohort studies (both retrospective and prospective), and single-arm studies. Excluded studies were salvage therapy or non-WG approaches. Publications were considered eligible if ≥50 patients were included, and a minimum of 5 yr of mean/median follow-up was observed. We excluded articles published in non-English languages.

2.3. Selection of evidence sources

All identified studies were uploaded into Covidence (Covidence systematic review software; Veritas Health Innovation, Melbourne, Australia; www.covidence.org). Three authors (S.K., D.S., and Z.M.) carried out dual independent screening. Any conflicts between reviewers were resolved through adjudication by a fourth, senior author (T.J.P.). In the case of studies reporting the same outcome from the same dataset, only the study with the longest follow-up was included. Study selection is presented by a flowchart as per the PRISMA guidelines (Supplementary Fig. 1).

2.4. Data variables

Data extracted from each study included study design; IDEAL (idea, development, exploration, assessment, and long-term study) stage [16]; baseline patient characteristics such as age, preoperative biopsy findings, prostate-specific antigen (PSA), and risk stratification; follow-up; oncological outcomes including PSA metrics, biochemical recurrence (BCR), biopsy regimen and positivity rate, salvage treatments, recurrence-free survival (RFS), metastasis-free survival (MFS), and overall survival (OS); adverse events according to either the Clavien-Dindo scale or the Common Terminology Criteria for Adverse

Events (CTCAE) [17]; and functional outcomes based on patient-reported outcome measures (PROMs), leak-/pad-free continence, and erections sufficient for sexual intercourse.

2.5. Definition of outcomes and endpoints

A meta-analysis was used to evaluate oncological outcomes such as BCR-free survival (BCRFS), RFS, disease-specific survival (DSS), MFS, and OS. Although the BCR criteria varied among the included studies, such as Phoenix (PSA nadir + 2 ng/ml) [18], American Society for Therapeutic Radiology and Oncology (ASTRO; three consecutive PSA rises after a nadir with the date of failure as the point halfway between the nadir date and the first rise or any rise great enough to provoke initiation of therapy) [19], and Stuttgart (PSA nadir + 1.2 ng/ml) [20], the majority (21/24, 88%) utilized the Phoenix criteria. RFS was defined as freedom from cancer on follow-up biopsy, clinical recurrence, or salvage treatment.

A meta-analysis was used to evaluate functional outcomes, including pad-free rates and erectile function. Pad-free rate was defined as no pad used after ablation. Erectile function was defined as potency preservation in initially potent patients based on PROMs such as the ability to penetrate/have intercourse, erection sufficient for unassisted sexual activity, or International Index of Erectile Function (IIEF) ≥17. Other measures such as the International Prostate Symptom Score (IPSS), Stamey, and CTCAE criteria were also assessed.

The meta-analysis also evaluated commonly reported complications including urinary tract infection (UTI), urinary retention, stricture, and rectourethral fistula(RUF). Additional less reported complications including sepsis, urethral sloughing, and perineal pain were described. Severe toxicity was defined as per crude rates of grade ≥3 events according to CTCAE version 5 or the Clavien-Dindo criteria [17].

2.6. Study risk of bias assessment

To assess the risk of bias, RoB-2 and Robins-I tools were implemented for RCTs and the remainder of the selected articles, respectively [21], [22]. The high risk of bias is attributed to the heterogeneity of the included studies. Supplementary Figure 2summarizes the risk-of-bias evaluations.

2.7. Statistical analysis

We performed statistical analyses using R version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria) with the base, meta, and dplyr packages. The median/mean and range for continuous baseline variables were computed. After converting the proportions of each outcome to logit, we combined them using a random-effect method with an inverse variance approach. We utilized a random-effect model regardless of heterogeneity, considering the variation in study designs among the included studies. For outcomes with at least three studies, a meta-analysis was conducted, while the remaining outcomes were discussed as a review. Additionally, we performed subgroup analyses based on energy type. We assessed heterogeneity using I^2 and tau statistics. Tau statistics were computed utilizing the restricted maximum likelihood estimator. $I^2 > 50\%$ was considered to indicate significant heterogeneity. We used covariates including age, follow-up, neoadjuvant therapy, baseline PSA, baseline Gleason scores, and D'Amico risk stratification to determine the cause of heterogeneity using meta-regression. Variables included in the model were iterated to determine the final combination of covariates explaining the greatest amount of

heterogeneity, as measured by tau, I^2, and the test for heterogeneity. The likelihood of publication bias was evaluated using a funnel plot, and the significance was determined using Egger's test with a p value of 0.05.

2.8. Evidence assessment and incorporation of expert recommendations

Following the construction of the systematic review/data assessment, an expert panel (criteria: ten or more PCa publications, performing ≥50 PCa ablations per year, and leadership in the field) was presented the manuscript over two successive rounds. Best practice statements (BPSs) and recommendations presented herein were formulated through a combination of systematic review/meta-analysis and pooled expert opinion. The final manuscript draft/BPSs were again submitted to all coauthors for final approval prior to submission.

The overall quality of the evidence that exists for the recommendation and references used in this systematic review is graded according to the classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [23]. The strength of recommendations was graded as strong or weak based on the desirable effects of an intervention outweighing the undesirable effects [24].

Evaluation of the included literature and summarized expert guidance is provided in the Supplementary material, and Table 1 shows evidence-based recommendations.

3. Evidence synthesis

3.1. General

Twenty-nine studies met the final inclusion criteria, including 14 for CRYO [25], [26], [27], [28], [29], [30], [31], [32], [33], [34], [35], [36], [37], [38] and 15 for HIFU [20], [39], [40], [41], [42], [43], [44], [45], [46], [47], [48], [49], [50], [51], [52]. Included studies meeting all the criteria were published from 2000 to 2021. The majority (n = 23) were retrospective, with six prospective including one RCT [27]. Regarding IDEAL levels, one study was categorized as 2a, 20 were classified as 2b, one was classified as 3, and seven were categorized as 4. The median sample size was 261 (range: 70–4062) and follow-up was 72 (60–181.2) mo, with two studies having a median long-term follow-up of 14 yr [26], [52]. Only eight studies reported the percentage of individuals lost to follow-up, which varied from 1.8% to 44.86% [26], [30], [31], [32], [40], [43], [46], [52]. Table 2 summarizes the baseline clinical characteristics of the included studies.

3.2. Patient selection

All included studies focused on nonmetastatic, localized PCa. In certain cases, other selecting parameters were utilized such as clinical T stage, PSA, Gleason score, life expectancy, or risk stratification (D'Amico vs National Comprehensive Cancer Network [NCCN]). The median age was 69 (65–82) yr, with approximately 13 studies (45%) having patients with median age ≥70 yr. The median PSA of the entire cohort was 7.9 (5–26) ng/ml. The risk stratification was based on D'Amico risk stratification in 23/29 (80%) of the studies; clinical staging in three studies and NCCN guidelines in one study. Biopsy method was reported only in five studies (all transrectal ultrasound[TRUS] guided) [27], [34], [37], [41], [51]. Preoperative imaging was discussed in eight papers; one

used multiparametric magnetic resonance imaging (mpMRI) [38], two used mpMRI and bone scan [32], [40], two used TRUS only [41], [51], one used mpMRI or computerized tomography (CT) [44], and two used combined TRUS, CT, and bone scan [34], [46]. Neoadjuvant androgen deprivation therapy (ADT) was used in 17/29 (59%) studies. Ten studies addressed simultaneous transurethral resection of the prostate (TURP) with ablation to reduce prostate size and eliminate calcifications that could limit treatment efficacy (all HIFU); the median percentage of patients undergoing TURP was 73.4% (2.3–100%).

A Gleason score of ≤6 accounted for 52.45% (21–85%), 7 for 32% (14–56.5%) and ≥8 for 12% (2–57%) of the entire cohort. Studies predominantly included low- or intermediate-risk patients, although nine studies explicitly highlighted cT3 patients and 18 studies featured high-risk patients (3.7–100%) according to either D'Amico (n = 16) or NCCN (n = 1; one had neither) classification. The overall distribution of D'Amico risk among the included studies was as follows: 33% (8–56%) low, 45% (28–65%) intermediate, and 22% (4–62%) high risk. Supplementary Table 3 details the basic characteristics of the included studies.

3.3. Oncological outcomes

3.3.1. Surveillance protocols

Only eight studies commented on an imaging plan after ablation. TRUS q3 months was employed in two studies [46], [48]. Oishi et al. [34] utilized TRUS after ablation at 3, 6, and 12 mo and annually thereafter. Guo et al. [32] utilized MRI and bone single photon emission CT q6 months in the 1st year and after BCR, while Shoji et al. [51]performed mpMRI at one time 14–28 d postoperatively. One study obtained 18F-choline/prostate-specific membrane antigen positron emission tomography after ablation when BCR was identified with negative prostate biopsy or for those unwilling to undergo biopsy [38], while the remaining studies obtained imaging if clinically indicated [27], [40]. Seventeen studies described PSA regimens utilized, with the typical protocol being q3–6 month PSA values. In terms of biopsy regimen, 16 series described their sampling protocol. Six studies employed mandatory biopsies beginning as early as 3–6 mo, five performed biopsies solely for a suspicion of recurrence [32], [38], [40], [43], [49], and four used a combination of both [26], [34], [39], [52]. Supplementary Table 4 summarizes the surveillance and follow-up protocols of the included studies.

3.3.2. Biochemical and histological outcomes

PSA nadir was documented in 15 studies, ranging from 0.08 to 1.7 ng/ml and spanning 7.9–22.1 wk. Twenty-four studies assessed BCR, with 21 utilizing the Phoenix criteria [18], one HIFU study utilizing the Stuttgart criteria [20], one CRYO and two HIFU studies utilizing both the Phoenix and the Stuttgart criteria, and a final CRYO series utilizing a separate definition (Benoit et al. [25] considered <0.4 and <1.0 ng/ml). Figure 1 shows the oncological outcomes at 5 yr.

The overall BCRFS rates at 5 and 10 yr were 69% (95% confidence interval [CI]: 60–76; 97%) and 58% (95% CI: 49–65; 94%), respectively (Fig. 2). The pooled frequency of BCRFS at 5 yr in CRYO was 64% (95% CI: 53–74; 97%), while in HIFU at 5 and 10 yr, the frequencies were 73% (95% CI: 60–83; 98%) and 56% (95% CI: 46–66; 95%), respectively. One study reported 10-yr BCRFS of CRYO at 63% [26], and four studies [28], [34], [40], [49] used the D'Amico criteria to risk stratify BCRFS at 5-yr intervals, with results ranging from 66% to 89% for low, 40% to 78% for intermediate, and 21% to 80% for high risk. Regarding histological findings,

the percentage of patients undergoing biopsy ranged from 19% to 94%. The percentage of positive biopsy findings ranged from 10% to 59%. Similarly, the percentage of biopsy without malignancy varied from 23% to 87%; Supplementary Table 5 summarizes these outcomes of the included studies.

3.3.3. Recurrence-free survival

RFS or progression-free survival (PFS) was reported in nine studies. RFS at 5 yr ranged from 69% to 83% with CRYO and was 77% (95% CI: 69–83; 88%) with HIFU. Two studies provided the RFS outcomes at 10 yr ranging from 71% to 79% [48], [52]. Sung et al. [40] reported 5-yr PFS after HIFU at 73.5% for low risk, 46% for intermediate risk, and 29.2% for high risk with 100% follow-up. Bründl et al. [52] further reported overall 15-yr RFS of 73%, with 82% for low-risk, 73% intermediate-risk, and 47% for high-risk disease.

3.3.4. Metastasis-free survival

MFS was reported in 11 studies; MFS rates at 5 and 10 yr were 93% (95% CI: 88–96; 90%) and 84% (95% CI: 63–94; 98%), respectively. MFS at 5 yr was 93% for CRYO (95% CI: 86-97; 73%) and was also 93% for HIFU (95% CI: 84–97; 94%). A HIFU study reported MFS at 15 yr to be 85%, with 91% for low-risk, 85% for intermediate-risk, and 58% for high-risk disease [52].

3.3.5. Disease-specific survival

Twenty studies reported DSS outcomes; 5- and 10-yr rates were 98% (95% CI: 96–99; 90%) and 96% (95% CI: 92–97; 94%), respectively. The 5-yr DSS rate in CRYO was 98% (95% CI: 96–99; 75%), while in HIFU, the rates at 5 and 10 yr were 98% (95% CI: 94–99; 90%) and 95% (95% CI: 91–97; 91%), respectively. Guo et al. [35] reported 10-yr DSS of 98% for CRYO, whereas Bründl et al. [52] reported 15-yr DSS on HIFU: 89% overall and 95%, 89%, and 65% across low- to high-risk stratifications. Supplementary Figures 4 and 5 depict the oncological outcomes of HIFU at 5 and 10 yr, respectively.

3.3.6. Overall survival

OS was mentioned in 16 series; 5- and 10-yr OS rates were 92% (95% CI: 89–94; 79%) and 63% (95% CI: 33–86; 99%), respectively. The OS rate at 5 yr in CRYO was 91% (95% CI: 87–94; 69%), while in HIFU, the rates at 5 and 10 yr were 93% (95% CI: 88–96; 81%) and 64% (95% CI: 27–89; 99%), respectively. Guo et al. [35] reported 10-yr CRYO OS of 61%, and Rosenhammer et al. [48] found 15-yr OS of 57.0%, with 66.0% for low risk, 56.0% for intermediate risk, and 35.0% for high risk.

3.4. Morbidity

Complications were not consistently described in all series; nonetheless, certain major adverse events were often highlighted in those studies that might have an impact on the quality of life. Figure 3 shows the complication rates of the included studies, with further summary in Supplementary Table 6 and Supplementary Figure 6.

3.4.1. Stricture

In nine studies (two CRYO and seven HIFU), stricture rates were 11% (95% CI: 6–19; 98%), specifically 5% with CRYO and 12% (95% CI: 7–21; 98%) with HIFU.

3.4.2. Urinary retention

Eleven studies (five CRYO and six HIFU) identified 10% (95% CI: 6–15; 93%) urinary retention, with a rate of 6% (95% CI: 3–13; 93%) in CRYO and 14% (95% CI: 8–23; 93%) with HIFU.

3.4.3. Urinary tract infection

In nine trials (eight HIFU and one CRYO), UTIs were 8% (95% CI: 5–13; 92%), including 10% with CRYO and 7% (95% CI: 4–12; 91%) with HIFU. Four studies (two CRYO and two HIFU) reported 3–6% and 18-s23% of severe UTIs [27], [34], [43], [44].

3.4.4. Rectourethral fistula

Sixteen studies (six CRYO and ten HIFU) reported on RUF, with a rate of 0.7% (95% CI: 0.6–0.9; 0%), including 0.8% (95% CI: 0.5–1.2; 0%) for CRYO and 0.7% (95% CI: 0.5–0.9; 0%) for HIFU. Limani et al. [43] reported 0.9% rate of severe RUF with HIFU.

3.4.5. Others

Sepsis was mentioned only in the CRYO study by Benoit et al. [25], reporting a 0.80% rate. Urethral sloughing ranged from 1% to 16%, including 1–16% for CRYO and 6% for HIFU. In nine studies (five CRYO and four HIFU), perineal pain was reported at 0.6–11%; ranges were 0.6–11% for CRYO and 0.7–7.9% for HIFU.

3.5. Functional outcomes

3.5.1. Urinary function/continence

Eighteen studies assessed urinary outcomes using various measures. Eight studies reported pad-related outcomes [31], [32], [34], [36], [37], [39], [41], [43], two used IPSS, and the remainder applied various other measures (Stamey criteria, CTCAE version 5, etc.).

3.5.1.1. Pad-related outcomes

Overall, pad-free rate was 96% (95% CI: 94–97, 74%), with 97% (95% CI: 95–98; 0%) for CRYO and 95% (95% CI: 87–98; 91%) for HIFU. Two CRYO studies reported 97.4% and 98.8% of 1-yr pad-free rates [31], [37]. Oishi et al. [34] reported a 2-yr postablation (CRYO) pad-free rate of 96.0%. Uchida et al. [47] reported pad-free rates after first and repeat HIFU of 97.7% and 96.6%, respectively. Supplementary Figures 6 and 7 display a subgroup analysis of the functional outcomes of CRYO/HIFU.

3.5.1.2. IPSS

Mearini et al. [46] observed that the median IPSS score after HIFU was 7 (range: 1–29), a 30% drop from baseline, but the exact assessment timing was not reported.

3.5.1.3. Male Urogenital Distress Index

Royce et al. [49] reported negligible post-HIFU urinary incontinence or lower urinary tract symptoms with median values of 32 (28–43) at 6 mo, 33 (29–41) at 12 mo, and 32 (29–46) at 24 mo.

3.5.1.4. CTCAE

Donnelly et al. [27] found no grade 3 or 4 urinary incontinence in 117 individuals undergoing CRYO. Levy and Jones [28] identified insignificant variations in urinary incontinence across prostate volumes (3.3% for <50 cc vs 2.1% for >50 cc), with functional recovery within 12 mo after CRYO. Shoji et al. [51] found only transitory incontinence in 3.7% of their HIFU cohort at 3 mo. Supplementary Table 7summarizes the functional outcomes of the included studies.

3.5.2. Erectile/sexual function

Sixteen studies addressed erectile/sexual function. Regarding PROMs, ten studies subjectively assessed erections with the capacity to penetrate/have intercourse, while others used the IIEF-5 score. Figure 4 depicts the functional outcomes of the included studies.

3.5.2.1. Unassisted erectile function

Preserved erectile function of preoperatively potent patients was 37% overall (95% CI: 26–48; 91%); it ranged from 23% (95% CI: 9–48; 94%) with CRYO to 46% (95% CI: 38–54; 78%) with HIFU. Ward et al. [31] found pretreatment prostate size to have minimal influence on potency preservation at 12 mo after CRYO (30.3% for <50 cc and. 32.3% for >50 cc).

3.5.2.2. Assisted erectile function

Reporting of pharmacotherapy and other forms of intercourse assistance after ablation was variable; only three studies expressly remarked on new usage of phosphodiesterase type-5 inhibitors after the procedure, with implementation ranging from 12.8% to 66.7% [41], [43], [44]. Regardless of assistance type, potency was maintained in 24.9–69.1% of the included studies, independent of all measures (both subjective and IIEF-5 based) [30].

3.6. Meta-regression

As we found heterogeneity in the pooled prevalence of the outcomes, we conducted a meta-regression analysis. Meta-regression was performed for 5-yr BCRFS, 5-yr OS, erectile function, and UTIs, as these outcomes were reported in a sufficient number of studies compared with the number of covariates. A model created for 5-yr BCRFS using age, baseline PSA, neoadjuvant ADT, Gleason score ≤6, Gleason score 7, and Gleason score ≥8 as covariates explained the heterogeneity. The tau was reduced to 0.29 from an initial value of 0.79 and I^2 reduced to 72.4% from an initial value of 97.3%, but the test for residual heterogeneity was significant ($p = 0.03$), thereby suggesting that there may still be unexplained covariates. The model showed a negative association of the 5-yr BCRFS prevalence with neoadjuvant ADT (odds ratio, 0.92; 95% CI: 0.89–0.96) suggesting that ADT did not influence/augment survival. The model's covariates were able to explain 100% heterogeneity for UTIs, with tau reduced to 0 from an initial value of 0.78, I^2 reduced to 0% from 91.6%, and the test for residual heterogeneity turned nonsignificant ($p = 0.71$). The covariates could not account for the heterogeneity seen for 5-yr OS and erectile function. Egger's test did not show any publication bias and the p value was nonsignificant ($p = 0.72$). Supplementary Table 2 shows the meta-regression analysis.

3.7. Summary

Whole-gland ablation (WGA) in the salvage setting after RT has already been incorporated into several international guidelines [12], [53]. Primary ablation is similarly well accepted by PCa experts and has widely been implemented for >25 yr. Several guidelines generally authorize its use in low- to intermediate-risk PCa after the patient has made an informed decision regarding risks/benefits on oncological/functional outcomes; indeed, informed decision-making applies to radical treatments as well, as every intervention has its own advantages and complications.

Nonetheless, as image-guided focal therapy has emerged, it is increasingly important to define best practice recommendations and establish a foundation for WGA. The focus of this systematic review was on HIFU and CRYO, as these energy modalities have the most real-world experience to date. The decision between CRYO and HIFU should be based on clinician experience and patient preference since comparative studies are scarce [30]. While other, newer energy modalities exist, literature supporting their use as WG options is limited due to short follow-up and preferential study now aimed at focal techniques. Extrapolation from CRYO and HIFU series to other ablative energy sources should not be made without proper study.

In a literature review comparing oncological outcomes among radical approaches, Goy et al. [54] compared RP, external beam RT (EBRT), and brachytherapy (BT) for intermediate-

risk PCa at 10 yr. The BCRFS, RFS, DSS, and MFS were 57.1%, 64.6%, 96.6%, and 94%, respectively, for RP; 57%, 73%, 96.2%, and 90.6%, respectively, for EBRT; and 80%, 90%, 95.4%, and 94%, respectively, for BT. As a reference, the well-conducted ProtecT trial demonstrated that DSS rates in low-risk PCa for RP and RT were 99% and 99.6%, respectively [55]. We acknowledge that our meta-analysis results were based mostly on retrospective studies with observed heterogeneity, but at 10 yr the oncological outcomes were found to be comparable, given that 22% of the pooled cohort was at a high risk. The 10-yr OS rate was slightly lower at 63% as compared with 78% for BT, 85.5% for RP, and 75.5% for EBRT, as this may be attributed to the elderly nature (>50% were >70 yr old) of our population.

Two RCTs compared the therapeutic efficacy of CRYO to EBRT. According to Donnelly et al. [27], CRYO had similar 3- (17.1% vs 13.2%), 5- (25% vs 25.1%), and 8-yr (27% vs 31.7%) BCR; 5-yr OS (89.7% vs 88.3%, $p = 0.78$); and 5-yr DSS (96.4% vs 96.1%) to EBRT. Although there was some concern about CRYO's therapeutic efficacy due to methodology (noninferiority) and the unconventional radiation dosage used in the trial, the positive biopsy rate at 3 yr was significantly less with CRYO (7.7% vs 28.9%, $p = 0.0004$), proving the therapeutic efficacy of CRYO. While contemporary radiation dosages would likely have improved EBRT results, ablation has also experienced evolutionary development in techniques, real-time imaging support, and better user interface. In contrast, Chin et al. [56] found that CRYO had inferior BCRFS to EBRT (17% vs 59%) at 8 yr in treating T2c-T3b PCa, but the intermediate- and long-term outcomes of DSS and OS were similar. Thus, level 1 evidence, although notably likely underpowered, demonstrates CRYO to have comparable positive biopsy rate at 3 yr with long-term DSS and OS, particularly in frail patients with high-risk disease. The real-world evidence from our meta-analysis also supports its use in such cases; nonetheless, patients should be advised about possibly lower BCRFS and the requirement of salvage therapies/multimodality approaches.

The utility of WGA is further bolstered by the negative effect on functional quality of life outcomes associated with radical approaches. The urinary incontinence and erectile dysfunction rates with RP (robotic/open) at 12 mo have been described as 21.3%/20.2% and 70.4%/74.7%, respectively [57]. Pad-free and erectile preservation rates at 12 mo were, respectively, 29.4% and 14.6% for RP, and 61.5% and 37.6% for EBRT [58]. Conversely, in ablation, the pad-free rates overall, at 1 yr, and at 2 yr were 96%, 98%, and 96%, respectively; the preserved erectile function rate was 37%. Thus, ablation techniques consistently provide better urinary continence than and comparable erectile function to radical approaches.

Even though eight studies evaluated pad-free rates, two studies mentioned a 1-yr pad-free rate and one study mentioned a 2-yr pad-free rate. The precise timing of the functional outcome measurement was not specified in the other studies. We acknowledge that there is sufficient evidence of continuous improvement in functional outcomes following initial insult after primary ablative therapy, as is similarly evident in RP or RT, unless the patient develops primary urinary incontinence, either due to increasing age or secondary to the presence of other comorbidities such as diabetes or neuropathies. After ablation, patients' urinary continence returns within a year and otherwise remains stable. In short, confounders might influence long-term functional outcomes, limiting their significance.

In terms of WGA treatment adjuncts, ADT with ablation was historically used in a neoadjuvant fashion, intended to exact benefits through prostate downsizing and increasing the treatment coverage [56]. In our review, 36.5% (16–100%) of patients had neoadjuvant

ADT. However, ADT's role with WGA has been suggested to be limited due to different mechanisms of action with this combination [31], [40]. This was confirmed via a meta-regression analysis to determine the effect of ADT on BCRFS, observing a negative effect with a 0.92 odds ratio (95% CI: 0.89–0.96, p = 0.0004). Additionally, ADT was used as an adjuvant in several studies for varying durations (longest was 4 mo) reported by Gestaut et al. [33], limiting its confounder impact on long-term oncological outcomes.

Importantly, several large series with long-term (10+ yr) follow-up serve as a basis to appropriately recommend WG CRYO and HIFU as feasible alternative therapeutic choices for the management of select low- and intermediate-risk localized PCa patients in the primary setting. In the case of high-risk disease, WGA is best done within a clinical trial or registry, and patients should be advised about the possible uncertainties with recurrence, as is typically the case with RP and RT as well. Given historical critiques of WGA for a lack of long-term follow-up data and standardized protocols, this meta-analysis supports the conclusion that ablation offers mild functional changes, particularly regarding the preservation of urinary continence in the primary setting, with adequate oncological outcomes despite modest availability of RCT-level data. Nonetheless, the pursuit of well-designed RCTs and further high-level data should never cease, and this will remain a future goal. Importantly, these data should help inform patients and physicians alike to optimize decision-making at this critical juncture in a patient's disease course.

4. Conclusions

The oncological and technical safety profiles of CRYO and HIFU appear to be comparable with those of current radical therapies. Through a comprehensive systematic review and meta-analysis, we present real-world data to help guide physicians and patients with decision-making when considering ablative therapy for the treatment of clinically localized PCa in the primary setting. The mid- to long-term data and the safety profiles of CRYO and HIFU are sound to support and be offered as primary treatment for appropriate patients with localized PCa.

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