SEMMELWEIS EGYETEM
DOKTORI ISKOLA

Ph.D. értekezések

3436.

SKRIBEK BENJAMIN

Szív- és érrendszeri betegségek élettana és klinikuma
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THE ROLE OF ONCO-INTERVENTIONAL RADIOLOGY IN MODERN HEALTHCARE

Ph.D. Thesis

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Budapest

2026

“Tell me and I forget. Teach me and I remember. Involve me and I learn.”

Benjamin Franklin

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1. LIST OF ABBREVIATIONS

AMSTAR 2	A Measurment Tool to Assess Systematic Reviews
APA	Aldosterone-Producing Adenoma
ARR	Aldosterone-to-Renin Ratio
AS	Active Surveillanc
AVS	Adrenal Vein Sampling
BRFS	Biochemical Recurrence-Free Survival
CI	Confidence Interval
CSS	Cancer Specific Survival
CT	Computed Tomography
ECT	Electrochemotherapy
FT	Focal Therapy
HIFU	High-Intensity Focused Ultrasound
HR	Hazard Ratio
IRE	Irreversible Electroporation
IQR	Interquartile Range
LA	Laparoscopic Adrenalectomy
LOS	Length Of hospital Stay
MD	Mean Difference
MFS	Metastasis-Free Survival
MRI	Magnetic Resonance Imaging
MWA	Microwave Ablation
NA	Not Applicable
NCCN	National Comprehensive Cancer Network

ND	Not Defined
OR	Odds Ratio
OS	Overall Survival
PCA	Prostate Cancer
PH	Primary Hyperaldosteronism
PICO	Population Intervention Comparison Outcome
PI	Prediction Interval
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Prostate-Specific Antigen
QUIPS	Quality In Prognosis Studies
RCT	Randomized Controlled Trial
RFA	Radiofrequency Ablation
ROB 2	Risk Of Bias 2
ROBINS-I	Risk Of Bias In Non-randomized Studies - of Interventions
RP	Radical Prostatectomy
RT	Radiotherapy
SD	Standard Deviation
SPECT	Single-Photon Emission Computed Tomography
TACE	Transarterial Chemoembolization
TAE	Transarterial Embolization
TARE	Transarterial Radioembolization
TNM	Tumor Node Metastasis
USA	United States of America

2. STUDENT PROFILE

2.1. Vision and mission statement, specific goals

My vision is that minimally invasive, image-guided therapies will become widely accessible and routinely applied in the treatment of a broad range of diseases, offering patients effective and organ-preserving alternatives to traditional therapies. My mission is to simplify and improve the care of individuals with benign and malignant conditions by advancing safe, humane, and evidence-based interventional procedures. Through rigorous scientific evaluation of novel interventional techniques, I aim to support their wider clinical adoption in oncological care.

2.2. Scientometrics

Number of all publications:	4
Cumulative IF:	17.5
Av IF/publication:	4.375
Ranking (SCImago):	D1: 1, Q1: 3
Number of publications related to the subject of the thesis:	2
Cumulative IF:	8.0
Av IF/publication:	4.0
Ranking (Sci Mago):	Q1: 2
Number of citations on Google Scholar:	12
Number of citations on MTMT (independent):	6
H-index:	2

The detailed bibliography of the student can be found on pages 77-78.

2.3. Future plans

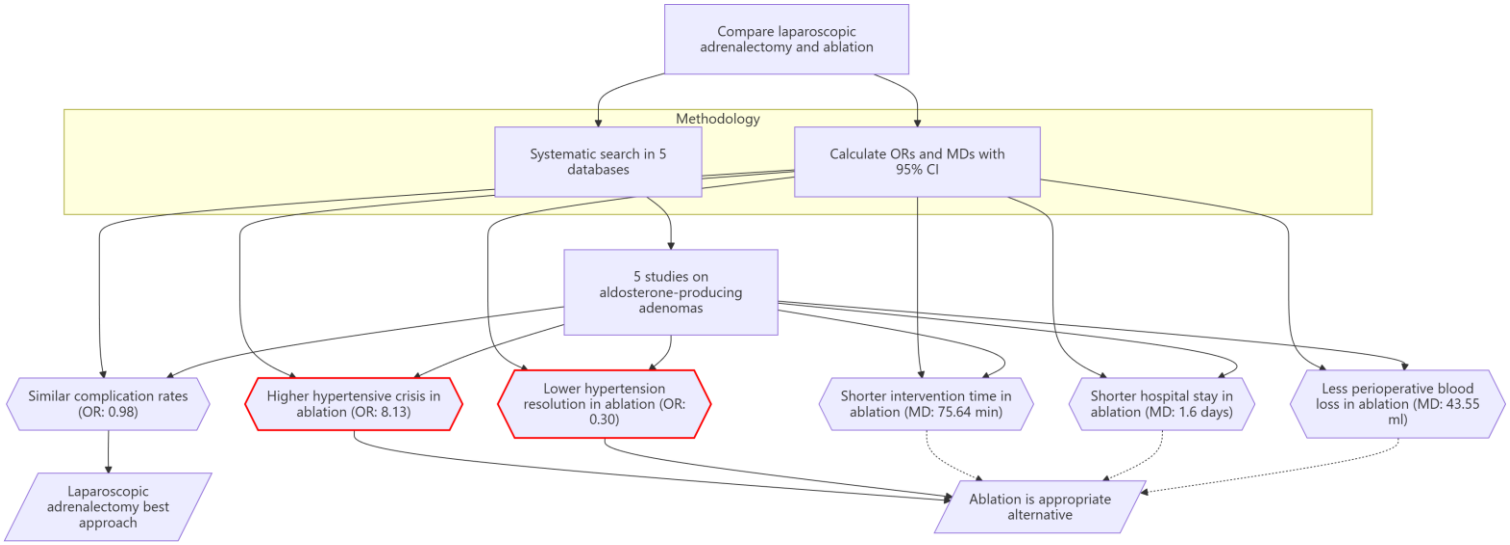
In the future, I intend to continue my research in onco-interventional radiology. After completing my radiology board examination, I plan to obtain a license in interventional radiology. My long-term goals include further developing and applying the techniques I have studied throughout my research.

3. SUMMARY OF THE THESIS

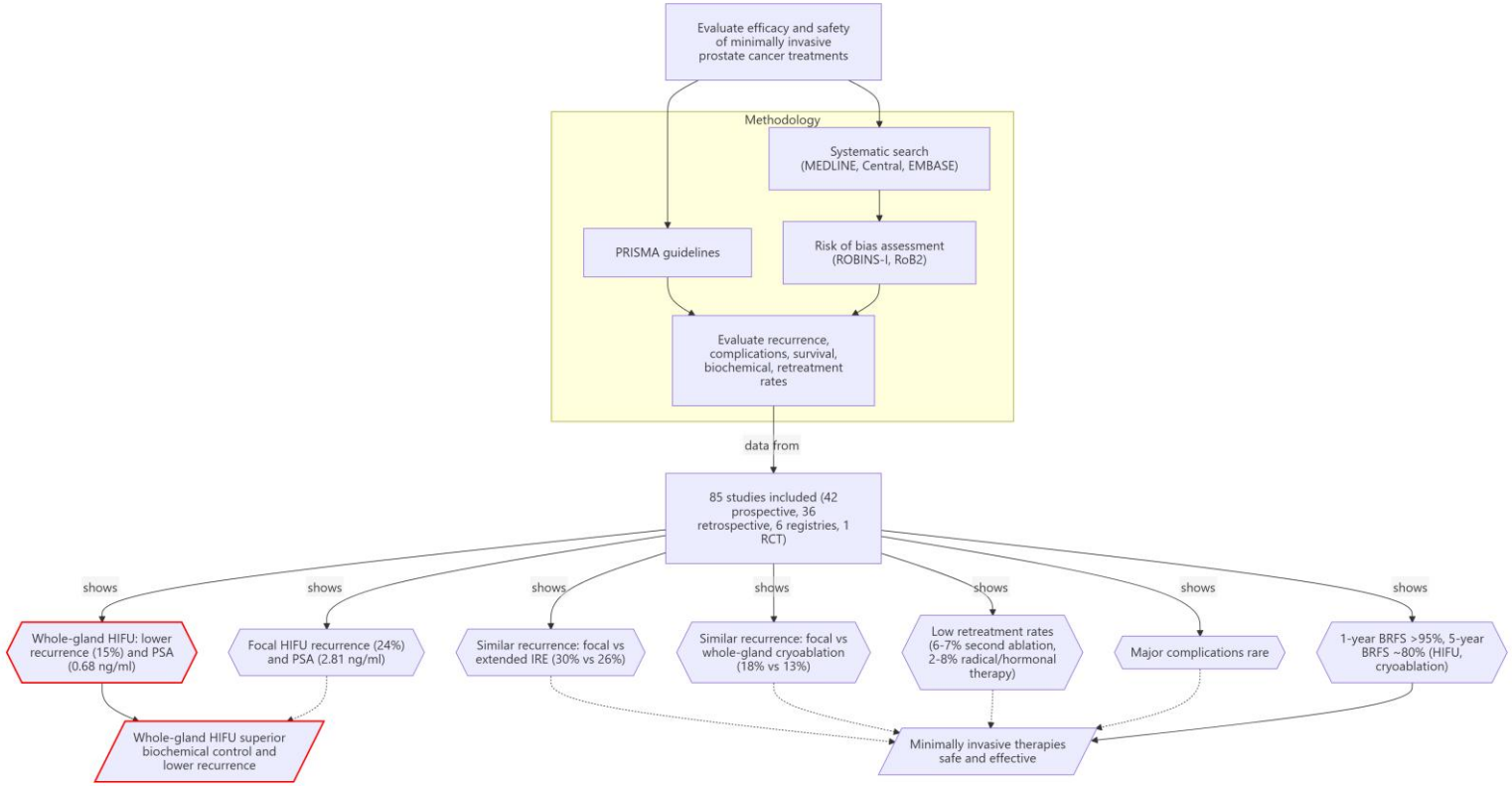
This thesis explores the role of minimally invasive, image-guided interventional procedures, specifically focusing on benign adrenal aldosterone-producing adenomas and low- to intermediate-risk prostate cancer. Study I provides a systematic review and meta-analysis comparing laparoscopic adrenalectomy with ablation techniques. Although ablation is associated with shorter operation times and reduced hospital stays, laparoscopic adrenalectomy remains superior in achieving resolution of hypertension and is associated with a lower risk of perioperative hypertensive crisis. Study II synthesizes evidence from focal and whole-gland interventional treatments, including high-intensity focused ultrasound (HIFU), cryoablation, and irreversible electroporation (IRE), showing consistently high survival rates and low major complication rates across modalities. The analysis highlights that whole-gland HIFU provides better biochemical control and lower recurrence rates than focal HIFU, while focal and whole-gland approaches perform comparably for IRE and cryoablation. Overall, the findings underscore the expanding role of onco-interventional therapies as alternative options to traditional treatments. The thesis emphasizes the need for standardized outcome reporting, long-term follow-up, and high-quality comparative trials to strengthen clinical decision-making. Ultimately, this work adds to the growing evidence that will help integrate advanced interventional techniques into patient-centered cancer care.

4. GRAPHICAL ABSTRACT

4.1 Study I.



4.2 Study II.


Evaluate efficacy and safety of minimally invasive prostate cancer treatments
Methodology
Systematic search (MEDLINE, Central, EMBASE)
PRISMA guidelines
Risk of bias assessment (ROBINS-I, RoB2)
Evaluate recurrence, complications, survival, biochemical, retreatment rates
data from
85 studies included (42 prospective, 36 retrospective, 6 registries, 1 RCT)
shows
Whole-gland HIFU: lower recurrence (15%) and PSA (0.68 ng/ml)
Focal HIFU recurrence (24%) and PSA (2.81 ng/ml)
Similar recurrence: focal vs extended IRE (30% vs 26%)
Similar recurrence: focal vs whole-gland cryoablation (18% vs 13%)
Low retreatment rates (6-7% second ablation, 2-8% radical/hormonal therapy)
Major complications rare
1-year BRFS >95%, 5-year BRFS ~80% (HIFU, cryoablation)
Whole-gland HIFU superior biochemical control and lower recurrence
Minimally invasive therapies safe and effective

5. INTRODUCTION

5.1. Onco-interventional radiology

Onco-interventional radiology has become an essential component of oncological practice, combining high-resolution diagnostic imaging with minimally invasive, image-guided therapeutic procedures. These interventions involve thermoablative techniques, including high-intensity focused ultrasound (HIFU), radiofrequency ablation (RFA), microwave ablation (MWA), and cryoablation, as well as electrochemotherapy (ECT), transarterial embolization (TAE), chemoembolization (TACE), and radioembolization (TARE). Minimally invasive treatment strategies provide precise and organ-preserving interventions for both benign and malignant lesions, thereby expanding therapeutic options in multidisciplinary cancer care (1). Despite their increasing clinical applications, onco-interventional procedures remain inconsistently evaluated, and high-quality comparative evidence, both among these techniques and in comparison with gold-standard surgical and systemic treatments, is still limited. This lack of evidence complicates treatment selection and the formulation of clinical guidelines for practising physicians. Therefore, systematically assessing the efficacy, safety, and clinical value of these interventional procedures represents an essential step toward optimizing evidence-based oncological care.

5.2. Aldosterone-producing adrenal tumors

The prevalence of adrenal gland tumours in the adult population ranges from 0.2% to 3.2% (2). Aldosterone-producing adenomas (APA) represent a clinically relevant subtype responsible for primary hyperaldosteronism (PH), manifesting with hypertension and hypokalemia (3). While PH remains relatively uncommon in the general population, it contributes to approximately 5–10% of all hypertension diagnoses. It is associated with considerable morbidity, including elevated risks of stroke, myocardial infarction, cardiac arrhythmias, and progressive renal dysfunction (4-6).

Laparoscopic adrenalectomy (LA) is the gold-standard therapy for APA-related PH. Nevertheless, its suitability may be limited by factors such as obesity, previous abdominal surgery, coagulation disorders, and cardiopulmonary diseases (7). Furthermore, LA carries a higher risk of injury to surrounding anatomical structures, including the colon,

pancreas, spleen, and diaphragm (8). These limitations collectively highlight the need for alternative therapeutic options. Potential minimally invasive alternatives to LA include ultrasound- or computed tomography (CT)-guided percutaneous cryotherapy, MWA, RFA, catheter-based ethanol ablation, and adrenal artery embolization techniques. Hormone-producing adrenal adenomas can be successfully treated with ablative techniques (9-11). However, available data indicate that these procedures carry a substantially higher risk of hypertensive crisis than LA (12-14).

5.3. Localized prostate cancer

The prevalence of prostate cancer (PCa) is approximately 5% below the age of 30 years and increases by an odds ratio (OR) of 1.7 per decade, reaching nearly 59% in men over 79 years of age (15). Low- and intermediate-risk PCa is typically asymptomatic, but local progression may lead to erectile dysfunction, urinary retention, pain, or hematuria. Based on patient eligibility, the initial management strategy is active surveillance (AS), which aims to delay or avoid radical treatment (16). One of the most significant prospective studies on low-risk PCa managed with AS, conducted by Tosoian et al., followed 1,298 men and reported a median treatment-free survival of 8.5 years, along with a 31% cumulative incidence of grade reclassification during the follow-up period (17). For patients who are not eligible for AS, radical prostatectomy (RP) or radiotherapy (RT) is considered to be the next therapeutic option (18, 19). However, all radical treatments carry the risk of significant adverse effects, most commonly incontinence, erectile dysfunction, and infection; therefore, alternative treatment strategies are essential (20).

Alternative therapeutic approaches such as HIFU, MWA, RFA, cryoablation, and IRE aim to reduce complications and treatment-related toxicity while maintaining equivalent oncological effectiveness (21, 22). Focal therapy (FT) selectively targets specific lesions or regions to preserve healthy tissue and reduce side effects, whereas whole-gland treatments involve the complete ablation of the prostate (23, 24). Both focal and whole-gland treatments offer viable options for managing low- and intermediate-risk PCa.

6. OBJECTIVES

6.1. Study I. – Ablation and laparoscopic adrenalectomy: Balancing efficacy and safety in the treatment of benign adrenal gland tumors: A systematic review and meta-analysis

The aim of this study was to systematically compare laparoscopic adrenalectomy with minimally invasive interventional procedures in the management of benign adrenal tumors, focusing on perioperative complications and biochemical cure rates. Furthermore, we sought to assess if interventional approaches, such as ablation techniques, could replace laparoscopy as the preferred gold standard of care.

6.2. Study II. – Oncological Efficacy and Safety of Minimally Invasive Focal and Whole-Gland Interventions in the Treatment of Low- and Intermediate-Risk Prostate Cancer: A Systematic Review and Meta-Analysis

This review aims to evaluate the oncological effectiveness and safety of focal and whole-gland interventional therapies in the management of low- to intermediate-risk prostate cancer. We conducted a systematic review and meta-analysis of oncological, biochemical, and complication outcomes to provide an updated synthesis of the available evidence. Additionally, subgroup analysis was conducted to evaluate clinical differences between focal and whole-gland approaches.

7. METHODS

7.1. Study I.

7.1.1. Methodology and Protocol

We followed the methodological recommendations of the Cochrane Handbook, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, and the AMSTAR 2 (A Measurement Tool to Assess Systematic Reviews) framework during the study selection and data extraction phases (25-27). The study protocol was registered in the PROSPERO database before initiation (registration number: CRD42022367148).

7.1.2. Eligibility Criteria

We formulated our clinical question using the PICO (Population, Intervention, Comparison, Outcome) framework. The identified studies were selected according to the following criteria: (P) patients who underwent LA or an interventional radiological procedure to treat early-stage adrenal gland tumors (I, C). Possible ablative techniques included cryoablation, RFA, MWA, chemoablation, intravascular embolization, HIFU, laser therapy, silicone gel therapy, or IRE, which were compared to laparoscopic adrenalectomy; (O) in terms of outcomes: complication rate, which was calculated based on mortality, major and minor morbidity factors; the proportion of hypertensive crisis; resolution of hypertension, described as achieving a normalized aldosterone-to-renin ratio (ARR) and no longer requiring additional antihypertensive medications following interventions; perioperative blood loss; operation time; length of hospital stay; and postoperative pain treatment. The study design included cohort studies, case-control studies, and randomized controlled trials. No language restrictions were applied to the selection process.

Studies were excluded if they were (a) reviews, meta-analyses, systematic reviews, case reports, and case series; (b) non- comparative studies; (c) preclinical or animal studies; (d) research on patients with advanced tumors or metastases. Data from conference abstracts and papers for which the full text could not be retrieved were also excluded.

7.1.3. Information Sources and Search Strategy

Five databases, MEDLINE via PubMed, Central, Scopus, Web of Science, and Embase were searched for relevant articles. The search date was November 5, 2022, and the last update was on July 25, 2024; the main domains of our search key were adrenal tumors, laparoscopy, and minimally invasive interventions. No filters or other restrictions were used.

7.1.4. Study Selection and Data Extraction

Endnote v9.0 (Clarivate Analytics, Philadelphia, PA, USA) reference manager software and Ryyan (Rayyan Systems Inc., Cambridge, MA 02142, USA) were used to select studies. After the automatic and manual removal of duplicate records, two co-investigators (BS and JÁ) separately evaluated the eligibility of articles by first author, title, and abstract, then the remaining articles by full text. Discrepancies were resolved by a third investigator (AS). To check reliability, Cohen's kappa coefficient (κ) was calculated after each step (28). The complete study selection process was illustrated in the PRISMA flowchart (Figure 1).

Two authors (BS and JÁ) independently used a standardized data extraction table to extract data from eligible articles. The extracted data involved (a) general information on the article: name of the first author, year of publication, study design, study region, type of ablation procedure, and study period; (b) characteristics of the population: age, sex, tumor diameter, and location, highest systolic and diastolic blood pressure; (c) primary outcome parameters: complications, hypertensive crisis, biochemical success in terms of hypertension resolution, and secondary outcome parameters: perioperative blood loss, operation time, length of hospital stay and postoperative pain treatment.

The preferred data format for operation time, length of hospital stay, and perioperative blood loss was the mean with standard deviation (SD). The mean and standard deviation of blood loss were estimated from the median and quartile values based on the work by Sun et al. (29). Furthermore, the data on hospital stays from Cano et al. were calculated from the median, minimum, and maximum ranges for mean and SD (12).

7.1.5. Risk of Bias and Quality of Evidence Assessment

Two independent review authors (BS and JÁ) used the Quality in Prognosis Studies (QUIPS) tool to assess the risk of bias as recommended by the Cochrane Handbook (25, 30). Categories of risk assessment were pre-defined for each domain. Disagreements were resolved by a third review author (AM).

7.1.6. Data Synthesis and Analysis

The statistical analyses were performed using the R software (R Core Team 2020, version 4.0.3), and the meta (version 6.1-0) package was used for calculations and plots (31).

For continuous outcomes, the mean difference (MD) was calculated as the effect size measure with a 95% confidence interval (CI). To calculate the MD and its standard deviation, the extracted values were the sample size, the mean, and the standard deviation for both groups. In the rare cases where a study did not report these, the mean was estimated using the method proposed by Luo et al., and the standard deviation was calculated using the method proposed by Shi et al. based on the median, quartile, minimum, and maximum values (32, 33). When such a calculation was needed, we indicated it on the forest plot.

The OR with 95% CI was used to measure the effect of binary outcomes. The OR was calculated by subtracting the total number of patients in each group and the total number of patients with the event of interest from each study. For the summary OR estimate, we used the Mantel-Haenszel method (without continuity correction) with the Paule-Mandel estimator for the between-study variation τ following the recommendation of Harrer (34). Raw data from the selected studies were summarized using the random-effects model. We used the Hartung-Knapp adjustment for each analysis to avoid false positive conclusions (35). Where applicable, we reported the 95% summary prediction interval (PI), following the recommendation of IntHout (36).

Cochrane's Q test was evaluated to assess statistical heterogeneity, while the I2 index was utilized to quantify the extent of heterogeneity between studies. Additionally, funnel plots were employed to report and visually represent any potential publication bias effectively. We performed a sensitivity analysis using the "Leave one out" method.

We used forest plots to summarize the results graphically. Statistical significance was defined as p-value <0.05 for all outcomes.

No subgroup analysis was performed.

7.2. Study II.

7.2.1. Methodology and Protocol

During the selection and extraction stages, we followed the recommendations of the Cochrane Handbook, Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (25, 26). Our study protocol was registered on PROSPERO before the start date under registration number CRD42023414131.

7.2.2. Eligibility Criteria

We formulated our clinical question using the PICO (Population, Intervention, Comparison, Outcome) framework. Studies included were identified according to the following criteria: (P) Patients who had received any interventional radiological treatment for their low- or intermediate-risk PCa; and (I, C) minimally invasive interventional procedures commonly used in clinical practice, including HIFU, IRE, RFA, MWA, cryoablation, intravascular embolization, and chemical ablation, either separately or compared to one another. For IRE, focal and extended treatment strategies were compared, while for cryoablation and HIFU, our analysis examined focal approaches - including targeted, partial, quadrant, and hemigland ablation - in comparison to whole-gland ablation. (O) As for outcomes, biopsy-proven in-field recurrence, defined as cancer persisting or reappearing within the initially treated zone, and out-of-field recurrence, indicating cancer detected outside the treated area, were assessed using 6-month, 12-month, and pooled data when different follow-up times were not considered; complication rates were reported according to the Clavien–Dindo classification, with grade 3 or higher adverse events categorized as major complications; the survival endpoints evaluated comprised overall survival (OS), cancer-specific survival (CSS), and metastasis-free survival (MFS); functional outcomes, including postoperative urinary incontinence and erectile dysfunction; and biochemical outcomes were assessed based on postoperative mean prostate-specific antigen (PSA) levels and biochemical recurrence-free survival rates (BRFS) as defined by the Phoenix criteria.

The study design consisted of randomized controlled trials (RCTs), prospective and retrospective cohort studies, case–control studies, and registries. No language restrictions were applied to the selection process.

Studies were excluded if they were (a) reviews, meta-analyses, systematic reviews, case reports, or case series; (b) preclinical or animal studies; (c) studies on low- and intermediate-risk patients could not be separated from high-risk cases or metastatic prostate tumors; and (d) studies on patients with previous treatment. Data from conference abstracts and papers without accessible full texts were also excluded.

7.2.3. Information Sources and Search Strategy

We systematically searched for relevant articles in three databases using consistent search terms: MEDLINE via PubMed, Central, and EMBASE. The search was conducted on 7 May 2023, and the last update was on 5 January 2025; the domains of our search key included prostate, low-intermediate-risk tumors, and minimally invasive interventional radiological treatments.

No filters or other restrictions were used.

7.2.4. Study Selection and Data Extraction

EndNote v9.0 (Clarivate Analytics, Philadelphia, PA, USA) reference manager software and Ryyan (Rayyan Systems Inc., Cambridge, MA 02142, USA) were used during the study selection process. After automatic and manual removal of duplicate records, two coinvestigators (BS and JÁ) independently assessed the eligibility of articles by first author, title, and abstract, then the remaining articles by full text. A third investigator resolved any discrepancies (AS), and Cohen's kappa coefficient (κ) was calculated at each stage to assess inter-rater reliability (28). The entire study selection process is illustrated in the PRISMA flowchart (Figure 5).

Two authors (BS and JÁ) independently extracted data from eligible publications using a standardized data extraction table. The data extracted included (a) general details of the article: name of the first author, year of publication, study design, study region, type and subgroups of interventions, and brand of the device used; (b) essential characteristics of the study population: age, tumor grading including Gleason score, National Comprehensive Cancer Network system (NCCN), and clinical Tumor Node Metastasis

classification (TNM), and preoperative PSA levels; (c) outcome parameters included recurrence rates, biochemical control, retreatment rates, and complication rates according to Clavien–Dindo classification (37).

7.2.5. Risk of Bias and Quality of Evidence Assessment

Two independent reviewers (BS and JÁ) assessed the risk of bias using the Risk of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool for non-randomized studies and the Risk of Bias 2 (RoB 2) tool for randomized trials, following the guidelines outlined in the Cochrane Handbook (25, 38, 39). For the risk assessment of the ROBINS-I and RoB 2 tools, pre-defined categories were established for each domain. Any disagreements were resolved by a third reviewer (BG).

7.2.6. Data Synthesis and Analysis

Statistical analyses were conducted with R software version 4.1.3, using the meta and metafor packages. All analyses employed a random effects model with Hartung–Knapp adjustments to minimize false positive conclusions (35). We used the Q test and I2 statistics to evaluate statistical heterogeneity. Findings were presented in forest plots, with the mean effect size and its 95% CI as summary statistics. Where possible, we included the 95% prediction interval, following the recommendation of IntHout et al. (36). Raw complication, recurrence, and survival rates were logit-transformed, pooled using the random effects model, and back-transformed for presentation on the original scale (34). For the analysis of postoperative PSA levels, the mean PSA values were assessed. In cases where the mean and standard deviation were not directly reported, median values, quartiles, and minimum–maximum ranges were extracted, and the mean was estimated using the method proposed by Luo et al., while the standard deviation was calculated according to the method described by Shi et al. (32, 33). The leave-one-out method was used for sensitivity analysis. Statistical significance was set at $p < 0.05$.

8. RESULTS

8.1. Study I: Ablation and laparoscopic adrenalectomy: Balancing efficacy and safety in the treatment of benign adrenal gland tumors: A systematic review and meta-analysis

8.1.1. Study Search and Selection

A total of 7017 articles were found, of which five studies were eligible for our meta-analysis and systematic review (Figure 1) (12, 13, 29, 40, 41).

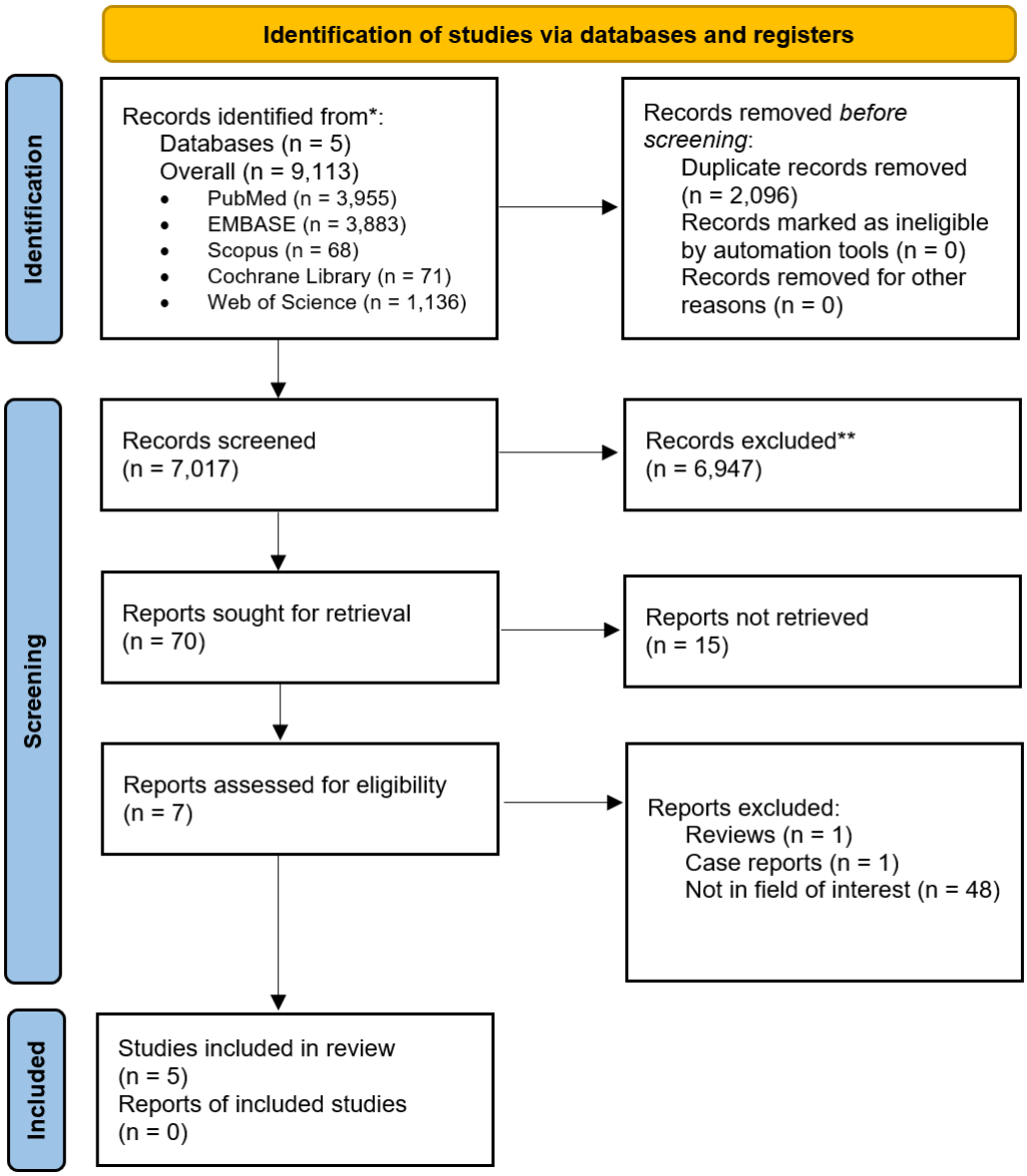


Figure 1. PRISMA 2020 flowchart showing the study selection process.

The five articles used were all retrospective cohort studies. The baseline characteristics of these studies are detailed in Tables 1 and 2. All studies focused on adrenal aldosterone-producing adenomas. Altogether, 119 patients were treated with adrenal ablation, and 161 underwent laparoscopic adrenalectomy in 14 centers in Europe, Asia, and the United States of America (USA). CT or magnetic resonance imaging (MRI) and adrenal venous sampling were performed in most cases prior to the diagnosis of APA. In four studies, percutaneous CT-guided RFA was the ablative procedure of choice, and catheter-based ethanol ablation was used only in one case.

Table 1. Basic characteristics of included studies.

Author (year)	Study site	Study design	Study period	Study participa-tion	Age (year) * Ablation group	Age (year) * LA group	Sex (female % of total)	Follow-up period (months) *
Liu et al. (2016)	China	Retrospective	2004-2012	63	52.2± 10.4	50.7±10.3	55.6	68.4 (22.8-127.2)
Yang et al. (2016)	Taiwan	Retrospective	2009-2013	25	54 (29-74)	45 (20-69)	56	ND (3-6)
Sarwar et al. (2016)	USA	Retrospective	2008-2013	44	51±11	50±11	47.7	11.4 ±12.8
Cano-Valderrama et al. (2021)	Spain	Retrospective	2007-2019	34	54.3 (49.1–59.5)	55.5 (50.3–60.8)	35.3	46.2 (3.4-147.5)
Sun et al. (2022)	China	Retrospective	2016-2019	112	45 (36–52)	43 (37–50)	50.1	6 (ND)

***Parameters represented as mean with standard deviation, or median with range (minimum and maximum)**

LA: Laparoscopic adrenalectomy; ND: not defined; USA: United States of America

Table 2. Baseline diagnostic and treatment characteristics of included studies.

		Ablation			Laparoscopic adrenalectomy		
Author (year)	**Diagnostic method**	**Type of ablation, number of patients**	**Tumor size (mm) ***	**Tumor laterality (right/left)**	**Number of patients**	**Tumor size (mm) ***	**Tumor laterality (right/left)**
Liu et al. (2016)	CT/MRI; laboratory test and AVS selectively	RFA; 36	16±5	17/19	27	14±5	12/15
Yang et al. (2016)	CT and laboratory test	RFA; 7	19 (11-25)	2/5	18	18 (8-25)	8/10
Sarwar et al. (2016)	AVS and laboratory test	RFA; 12	15.5± 5	ND	32	ND	ND
Cano-Valderrama et al. (2021)	Laboratory test, AVS + SPECT/CT selectively	RFA; 10	ND	ND	24	ND	ND

Sun et al. (2022)	AVS+CT	Ethanol; 52	12.2± 0.8	28/23	60	15.4± 1.2	25/35

*** Parameters represented as mean with standard deviation, or median with range (minimum and maximum)**

CT: computed tomography; MRI: magnetic resonance imaging; AVS: adrenal vein sampling; SPECT: single-photon emission computed tomography; RFA: radiofrequency ablation; ND: not define

8.1.2. Primary Outcomes

Resolution of hypertension

Results for the resolution of hypertension are presented in Figure 2. Compared with LA and ablation in resolving hypertension, i.e., biochemically measured clinical success, LA was significantly more effective than ablation (OR: 0.30; 95% CI: 0.16-0.56; p = 0.006).

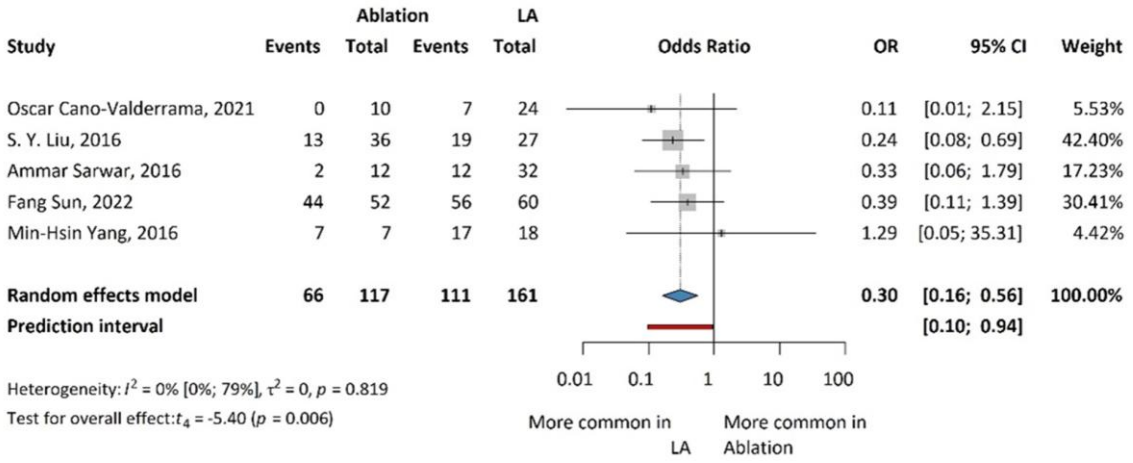


Figure 2. Forest plot summarizing the odds ratios (OR) of resolution of hypertension associated with ablation and laparoscopic adrenalectomy for aldosterone-producing adrenal tumors.

Complications

The results for complications are summarized in Figure 3. The complication rate was determined by considering mortality, major and minor complications, excluding hypertensive crises. No clinically relevant differences were found between the ablation procedures and LA (OR: 0.98; 95% CI: 0.35-2.69; p = 0.948). However, our results are not statistically significant.

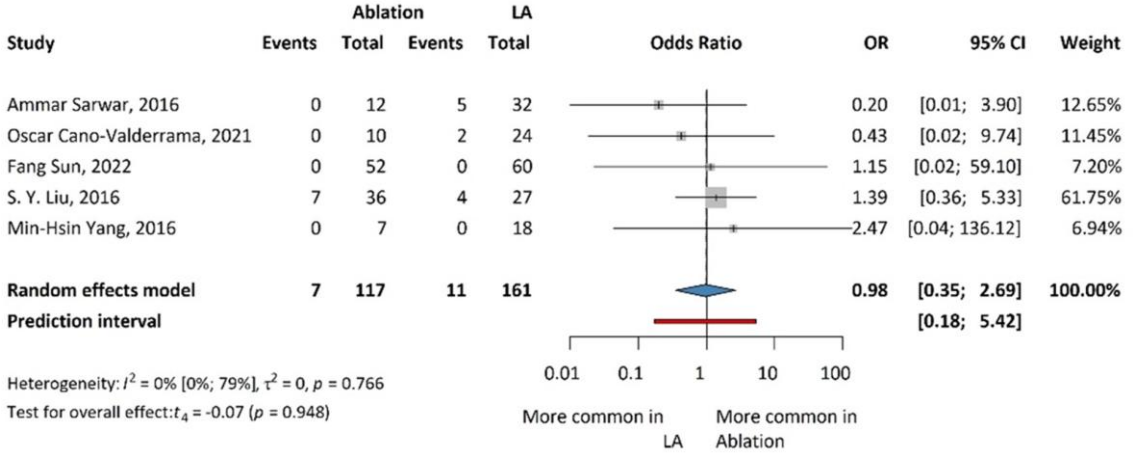


Figure 3. Forest plot summarizing the odds ratios (OR) of complications associated with ablation and laparoscopic adrenalectomy for aldosterone-producing adrenal tumors.

Hypertensive crisis

Results for the hypertensive crisis are presented in Figure 4, revealing significant differences between ablation and LA (OR: 8.13; 95% CI: 1.14-58.11; p = 0.042) with the results in favor of surgery. Ablation has a statistically significant higher probability of being associated with hypertensive crisis.

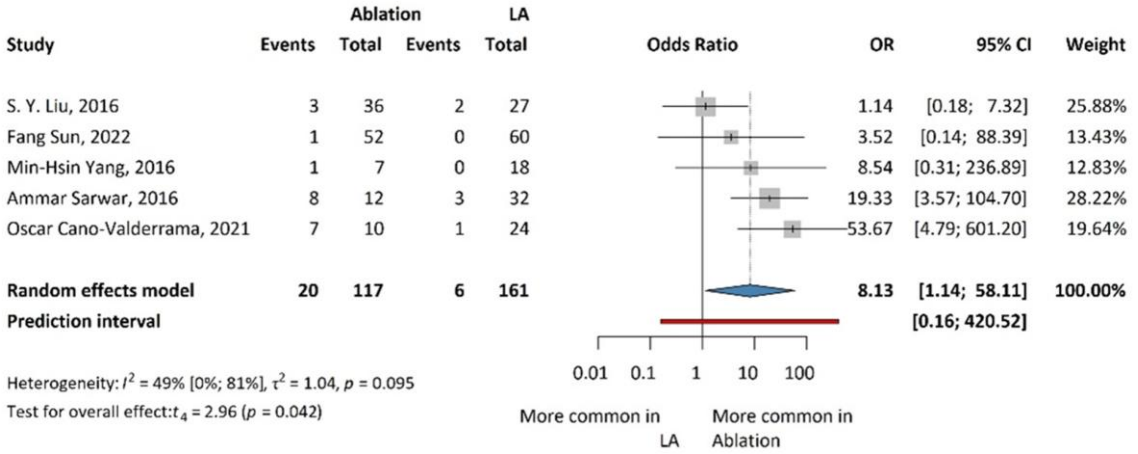


Figure 4. Forest plot summarizing the odds ratios (OR) of hypertensive crisis associated with ablation and laparoscopic adrenalectomy for aldosterone-producing adrenal tumors.

8.1.3. Secondary Outcomes

Operation time

Data on operation time were available in four studies. For ablation procedures, intervention times were significantly shorter than for LA (MD: 75.64 minutes; 95% CI: 6.33-144.95; p = 0.040), with intervention times varying from an average of 12 to 158 minutes.

Length of hospital stay

Data on length of hospital stay (LOS) were reported in four studies. Postoperative hospitalization time was significantly shorter in the ablation group than in the LA group (MD: 1.6 days; 95% CI: 0.88-2.31; p = 0.006).

Perioperative blood loss, postoperative pain treatment

The reviewed studies indicated a higher perioperative blood loss with LA. Sun et al.'s research showed less blood loss with ablation (3.41±3.05 ml) compared to laparoscopy (48.26±60.70 ml), and the study by Sarwar et al. also favored ablation procedures (1.20±3.00 ml versus 40.00±85.00 ml). In addition, both Liu et al. and Sarwar et al. observed less postoperative pain in the ablation group than in LA.

8.1.4. Risk of Bias Assessment

The risk of bias for study participation was mainly low, whereas study attrition was not applicable to any of the studies due to their retrospective design. The risk of bias was mostly moderate for prognostic factors and outcome measurement. Next, we evaluated study confounding, which was moderate in all included articles. Finally, a low risk of bias was attributed to statistical analyses. Sensitivity analysis was performed using the Leave-One-Out test, demonstrating our analysis's robustness as it showed minimal sensitivity. Egger's test could not be performed due to the low number of articles.

Significant heterogeneity was found for operation time (I2=91%, 95% CI: 81%; 96%) and postoperative pain treatment (I2=84%, 95% CI: 36%; 96%), and heterogeneity was

moderate for hypertensive crisis (I2=49%, 95% CI: 0%; 81%) and hospital stay (I2=37%, 95% CI:0%; 78%).

8.1.5. Quality of Evidence

The quality of evidence in Study I is low to moderate, primarily because all five included studies were retrospective cohort studies. The QUIPS-based risk of bias assessment also showed a moderate risk in several domains. No randomized or prospective comparative data were available, and heterogeneity was high for several outcomes.

8.2. Study II: - Oncological Efficacy and Safety of Minimally Invasive Focal and Whole-Gland Interventions in the Treatment of Low- and Intermediate-Risk Prostate Cancer: A Systematic Review and Meta-Analysis

8.2.1. Study Search and Selection

A total of 14,568 articles were identified, with 10,118 remaining after duplicate removal. After title and abstract selection, 928 articles were found, and 85 full-text articles were eligible for analysis. (Figure 5). Our meta-analysis and systematic review included 82 single-arm studies, 14 studies on IRE (42-55), 28 on cryoablation (56-83), 40 on HIFU (84-122), and three comparative articles investigating both cryoablation and HIFU (123-125).

In terms of study design, 49.5% (42/85) of the articles included were prospective cohort studies, 42.5% (36/85) were retrospective cohort studies, 7% (6/85) were registries, and 1% (1/85) were randomized controlled trials. The baseline characteristics of these studies are detailed in Tables 3-5. A total of 15,488 patients with a mean age ranging from 60 to 74 years were included in our review, of whom 682 were treated with IRE, 7,371 with cryoablation, and 7,435 with HIFU worldwide.

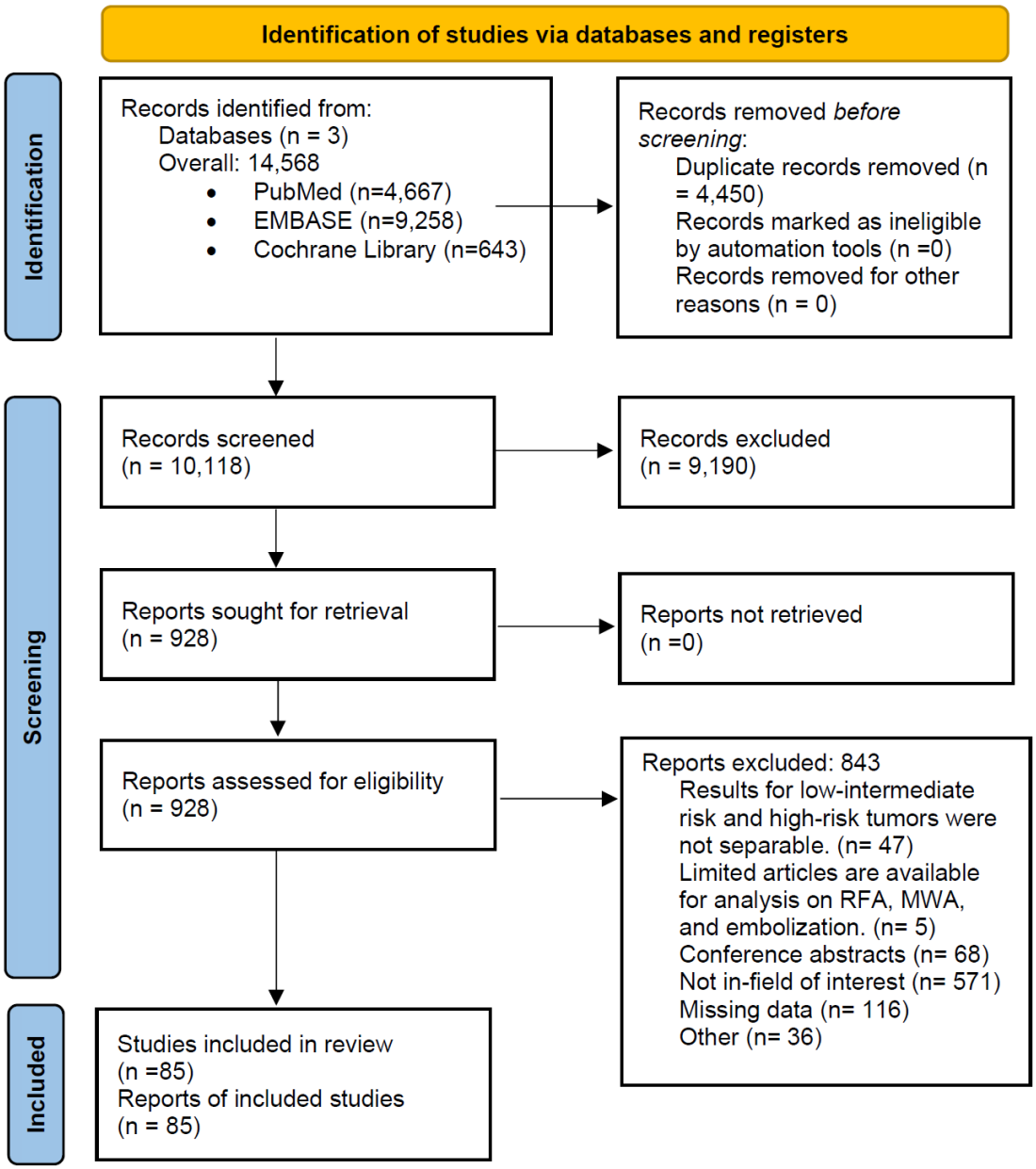


Figure 5. PRISMA 2020 flowchart representing the study selection process

Table 3. Basic characteristics of included studies regarding irreversible electroporation (IRE).

Author (year)	Study site	Study design	Study period	Modality	Study participation	Age (years) ‡	Gleason score (No: ≤6; 7)	NCCN risk category (No: low; intermediate)	Clinical stage (No: T1; T2)	Preoperative PSA (ng/mL) ‡
Rosette et al. (2023)	Netherland	RCT	2015-2020	Focal	51	64 (58;64)	28;23	28;23	45;6	5.93 (4.34; 8.96)
				Extended	55	64 (57;68)	32;23	32;23	49;6	6.05 (4.5;8.64)
Collettini et al. (2019)	Germany	Prospective cohort	2014-2017	Focal	30	65.5 (60; 68.8)	7;23	4;26	NA	8.65 (5;11)
Wang et al. (2022)	China	Prospective cohort	2018-2019	Extended	109	67 (8)	47;62	27;82	32;77	9 (6;12.7)

Shin et al. (2023)	South - Korea	Prospective cohort	2021-2022	Focal	17	66.1 (9.3)	11;6	10;7	0;17	7.5 (3.9)
Giganti et al. (2019)	UK	Retrospective cohort	2011-2016	Focal	30	63 (60;67)	7;23	NA	NA	NA
Blazevski et al. (2019)	Australia	Prospective cohort	2013-2018	Focal	123	68 (62;73)	12;111	11;112	NA	5.73 (3.8;8)
Popeneciu et al. (2024)	Germany	Prospective cohort	2018-2021	Focal	24	65.2 (4.9)	14;10	14;10	NA	7.9 (3.5)
Yaxley et al. (2022)	Australia	Retrospective cohort	2018-2021	Focal	52	72 (51-87)	4;48	4;48	NA	NA
Altan et al. (2023)	Turkey	Prospective cohort	2020-2023	Focal	18	61.1 (6.5)	NA	5;13	NA	6.73 (2.98)

Murray et al. (2016)	USA	Prospective cohort	2011-2014	Focal	25	63.1 (59.3;67.6)	18;7	18;7	NA	4.3 (3.3;5.6)
Ting et al. (2015)	Australia	Prospective cohort	2013-2014	Focal	25	67 (60; 71)	2;23	2;23	11;14	6 (4.3;8.6)
Valerio et al. (2016)	UK	Prospective cohort	2013-2015	Focal	19	60 (53; 66)	8;11	7;12	18;1	7.75 (5.5; 10.03)
Bos et al. (2017)	Australia	Prospective cohort	2013-2016	Focal	63	67 (61-71)	9;54	8;55	NA	6 (3.2;8.4)
López et al. (2023)	Spain	Prospective cohort	2014-2021	Focal	41	65.8 (8.34)	30;11	NA	NA	6.9 (2.76)

‡ **Parameters are represented as mean with standard deviation (SD) or median with interquartile range (IQR min; IQR max) or range (minimum-maximum).** UK: United Kingdom; USA: United States of America; RCT: randomized controlled trial; NCCN: National Comprehensive Cancer Network; PSA: Prostate-specific antigen; NA: not applicable

Table 4. Basic characteristics of included studies regarding cryoablation.

Author (year)	Study site	Study design	Study period	Modality	Study participation	Age (years) ‡	Gleason score (No: ≤6; 7)	NCCN risk category (No: low; intermediate)	Clinical stage (No: T1; T2)	Preoperative PSA (ng/mL) ‡
Tokuda et al. (2023)	Japan	Retrospective cohort	2017-2021	Focal	16	69 (51-81)	0;16	0;16	0;16	8.22 (4.14-14)
Wysock et al. (2020)	USA	Prospective cohort	2017-2019	Partial/ Hemi/ Whole	83	64 (59;70)	9;74	9;74	NA	6.18 (4.6;7.8)
Sze et al. (2019)	USA	Retrospective cohort	2012-2016	Focal	17	NA	12;5	12;5	NA	8.7 (6.7;11.76)
Kim et al. (2012)	Brazil	Retrospective cohort	2010-2011	Partial/ Hemi/ Whole	10	66.2 (10.8)	6;4	5;5	NA	7.8 (2.8)
Bahn et al. (2012)	USA	Retrospective cohort	2002-2010	Focal	73	64 (47-79)	30;43	24;49	41;32	5.9 (3.9)

Barqawi et al., (2017)	USA	Prospective cohort	2007-2015	Focal/ Partial/ Whole	393	65 (60;71)	NA	NA	NA	NA
Hayek et al. (2008)	Brazil	Prospective cohort	2000-2004	Focal	13	70.9 (55-83)	NA	13;0	NA	5.5 (NA)
Gregg et al. (2021)	USA	Prospective cohort	2009-2012	Partial/ Hemi/ Whole	23	62.2 (6.8)	18;5	18;5	NA	3.9 (2.1)
Lambert et al. (2007)	USA	Retrospective cohort	2002-2005	Focal	25	69 (48-78)	13;12	NA	25;0	6 (1-13.1
Lian et al. (2015)	China	Retrospective cohort	2006-2013	Focal	41	67 (56-76)	24;17	23;18	26;15	7.1 (2.6-14.1)
Mendez et al. (2015)	USA	Registry	2007-2013	Focal	317	66.5 (6.6)	317;0	317;0	NA	NA
				Partial/ Hemi/ Whole	317	66.5 (6.6)	317;0	317;0	NA	NA
Marra et al. (2021)	France	Prospective cohort	2008-2018	Focal	121	66 (62;71)	92;29	92;29	101;20	6.42 (5.03;8.08)

Barret et al. (2013)	France	Prospective cohort	2009-2011	Focal	50	66.5 (61;73)	50;0	50;0	NA	6.2 (5;7.9)
Enikeev et al. (2020)	Russia	Prospective cohort	2016-2017	Partial/ Hemi/ Whole	45	64.4 (3.8)	45;0	45;0	NA	8.6 (1.2)
Durand et al. (2014)	France	Prospective cohort	2009-2012	Hemi	48	66.6 (50.4-77.1)	48;0	48;0	42;6	6.1 (4.9;7.1)
Hale et al. (2013)	USA	Prospective cohort	2006-2012	Hemi/ Subtotal	26	65	25;1	23;3	26;0	NA
Boissier et al. (2020)	Spain	Prospective cohort	2010-2018	Hemi/ Whole	66	76 (71-80); 74 (42-81)	20;46	12;54	44;22	7.9 (3.3-11.9); 6.7 (1.2-11.6)
Rodríguez et al. (2014)	Spain	Prospective cohort	2001-NA	Whole	62	NA	NA	28;34	NA	NA
Elkjær et al. (2014)	Den-mark	Prospective cohort	2006-2012	Whole	27	NA	NA	6;21	NA	NA
Guo et al. (2020)	USA	Registry	2004-2015	Focal/ Whole	1942	68.6 (7.4)	939; 1003	805;1137	1645; 297	NA

Aker et al. (2023)	USA	Prospective cohort	2017-2021	Partial	97	NA	NA	97;0	NA	NA
Ekish et al. (2013)	USA	Retrospective cohort	2008-2011	Focal/ Whole	21	68 (54-89)	NA	10;21	NA	NA
Johansen et al. (2007)	Norway	Retrospective cohort	2003-2007	Whole	64	64.65 (53-75)	NA	27;37	NA	8.2 (0.5-16)
Cohen et al. (2008)	USA	Retrospective cohort	1991-1996	Whole	116	NA	NA	36;80	NA	NA
Dhar et al. (2011)	USA	Registry	NA	Whole	576	NA	NA	127;446	NA	NA
Grossgold et al. (2014)	USA	Registry	NA	Whole	2090	NA	NA	682;1408	NA	NA
Liu et al. (2014)	Tai-wan	Retrospective cohort	2008-2013	Whole	43	NA	NA	19;24	NA	NA
Mercader et al. (2020)	Spain	Retrospective cohort	2008-2017	Whole	148	NA	NA	57;91	NA	NA

Oishi et al. (2018)	USA	Retrospective cohort	2002-2012	Whole	69	NA	NA	24;45	NA	NA
Tourinho-Barbosa et al. (2020)	France	Retrospective cohort	2009-2018	Focal/ Whole	119	66 (62;71)	91;28	79;40	NA	6.5 (5-8.3)
Lepor et al. (2024)	USA	Prospective cohort	2017-2024	Partial	313	65 (60.9; 70.1)	NA	0;313	NA	NA

‡ Parameters are represented as mean with standard deviation (SD) or median with interquartile range (IQR min; IQR max) or range (minimum-maximum).

USA: United States of America; NCCN: National Comprehensive Cancer Network; PSA: Prostate-specific antigen; NA: not applicable

Table 5. Basic characteristics of included studies regarding high-intensity focused ultrasound (HIFU)

Author (year)	Study site	Study design	Study period	Modality	Study participation	Age (years) ‡	Gleason score (No: ≤6; 7)	NCCN risk category (No: low; intermediate)	Clinical stage (No: T1; T2)	Preoperative PSA (ng/mL) ‡
Westhoff et al. (2023)	Germany	Prospective cohort	2014-2020	Focal	50	68 (63;74)	27;23	35;15	50;0	6.5 (4.9;8.3)
Glybochko et al. (2019)	Russia	Retrospective cohort	2013-2016	Hemiablation	35	65 (NA)	NA	NA	35;0	6 (1.5)
Ahmed et al. (2011)	UK	Prospective cohort	2006-2008	Hemiablation	20	60.4 (5.4)	NA	5;15	NA	7.3 (2.8)

Aoun et al. (2015)	Belgium	Retrospective cohort	2001-2012	Whole	70	74 (62;86)	51;19	31;39	39;31	12.1 (4.1)
Blana et al. (2004)	Germany	Retrospective cohort	1997-2002	Whole	146	66.9 (6.7)	NA	NA	NA	7.6 (3.4)
Capogrosso et al. (2018)	France	Prospective cohort	2005-2014	Whole	84	72 (72;76)	56;28	47;37	44;40	6.32 (5.2-7.7)
Dellabella et al. (2021)	Italy	Prospective cohort	2017-2019	Focal/ Hemiablation	189	70 (59;81)	92;97	NA	NA	5.8 (2.8;8.8)
Duwe et al. (2023)	Germany	Prospective cohort	2016-2021	Focal/ Hemiablation	29	66 (61.5; 72.5)	20;9	NA	NA	6.8 (5.1;8.9)
Fegoun et al. (2011)	France	Retrospective cohort	1997-2000	Hemiablation	12	70 (4.8)	10;2	0;12	NA	7.3 (2.44)

Feijoo et al., (2015)	France	Prospective cohort	2009-2013	Hemiablation	67	70.2 (6.8)	58;9	NA	NA	6.1 (1.6;15.5)
Ganzer et al. (2018)	Germany	Prospective cohort	2013-2016	Hemiablation	51	63.4 (8.3)	43;8	NA	NA	6.2 (2.1)
Hoquetis et al. (2016)	France	Retrospective cohort	2009-2014	Hemiablation	25	66 (7.3)	19;6	NA	17;8	6.13 (2.5)
Nyk et al. (2021)	Poland	Retrospective cohort	2016-2019	Focal/ Hemiablation	30	64.5 (NA; NA)	20;10	NA	17;13	6.6 (NA)
Pinthus et al. (2012)	Canada	Retrospective cohort	2005-2010	Focal	402	62.7 (7.5)	209;193	183;219	309;93	6.6 (3.1)
Poissonnier et al. (2007)	France	Retrospective cohort	1993-2003	Hemiablation / Whole	227	68.8 (5.82)	152;75	NA	122;105	6.99 (3.48)

Ghai et al. (2021)	Canada	Prospective cohort	2016-2019	Focal	44	67 (62;70)	0;44	0;44	NA	6.4 (4.3;9.6)
Rischmann et al. (2016)	France	Prospective cohort	2009-2014	Hemiablation	111	64.8 (6.2)	82;29	75;36	77;34	6.2 (2.5)
Sivaraman et al. (2020)	France France	Retrospective cohort	2009-2019	Hemiablation (Cohort-1: US-guided)	88	68 (6.9)	73;15	NA	NA	7.1 (2.9)
				Hemiablation (Cohort-2: MRI-guided)	54	67.6 (7.3)	36;16	NA	NA	7.7 (2.6)
Velthoven et al. (2016)	Belgium	Prospective cohort	2007-2015	Hemiablation	50	74 (70;77)	30;20	24;26	16;34	6.3 (3.9-8.3)
Hardenberg et al. (2018)	Germany	Prospective cohort	2014-2016	Focal	24	70 (52-78)	17;7	NA	NA	6.53 (0.99-9.36)

Arnouil et al. (2018)	France	Retrospective cohort	2008-2014	Focal/ Hemiablation	53	65.11 (6.08)	40;13	33;20	47;6	6.32 (2.68)
Crouzet et al. (2011)	France	Retrospective cohort	2005-2009	Whole	297	71.4 (5.1)	190;107	149;148	172;125	6.49 (3.43)
Luca et al. (2023)	Italy	Prospective cohort	2018-2020	Focal/ Hemiablation /Whole	100	73.7 (6.6)	33;67	33;67	NA	5.92 (2.5)
Barret et al. (2013)	France	Prospective cohort	2009-2011	Hemiablation	21	66.5 (60;73)	21;0	21;0	NA	6 (5.1;8.1)
Enikeev et al. (2020)	Russia	Prospective cohort	2016-2017	Whole	45	63.9 (3.7)	45;0	45;0	NA	8.7 (0.9)
Tourinho-Barbosa et al. (2020)	France	Retrospective cohort	2009-2018	Focal/ Hemiablation	190	68 (62;73)	130;60	103;87	NA	7.1 (5.5;9)

Misraï et al. (2008)	France	Retrospective cohort	2001-2006	Whole	115	NA	NA	65;50	NA	NA
Rosenhammer et al. (2019)	Germany	Retrospective cohort	1997-2009	Whole	402	NA	NA	209;193	NA	NA
Shoji et al. (2020)	Japan	Prospective cohort	2016-2018	Focal	75	68.76 (39-85)	46;29	31;44	0;75	7.5 (2.48-19.05)
Rivera et al. (2018)	Spain	Retrospective cohort	2007-2016	Whole	65	NA	40;25	35;30	NA	NA
Wu et al. (2020)	Taiwan	Retrospective cohort	2009-2015	Whole	66	NA	35;31	14;52	NA	NA
Abreu et al. (2020)	USA	Retrospective cohort	2015-2019	Hemiablation	69	NA	NA	25;44	NA	NA

Chen et al. (2018)	Taiwan	Retrospective cohort	2009-2015	Whole	85	NA	NA	23;62	NA	NA
Dickinson et al, (2016)	UK	Registry	2004-2012	Whole	532	NA	NA	161;371	NA	NA
Reddy et al. (2022)	UK	Registry	2005-2020	Focal	916	NA	NA	20;896	NA	NA
Komura et al. (2013)	Japan	Prospective cohort	2004-2008	Whole	99	NA	NA	52;47	NA	NA
Limani et al. (2014)	Belgium	Retrospective cohort	2001-2012	Whole	89	NA	NA	40;49	NA	NA
Mearini et al. (2014)	Italy	Prospective cohort	2004-2007	Whole	127	NA	NA	80;47	NA	NA

Pfeiffer et al. (2012)	Germany	Retrospective cohort	2002-2006	Whole	138	NA	NA	72;66	NA	NA
Ripert et al. (2010)	France	Retrospective cohort	2004-2010	Whole	53	72.5 (60-79)	43;10	28;25	34;19	8.5 (4)
Tsai et al. (2023)	Taiwan	Retrospective cohort	2021-2022	Whole	43	NA	NA	15;28	NA	NA
Ploussard et al, (2024)	France	Prospective cohort	2015-2019	Whole	1967	74.7 (72.4; 77.6)	NA	1109; 858	NA	NA
Nahar et al. (2024)	USA	Prospective cohort	2016-2023	Focal/ Hemiablation	80	NA	NA	24;56	NA	NA

‡ Parameters are represented as mean with standard deviation (SD) or median with interquartile range (IQR min; IQR max) or range (minimum-maximum).

UK: United Kingdom; NCCN: National Comprehensive Cancer Network; PSA: Prostate-specific antigen; NA: not applicable

8.2.2. Primary Outcomes

Recurrence rates.

Forest plot illustrating recurrence rates following IRE is presented in Figure 6. In the extended subgroup at six months, two studies reported a recurrence rate of 0.26 (95% CI: 0.07–0.62; PI: NA; I2 = 93%). In the focal subgroup, eight studies yielded a six-month rate of 0.28 (95% CI: 0.19–0.40; PI: 0.07–0.66; I2 = 67%), and five studies reported a 12-month rate of 0.28 (95% CI: 0.15–0.46; PI: 0.03–0.85; I2 = 75%). The overall pooled recurrence rate across 14 studies was 0.29 (95% CI: 0.22–0.38; PI: 0.09–0.64; I2 = 74%). Subgroup analyses showed recurrence rates of 0.26 (95% CI: 0.07–0.62; PI: NA; I2 = 93%) for extended IRE and 0.30 (95% CI: 0.23–0.39; PI: 0.10–0.63; I2 = 68%) for focal IRE, with no significant difference between groups (p = 0.796). Among focal IRE studies, the pooled in-field recurrence rate was 0.14 (95% CI: 0.09–0.19; PI: 0.05–0.31; I2 = 36%), and the out-of-field recurrence rate was 0.15 (95% CI: 0.09–0.22; PI: 0.04–0.44; I2 = 57%). In- and out-of-field recurrence rates could not be assessed for extended IRE due to missing data.

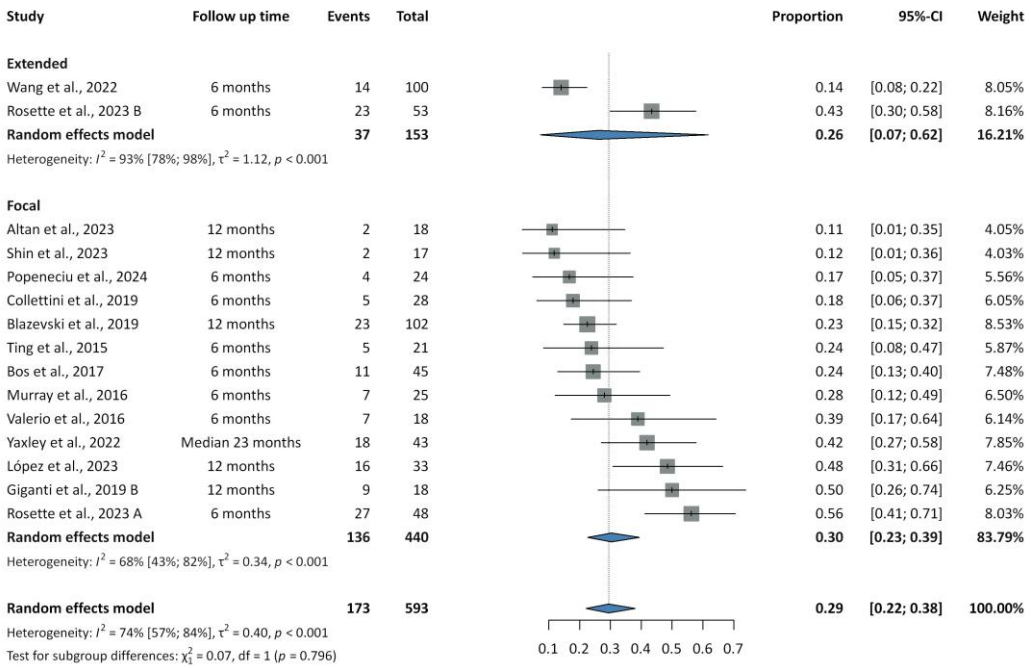


Figure 6. Summary forest plot of pooled recurrence rates for focal and extended irreversible electroporation.

The forest plot for cryoablation is presented in Figure 7. The pooled recurrence rate across 21 studies was 0.17 (95% CI: 0.12–0.23; PI: 0.04–0.48; I2 = 83%). When stratified by treatment strategy, recurrence rates were 0.18 (95% CI: 0.12–0.27; PI: 0.03–0.59; I2 = 86%) for focal and 0.13 (95% CI: 0.08–0.18; PI: 0.05–0.27; I2 = 0%) for whole-gland cryoablation, with no significant difference between groups (p = 0.424). In analyses combining both focal and whole-gland procedures, the pooled rates of in-field, out-field, and concurrent in- and out-field recurrence were 0.05 (95% CI: 0.04–0.07; PI: 0.03–0.08; I2 = 0%), 0.10 (95% CI: 0.06–0.15; PI: 0.02–0.32; I2 = 53%), and 0.02 (95% CI: 0.01–0.03; PI: 0.01–0.04; I2 = 0%), respectively.

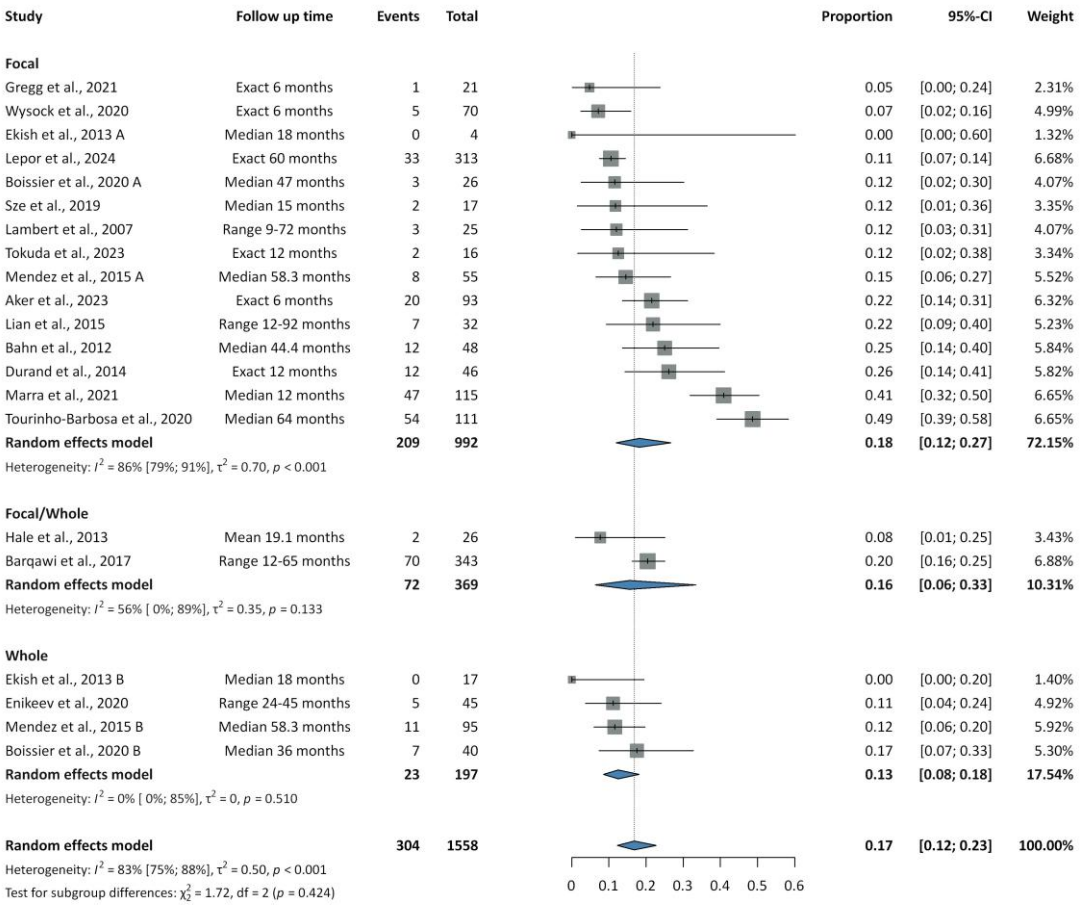


Figure 7. Summary forest plot of pooled recurrence rates for focal and whole-gland cryoablation.

Figure 8 presents the forest plot for recurrence rates associated with HIFU. Considering the 12-month follow-up time, we were able to analyze only the focal HIFU group, yielding a recurrence rate of 0.33 (95% CI: 0.25–0.42; PI: 0.11–0.65; I2= 77%). Across 25 studies, the overall pooled rate was 0.20 (95% CI: 0.16–0.25; PI: 0.05–0.53; I2 = 90%). However, whole-gland HIFU demonstrated a statistically significant reduction in recurrence, with a rate of 0.15 (95% CI: 0.12–0.19; PI: 0.07–0.30; I2 = 75%), compared to 0.24 (95% CI: 0.18–0.31; PI: 0.06–0.59; I2 = 84%) for FT (p = 0.010). The pooled rates of in-field, out-field, and concurrent in- and out-field recurrence were 0.10 (95% CI: 0.06–0.16; PI: 0.02–0.43; I2 = 77%), 0.09 (95% CI: 0.05–0.14; PI: 0.02–0.35; I2 = 72%), and 0.02 (95% CI: 0.01–0.04; PI: 0.01–0.08; I2 = 17%), respectively.

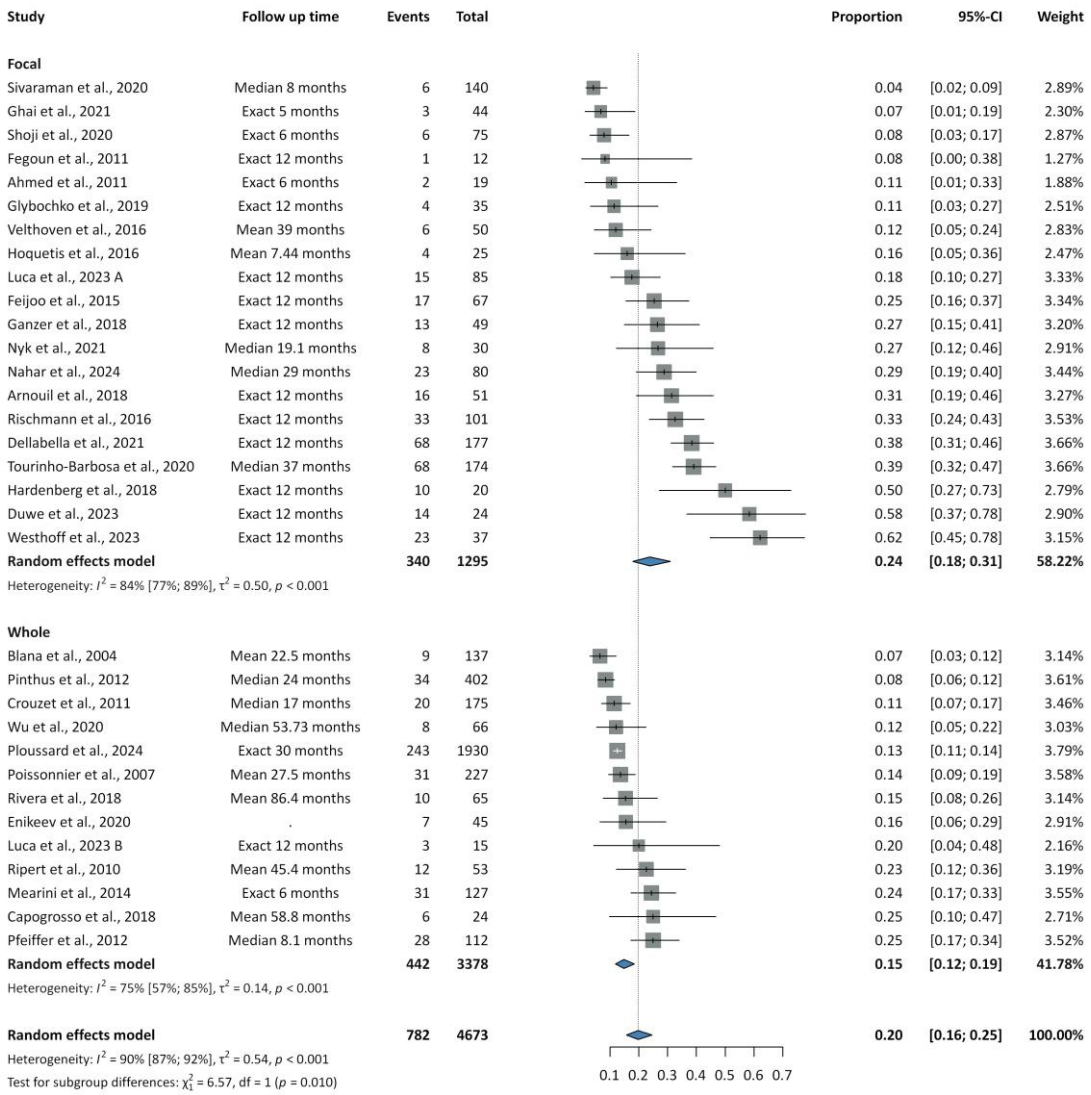


Figure 8. Summary forest plot of pooled recurrence rates for focal and whole-gland high-intensity focused ultrasound.

Complication rates

The overall complication rate associated with IRE was 0.37 (95% CI: 0.27–0.48; PI: 0.11–0.74; I2 = 82%). Subgroup analysis yielded rates of 0.43 (95% CI: 0.15–0.77; PI: NA; I2 = 94%) for extended IRE and 0.35 (95% CI: 0.25–0.47; PI: 0.10–0.73; I2 = 77%) for FT, with no statistically significant difference between groups (p = 0.683). Although the

incidence of major complications remained low in both groups, extended IRE demonstrated a rate of 0.02 (95% CI: 0.01–0.08; PI: NA; I2 = 23%), while focal IRE showed a rate of 0.03 (95% CI: 0.02–0.06; PI: 0.02–0.07; I2 = 0%).

Cryoablation was associated with an overall complication rate of 0.21 (95% CI: 0.14–0.31; PI: 0.05–0.60; I2 = 71%). When stratified by treatment approach, FT presented a complication rate of 0.19 (95% CI: 0.13–0.27; PI: 0.07–0.43; I2 = 49%), while whole-gland cryoablation showed a higher rate of 0.41 (95% CI: 0.10–0.82; PI: 0.00–1.00; I2 = 78%), although the difference was not statistically significant (p = 0.334). Major complications remained low for both modalities, reported at 0.03 (95% CI: 0.01–0.04; PI: 0.01–0.05; I2 = 0%) for FT and 0.02 (95% CI: 0.01–0.06; PI: 0.00–0.32; I2 = 50%) for whole-gland ablation.

Regarding HIFU, the pooled complication rate was 0.29 (95% CI: 0.23–0.36; PI: 0.11–0.57; I2 = 88%), with subgroup rates of 0.28 (95% CI: 0.18–0.40; PI: 0.05–0.75; I2 = 87%) for focal and 0.30 (95% CI: 0.22–0.38; PI: 0.09–0.65; I2 = 92%) for whole-gland therapy. There was no statistically significant difference between the two approaches (p = 0.828). Major complications were similarly low for both, at 0.04 (95% CI: 0.03–0.07; PI: 0.01–0.15; I2 = 42%) for focal HIFU and 0.04 (95% CI: 0.02–0.10; PI: 0.00–0.46; I2 = 91%) for whole-gland HIFU.

8.2.3. Secondary Outcomes

Survival Outcomes: OS, CSS, and MFS

Survival outcomes were consistently favorable across all treatments, with no significant differences between focal and whole-gland subgroups.

For focal IRE, one-year OS was 98% (95% CI: 94–99; PI: 91–100; I2 = 0%), CSS was 98% (95% CI: 94–99; PI: 91–100; I2 = 0%), and MFS reached 99% (95% CI: 94–100; PI: 0–100; I2 = 0%).

Among patients treated with focal or whole-gland cryoablation, pooled OS, CSS, and MFS were 98% (95% CI: 95–99; PI: 69–100; I2 = 84%), 99% (95% CI: 99–100; PI: 99–100; I2 = 0%), and 99% (95% CI: 98–100; PI: 98–100; I2 = 0%).

Similarly, pooled OS, CSS, and MFS following focal and whole-gland HIFU were 97% (95% CI: 95–98; PI: 83–88; I2 = 76%), 99% (95% CI: 98–100; PI: 88–100; I2 = 59%), and 98% (95% CI: 96–99; PI: 74–100; I2 = 72%), respectively.

Biochemical outcomes

During the follow-up periods, the mean postoperative PSA levels were 2.91 ng/mL (95% CI: 2.31–3.52; PI: 0.73–5.1; I2 = 86%) for IRE, 2.26 ng/mL (95% CI: 1.54–2.98; PI: 0.00–4.81; I2 = 93%) for cryoablation, and 2.39 ng/mL (95% CI: 1.83–2.96; PI: 0.00-4.85; I2 = 98%) for HIFU. Notably, a significant difference was observed between focal and whole gland HIFU, with mean postoperative PSA levels of 2.81 ng/mL (95% CI: 2.41–3.21; PI: 1.28–4.34; I2 = 86%) and 0.68 ng/mL (95% CI: 0.35–1.01; PI: 0.00–4.74; I2 = 91%), respectively, in favor of the whole-gland technique ($p < 0.001$).

The one-year BRFS according to the Phoenix criteria for cryoablation in the treatment of pooled low-intermediate risk PCa was 95% (95% CI: 93–97; PI: 87–98; I2 = 49%), with a five-year BRFS of 81% (95% CI: 75–86; PI: 57–93; I2 = 91%). BRFS rates were 99% (95% CI: 93–100; PI: 43–100; I2 = 59%) and 86% (95% CI: 72–93; PI: 63–95; I2 = 87%) at one and five years in low-risk PCa, while 95% (95% CI: 88–98; PI: 68–99; I2 = 64%) and 78% (95% CI: 62–89; PI: 47–94; I2 = 92%) in intermediate-risk PCa patients. For HIFU, the one-year pooled BRFS was 96% (95% CI: 92–98; PI: 69–100; I2 = 78%), while the five-year pooled BRFS was 78% (95% CI: 72–84; PI: 53–92; I2 = 83%). In low-risk PCa, BRFS rates were 97% (95% CI: 88–99; PI: 65–100; I2 = 76%) at one year and 85% (95% CI: 77–90; PI: 59–96; I2 = 82%) at five years, whereas in intermediate-risk patients they were 96% (95% CI: 92–98; PI: 75–99; I2 = 74%) and 72% (95% CI: 59–82; PI: 38–92; I2 = 90%), respectively. Due to insufficient data, the analysis for IRE could not be performed.

Functional outcomes

The incidence of newly developed urinary incontinence ranged from 0 to 14% following focal IRE, while data for extended IRE were insufficient to analyze. For cryoablation, rates were 0–15% with FT and 0–23% with whole-gland ablation. No clinically relevant

difference was observed between focal and whole-gland HIFU, with incidences of 0–20% and 0–22%, respectively. De novo erectile dysfunction after focal and extended IRE was reported in 0–24% of cases. Focal cryoablation was associated with 0–31% rates, whereas whole-gland cryoablation showed higher rates of 0–53%. HIFU rates ranged from 0–33% with FT, compared to 12–53% with whole-gland treatment.

Retreatment

In patients who underwent IRE, 7% (95% CI: 5–11; PI: 4–11; I2 = 0%) required a second IRE, 7% (95% CI: 4–13; PI: 2–27; I2 = 40%) received radical treatment, and 2% (95% I: 1–5; PI: 1–5; I2 = 0%) were managed with hormonal therapy. Following cryoablation, 7% (95% CI: 5–9; PI: 3–15; I2 = 40%) required a second cryoablation, 5% (95% CI: 2–9; PI: 1–32; I2 = 79%) underwent radical treatment, and 3% (95% CI: 1–6; PI: 0–28; I2 = 72%) were treated with hormonal therapy. Among those who received HIFU, 6% (95% CI: 4–9; PI: 2–21; I2 = 75%) required a second HIFU procedure, 8% (95% CI: 6–12; PI: 2–30; I2 = 83%) progressed to radical treatment, and 3% (95% CI: 2–5; PI: 0–17; I2 = 72%) underwent hormonal therapy.

8.2.4. Risk of Bias Assessment

The overall risk was mostly moderate in retrospective and prospective studies, with 16 of them showing serious risk, especially for participant selection and missing data. Bias due to confounding was generally moderate, while bias related to intervention classification and deviations from intended interventions was typically low. In contrast, outcome measurement and reporting biases ranged from low to moderate. The only RCT included showed a low risk of bias across most domains, though some concerns were noted regarding missing outcome data for recurrence rates. The sensitivity analysis confirmed the robustness of our results, showing minimal sensitivity.

We assessed publication bias visually using funnel plots and the trim-and-fill method, and statistically, we used Egger’s test. Our results all exceeded the 0.05 p-value threshold, indicating no significant publication bias.

8.2.5. Quality of Evidence

The quality of evidence in Study II is moderate to low, largely due to the predominance of observational studies. According to the ROBINS-I and RoB 2 assessments, the overall risk of bias was moderate, while a few studies demonstrated a serious risk, mainly related to confounding and missing data. Although heterogeneity was manageable and publication bias was not detected, the lack of adjusted head-to-head comparisons and substantial baseline variability across studies limits the certainty of the conclusions.

9. DISCUSSION

9.1. Summary of Findings, International Comparisons (including all studies)

In this meta-analysis, we examined the efficacy and safety of various onco-interventional procedures for treating different types of cancer. In Study I, we conducted a comparative evaluation of RFA and LA in the treatment of aldosterone-producing adenomas. Our results demonstrate that LA should remain the gold-standard therapy, as it is significantly more effective in resolving hypertension and is associated with a lower risk of perioperative hypertensive crisis. However, ablation offers notable advantages, including lower perioperative blood loss, shorter procedure times, reduced postoperative pain, and quicker postoperative recovery.

Our results showed that the risk of hypertensive crisis is approximately eight times higher during ablation. This elevated risk was particularly observed in the studies by Sarwar et al. and Cano-Valderrama et al. (12, 13). Several factors may contribute to this finding, including the very small sample sizes, variability in patient condition, and differences in preoperative management. Clinical evidence suggests that the use of preoperative alpha-blockers can reduce the risk of hypertensive crisis (126). However, Sarwar et al. did not provide information about their use regarding their administration. In contrast, the other included studies reported substantially lower rates.

Two meta-analyses have previously been published on this topic, comparing RFA with LA. Chen et al. (2021) included five comparative studies, partially overlapping with those identified in our review (127). Their analysis showed that ablation had a 45% lower probability of resolving hypertension than laparoscopy, whereas our findings indicated a difference of 70%. According to Chen's results, the risk of hypertensive crisis was 5.5 times higher during RFA than during LA. A major strength of the study by Chen et al. is that they evaluated several clinically relevant outcomes, including changes in serum potassium levels, reductions in diastolic and systolic blood pressure, and decreases in the aldosterone-to-renin ratio. However, their analysis had notable limitations, including the use of duplicated patient cohorts and heterogeneity in procedural techniques: Yang et al. employed retroperitoneoscopic-guided cool-tip RFA, whereas the remaining studies used CT-guided RFA (128). Guo et al. (2021) also published a meta-analysis comparing ablation with adrenalectomy in the treatment of adrenal gland tumors (129). They

reported a 28% lower rate of resolution of hypertension and a three times increased risk of hypertensive crisis with RFA compared with LA. This discrepancy may be explained by the inclusion of Yang et al.'s study, which utilized laparoscopic-guided ablation (128).

Study II evaluates the safety and efficacy of focal and whole-gland interventional modalities, including IRE, cryoablation, and HIFU, in patients with low- and intermediate-risk PCa. Recurrence rates were significantly lower with whole-gland HIFU than with the focal approach (15% vs. 24%). Conversely, no statistically significant differences were detected between focal and extended IRE (30% vs. 26%), nor between focal and whole-gland cryoablation (18% vs. 13%). Across all treatment modalities, in-field and out-of-field recurrence rates were similar. Retreatment rates were consistently low, with 6–7% receiving repeat ablation and 2–8% progressing to radical or hormonal therapy. Although overall complication rates were higher with IRE (37%) and HIFU (29%) compared to cryoablation (21%). Major complications were rare across all modalities. Survival outcomes were excellent, remaining above 97% in all groups. Whole-gland HIFU achieved superior biochemical control, with significantly lower postoperative mean PSA levels than focal HIFU (0.68 vs. 2.81 ng/mL). For both cryoablation and HIFU, one-year BRFS exceeded 95%, and five-year BRFS approached 80%.

Across 49 cohorts, Tay et al. reported excellent FT survival outcomes (OS 98.0%, CSS 99.3%, MFS 98.5%), consistent with our findings. Their analysis showed a biopsy-confirmed overall recurrence rate of 44.6%, of which 22.2% represented clinically significant cancer (8.9% in-field and 12.3% out-of-field), which differs from our results. Retreatment rates aligned with our results, with 5% of patients receiving a second ablation and 10.5% moving to radical therapy (130). Hopstaken et al.'s systematic review found an in-field HIFU recurrence rate of 15.4%, consistent with our observations. Regarding IRE, the in-field recurrence rate was 8.5%, whereas cryoablation showed a range of 0–20% within the treated area (23).

Bründl et al. conducted an analysis of 463 patients with low- to intermediate-risk PCa who underwent whole-gland HIFU. At 15-year follow-up, CSS reached 95% in low-risk patients and 89% in intermediate-risk patients, while MFS was 91% and 85%, respectively (131). In a cohort of 260 patients treated with whole-gland cryoablation, Tan

et al. reported a 10-year failure-free survival of 66% and an MFS of 96%. Overall complications occurred in 8.8% of cases, with 2.3% experiencing grade ≥3 events, similar to our results (132).

9.2. Strengths (including all studies)

Among the strengths of our analysis is the use of a preregistered protocol and a rigorous methodological framework, complemented by a comprehensive evaluation of clinically relevant outcomes. Study II included subgroup analyses contrasting focal and whole-gland treatments for all modalities. Our analysis integrated several recently published studies and applied multiple methodological improvements compared to previous reviews.

9.3. Limitations (including all studies)

This work is limited by the predominance of retrospective and prospective observational studies, incomplete reporting of preoperative variables, baseline heterogeneity in patient selection, a generally moderate risk of bias, and potential variability related to physician preference and operator skill. Furthermore, Study II was not based on adjusted, direct head-to-head comparisons, and differences between treatment groups or subgroups may reflect variations in baseline characteristics or study design.

10. CONCLUSIONS

10.1. Study I

Onco-interventional procedures have a higher risk of hypertensive crisis and lower biochemical effectiveness compared with laparoscopic adrenalectomy. Overall, our findings indicate that laparoscopic adrenalectomy should remain the gold-standard therapy for aldosterone-producing adrenal tumors. However, ablation may represent a suitable alternative option in selected cases.

10.2. Study II

IRE, cryoablation, and HIFU provide effective and safe focal and whole-gland treatment options for low- and intermediate-risk prostate cancer, with high survival and low major complication rates. Recurrence and postoperative PSA outcomes are comparable between focal and whole-gland IRE and cryoablation. In contrast, whole-gland HIFU provides better biochemical control and lower recurrence rates than focal HIFU, highlighting the importance of treatment extent in clinical decision-making.

11. IMPLICATIONS FOR PRACTICE

The implementation of scientific knowledge is pivotal in delivering meaningful benefits to the community (133, 134). Image-guided onco-interventional therapies provide safe and effective alternatives that expand treatment options for select patients. This thesis supports the incorporation of interventional techniques into clinical decision-making for suitable patients. The clinical implementation of these techniques has the potential to enhance patient outcomes, reduce treatment-related morbidity, and advance the delivery of personalized oncological care.

12. IMPLICATIONS FOR RESEARCH

12.1. Methodology and Study Design

Future research should prioritize well-designed prospective studies, randomized controlled trials, and standardized reporting frameworks to strengthen the evidence base for minimally invasive interventional therapies. Harmonizing definitions of oncological, biochemical, and functional outcomes, as well as establishing uniform follow-up protocols, would enable more reliable cross-study comparisons and reduce the methodological heterogeneity observed in current literature.

12.2. New Areas

Further investigations are needed to clarify the role of advanced imaging modalities and artificial intelligence–based decision-support tools can optimize patient selection and treatment planning in interventional oncology. Innovative approaches such as IRE, MRI-guided therapies, and combination techniques show promise for improving precision treatment and expanding minimally invasive options for benign and malignant diseases.

13. IMPLICATIONS FOR POLICY MAKERS

Policy makers should facilitate the wider adoption of minimally invasive, image-guided therapies by supporting standardized guidelines, investing in training, and ensuring equitable access to advanced interventional technologies. Broader reimbursement and stronger support for prospective research would facilitate safe and evidence-based implementation. Aligning policy with these advancements can improve resource efficiency and enhance patient outcomes in oncological care.

14. FUTURE PERSPECTIVES

Future developments in onco-interventional radiology will likely be driven by advances in imaging, device technology, and precision treatment planning, enabling even more targeted and organ-preserving therapies. The integration of artificial intelligence and predictive biomarkers has the potential to further refine patient selection and enhance therapeutic outcomes. As evidence grows, minimally invasive interventions are expected to become increasingly prominent in multidisciplinary oncological care.

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16. BIBLIOGRAPHY

16.1. Publications Related to the Thesis

Skribek Benjamin, Szabó Anett, Ács Júlia, Cavalcante Bianca Golzio Navarro, Sipos Boglárka Dorina, Hegyi Péter, Mátrai Péter, Nyirády Péter, Ács Nándor, Majoros Attila, Deák Pál Ákos

Oncological Efficacy and Safety of Minimally Invasive Focal and Whole-Gland Interventions in the Treatment of Low- and Intermediate-Risk Prostate Cancer : A Systematic Review and Meta-Analysis

CANCERS 17: 17 Paper: 2863, 22 p. (2025)

Közlemény: 36333287 | Összefoglaló cikk (Folyóiratcikk) | Tudományos

Scopus - Oncology SJR indikátor: Q1

Scopus - Cancer Research SJR indikátor: Q2

IF: 4,4

Skribek B, Szabó A, Ács J, Hegyi P, Mátrai P, Nyirády P, Ács N, Majoros A, Deák PÁ

Ablation and laparoscopic adrenalectomy: Balancing efficacy and safety in the treatment of benign adrenal gland tumors: A systematic review and meta-analysis

HELIYON 10: 19 Paper: e37868, 10 p. (2024)

Közlemény: 35426427 | Szakcikk (Folyóiratcikk) | Tudományos

Scopus - Multidisciplinary SJR indikátor: Q1

IF: 3,6

16.2. Publications not Related to the Thesis

Ács, Júlia ; Szabó, Anett ; Fehérvári, Péter ; **Skribek, Benjamin** ; Cavalcante, Bianca Golzio Navarro ; Váncsa, Szilárd ; Romics, Miklós ; Szarvas, Tibor ; Nyirády, Péter ; Ács, Nándor et al.

Risk factors for vaginal wall erosion after pelvic organ prolapse surgery with implant : a systematic review and meta-analysis

SCIENTIFIC REPORTS 15 : 1 Paper: 40780 , 10 p. (2025)

Folyóirat szakterülete: Scopus - Multidisciplinary SJR indikátor: Q1

IF: 3,9

Ács, Júlia ; Szabó, Anett ; Fehérvári, Péter ; Harnos, Andrea ; **Skribek, Benjamin** ; Tenke, Martin ; Szarvas, Tibor ; Nyirády, Péter ; Ács, Nándor ; Hegyi, Péter et al.

Safety and Efficacy of Vaginal Implants in Pelvic Organ Prolapse Surgery : A Meta-analysis of 161 536 Patients

EUROPEAN UROLOGY FOCUS 10 : 4 pp. 525-534. , 10 p. (2024)

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